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# Wiadomości Lekarskie
# Medical Advances

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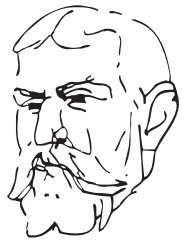

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# Medical Advances





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ORIGINAL ARTICLE

# MEDICAL AND SOCIAL ANALYSIS OF PATIENTS WHO DIED OF SARS-COV-2 IN THE SPECIALIZED INFECTIOUS DEPARTMENT OF THE CITY OF SUMY DURING THE FIRST WAVE OF THE EPIDEMIC

DOI: 10.36740/WLek202305101

**Vladyslav V. Smiianov, Svitlana M. Piven, Natalia O. Dryga, Olha I. Smiianova, Inna O. Plakhtiienko, Natalia G. Kuchma, Kateryna I. Zhuk**
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## ABSTRACT

**The aim** of the article is to analyze demographic indicators, clinical symptoms, concomitant pathology, and the course of acute respiratory viral infection (ARVI) caused by SARS-CoV-2 in patients with a fatal outcome of the disease.

**Materials and methods:** To achieve the goal, a statistical method, an analytical method, and a method of retrospective analysis of the medical histories of patients with fatal cases who were hospitalized with a diagnosis of ARVI caused by SARS-CoV-2 were used.

**Results:** Mortality among patients who were hospitalized with a diagnosis of ARVI caused by SARS-CoV-2 was 8.18 ± 2.17%. Among them, 62% were male and 38% were female. Cardiovascular pathology took first place in the structure of concomitant pathology of all age groups and accounted for 76%. Oncological diseases accounted for 62%, gastrointestinal diseases – 54%, endocrine diseases – 38%, and respiratory system diseases 23% of the total number of patients with fatal cases.

**Conclusions:** Mortality from coronavirus infection in the period March - July 2020 among the male population was 62%, of which 13% - from the age group 18-45 years, 38% - from the age group 46-64 years, and 50% - patients 65 years old and older. Among the female population, the mortality rate was 38%, of which 20% were women in the age group 46-64% and 80% were 65 years and older. The presence of no-hospital polysegmental pneumonia as a complication of ARVI caused by SARS-CoV-2 was 62% among all age groups of the studied patients with fatal cases.

**KEY WORDS:** mortality, pneumonia, diseases of the cardiovascular system, coronavirus infection

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## INTRODUCTION

The epidemic of the disease COVID-19, which began in China, very quickly covered the whole world. Clinical symptoms, features, and severity of the course of the disease were detailed by scientists from China, Western Europe, and America. The fatality rate among patients in China was 3.67%, and among patients over 80 years old — 18.4%. According to the results of the analysis in other countries, the fatality rate ranges from 2 to 12%, and is difficult to estimate it given the lack of testing among people with mild symptoms of the disease [1].

Data are confirmed in all countries that men are more often infected with SARS-CoV-2 and have a severe course [1]. In the United States of America, the mortality rate among men was 1.4 times higher than among women, and in China, it was 1.6 times higher. This is associated with a different hormonal background and the presence of more estrogen in the female body, which stimulates immunity [2].

Scientists have identified a number of concomitant diseases that increase the risk of a severe course of the disease and mortality, respectively. These include diabetes, hypertension, diseases of the cardiovascular system and oncology. Also, the risk factors include advanced age, overweight and the presence of bad habits, especially smoking. [2 - 4]. It has been proven that diabetes is not only a risk factor, but also arises as a complication of the transferred COVID-19.

In the world literature, a different course of the disease is described, from mild, which can pass without pronounced symptoms, to critical, which leads to the death of the patient. The general symptoms of the disease are the same: an increase in body temperature, dry cough and shortness of breath, weakness, but they are expressed in different degrees depending on the age, gender and individual characteristics of the body. In China, 87.9% of patients with ARVI caused by SARS-CoV-2 had fever, 67.7% had cough, and 38.1% had weakness. Scientists have described specific symptoms

of the disease, namely, the loss of the sense of smell and taste. As the results of international studies show, pneumonia is the most dangerous complication of coronavirus infection, but despite the fact that the virus mainly affects the respiratory system, frequent cases of multiple organ failure, septic shock, thrombosis, etc. have been described. [5 - 7].

However, many issues remain unanalyzed in Ukraine today, namely the mortality rate in different regions of the country and among different age groups of the population; dependence of the presence of risk factors, terms of seeking medical help and hospitalization with the severity of the course of the disease and mortality. Therefore, it will be relevant to conduct a retrospective analysis of the disease histories of patients with fatal cases in the specialized infectious department of Sumy.

## THE AIM

The purpose of our study is to analyze demographic indicators, clinical symptoms, concomitant pathology and the course of acute respiratory viral infection caused by SARS-CoV-2 in patients with a fatal outcome of the disease.

## MATERIALS AND METHODS

The study was conducted by the Department of Public Health of the Medical Institute of Sumy State University during March - July 2020. Research methods – statistical, analytical, retrospective analysis of disease histories of patients with fatal cases who were hospitalized with a diagnosis of SARS caused by SARS-CoV-2. The analysis of patient histories was carried out according to a specially developed form that took into account their distribution by age and gender (Table I).

A total of 158 disease histories of patients admitted to the hospital with a diagnosis of SARS caused by SARS-CoV-2 were analyzed, men – 56.33%, women – 43.68%. The disease ended fatally in 13 patients.

## RESULTS

Mortality among patients who were hospitalized with a diagnosis of ARVI caused by SARS-CoV-2 was 8.18 ± 2.17%. Among them, 62% were male and 38% were female. Research patients are divided into age groups, namely patients 18-44 years old, 45-64 years old, 65 years old and older. Therefore, the mortality among hospitalized patients of each age group was 7.69%, 30.77%, 61.54%, respectively. In the age group of 65 years and older, mortality was the highest and the same in quantitative composition among men and women (Table II).

46% of patients with fatal cases were referred by general practitioners of family medicine, and 54% by doctors of emergency medical care. A greater number of patients, 69%, were hospitalized on the 1st–3rd day from the moment of seeking medical help, and for 33% of patients, it was 1–3 days from the onset of the disease, 44% - 4–7 days from the onset of the disease, and for 23% - 14 days or more. 31% of patients were hospitalized for 4–6 days after seeking medical help. They were referred by family practice and emergency physicians in equal numbers. All patients with a fatal case had a positive polymerase chain reaction (PCR) test at the time of admission.

In the age group of patients 18–44 years, concomitant pathology of the cardiovascular and endocrine systems, diseases of the gastrointestinal tract, and oncology accounted for 25%. Oncological diseases accounted for the largest share of 30% of concomitant pathologies in the age group 45–64 years, the same share of 20% was observed for cardiovascular pathology, diseases of the respiratory system and gastrointestinal tract, and 11% were concomitant diseases of the excretory system. (Fig. 1, 2).

Among patients in the age group of 65 years and older, cardiovascular concomitant pathology was 33%, and an equal number of 19% were diseases of the endocrine system, gastrointestinal tract, and oncological diseases, and 5% were diseases of the respiratory system and the excretory system (Fig. 3).

But it should be noted that cardiovascular pathology took the first place in the structure of concomitant pathology of all age groups and accounted for 76%. Oncological diseases accounted for 62%, gastrointestinal tract diseases - 54%, endocrine diseases - 38%, and respiratory system diseases - 23% of the number of patients with fatal cases.

It should be noted that 40% of patients had concomitant pathology of the cardiovascular system and gastrointestinal tract, 38% - had cardiovascular and endocrine systems, and 23% - had cardiovascular, endocrine systems, gastrointestinal tract, and oncological diseases. Only one patient from the age group of 65 years and older did not have any of the concomitant pathologies, all others had one, two, or more diseases. Therefore, we can claim that ARVI caused by SARS-CoV-2 aggravated their condition and led to death.

46% of patients died on the 1st–3rd day of hospitalization, 38% of patients died on the 7–9th day, and 16% of patients died after the 13th day of hospitalization. The course of the disease in patients with fatal cases was also different: 39% - severe, 30% - undetermined, 23% - moderate, and 8% - critical.

62% of patients with fatal cases had nosocomial

**Table I.** Distribution of experimental patients by age and gender, %

| Age group / Gender | 18 – 44 years old | 45 – 64 years old | 65 years old and older |
|---|---|---|---|
| Males | 8,86 | 28,48 | 18,99 |
| Females | 10,13 | 23,42 | 10,13 |
| Total | 18,99 | 51,90 | 29,12 |

**Table II.** Distribution of experimental patients with fatal cases by age and gender, %

| Age group / Gender | 18 – 44 years old | 45 – 64 years old | 65 years old and older |
|---|---|---|---|
| Males | 7,69 | 23,08 | 30,77 |
| Females | 0 | 7,69 | 30,77 |
| Total | 7,69 | 30,77 | 61,54 |

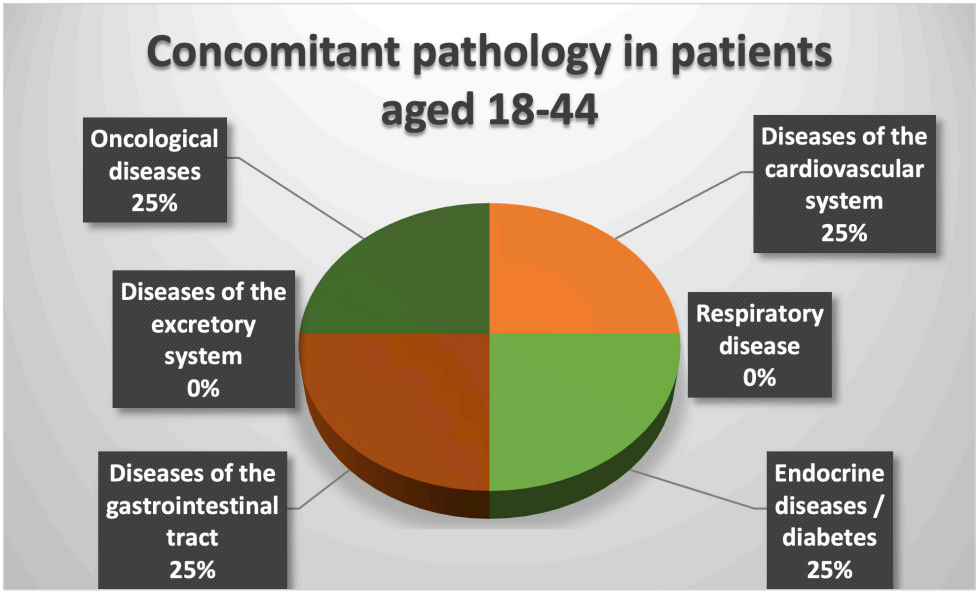


**Fig. 1.** Distribution of concomitant pathology among patients aged 18-44 years

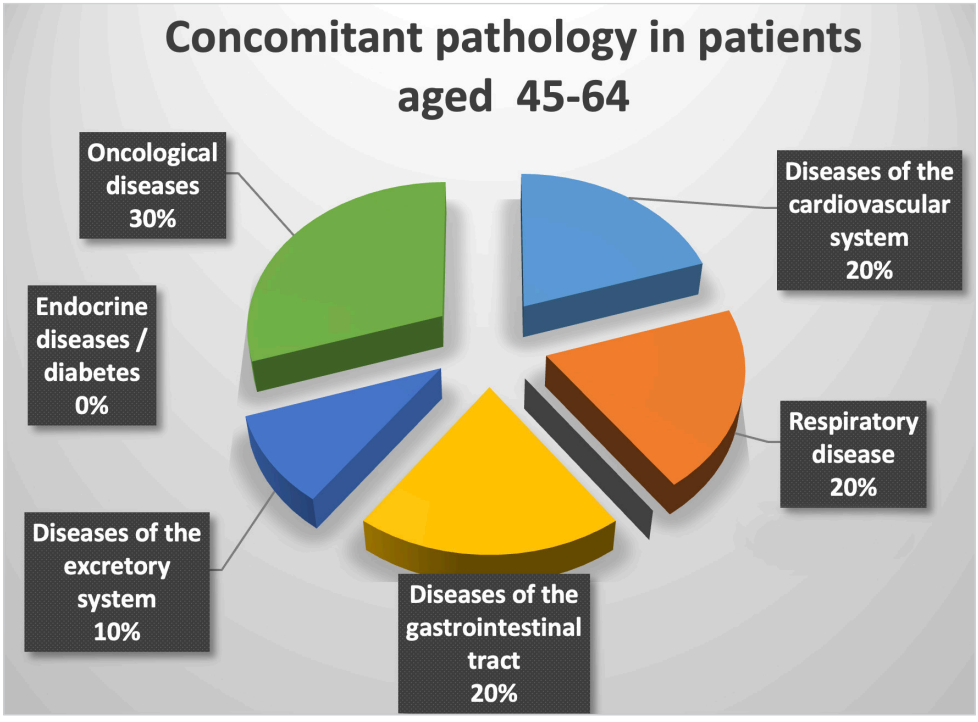


**Fig. 2.** Distribution of concomitant pathology among patients aged 45-64

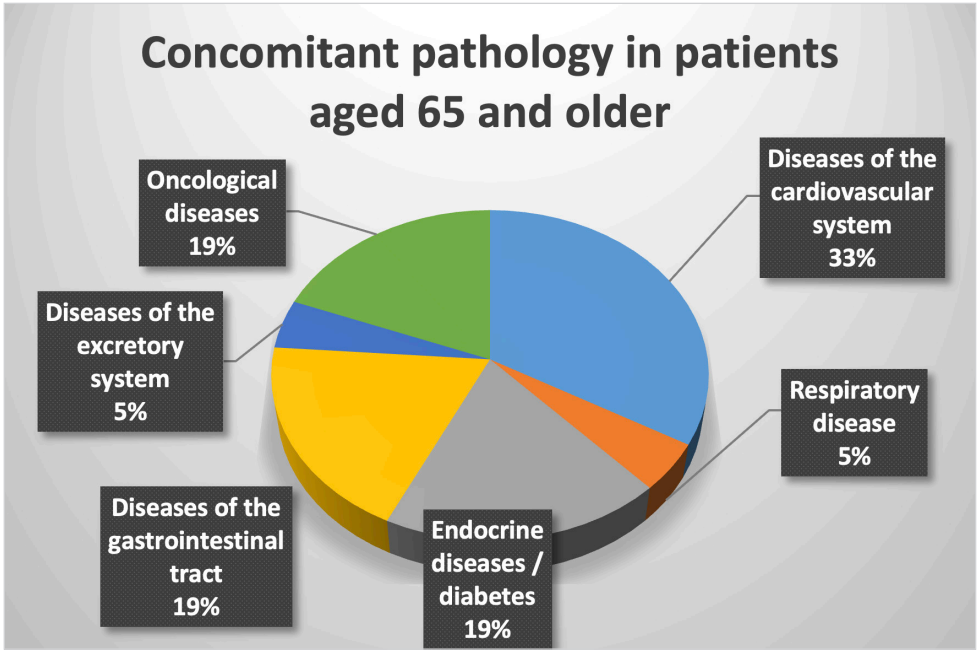


**Fig. 3.** Distribution of concomitant pathology among patients aged 65 and older

pneumonia and complications of the main disease - heart damage. They also had other complications: 37.5% - septic shock, 25% - kidney damage, and 12.5% - liver damage.

In patients with a fatal disease, an equal number of 23% observed an increase in body temperature from 37.0 to 37.5 °C and from 37.6 to 38.5 °C, in 54% - above 38.6 °C. 85% of patients who died had weakness and shortness of breath. At the same time, these patients had no complaints of headache, runny nose, or sore throat.

62% of patients had a dry or wet cough and 75% of them had community-acquired pneumonia confirmed by X-ray or computed tomography and a positive PCR test at the time of admission. Previously, all of them had contact with persons sick with COVID-19, that is, they had an unfavorable epidemiological environment.

## DISCUSSION

According to WHO data, the mortality rate from coronavirus infection in the world is 2.22%, and in Ukraine - 1.96%. During the conducted research (March - July 2020), the mortality rate in the world was 4.64% [11]. The research results showed that the mortality rate in the Sumy region in the above-mentioned period was 8.18%. According to the data of the Ministry of Health of Ukraine, the mortality rate in the regions of the country has decreased significantly and is 1.38% in the Sumy region. And although the percentage of mortality is still significant, the downward trend in different age groups of the population indicates that the medical system of the region is well-functioning.

The mortality rate among men in the Sumy region was 1.6 times higher than among women and amounted to 62%. Such results regarding the gender sensitivity of the disease are confirmed by WHO data and scientists from different countries of the world [1, 7 - 10, 12]. The age group of patients 65 years and older is the most vulnerable in the Sumy region, and 54% of comorbidities in these patients were diseases of the cardiovascular system. Scientists from China, America, and other countries of the world [2 - 4, 6, 13] identify various risk factors for complications and a severe course of the disease. Among them, the leading place belongs to hypertension, diabetes, heart ischemia, oncological diseases, and others. Among patients in the study group who died, endocrine and oncological diseases accounted for 19–25% and 19–30%, respectively.

Scientists have proven that the main and most common complication of coronavirus infection in the world is community-acquired polysegmental pneumonia [7, 14, 15]. 62% of patients who died had pneumonia as a complication of the disease and mainly severe and critical course.

The literature describes the symptoms of coronavirus infection, such as anosmia, ageusia, increased body temperature, weakness, chills, headache, cough, chest pain, and others. Among patients with a fatal outcome of the disease of all age groups, an increase in temperature up to 37.5° and 38.5° was observed in 23% of patients and above 38.6° in 54%. Weakness and shortness of breath were also found in 85%, dry or wet cough in 62%, and chest and muscle pain, anosmia, and ageusia in only 15% of patients with fatal cases.

## CONCLUSIONS

1. The mortality rate from coronavirus infection in the period March - July 2020 was 8.18%, and now it has decreased to 1.38%, which indicates the stability and efficiency of the medical system of the Sumy region.
2. High mortality among men was determined at 62%, of which 13% - were from the age group of 18-45 years, 38% - were from the age group of 46-64 years, and 50% - patients 65 years and older. In women, the mortality rate was 38%, of which 20% were women in the age group 46-64% and 80% - 65 years and older.
3. The most common symptoms among patients with a fatal outcome were: weakness and shortness of breath in 85%, cough in 62%, fever above 38.6° in 54%, chest and muscle pain, anosmia, and ageusia only in 15%.
4. The age group of patients 65 years and older with existing concomitant pathology of the cardiovascular system had the highest mortality rate of 54%.
5. The presence of community-acquired polysegmental pneumonia as a complication of ARVI caused by SARS-CoV-2 was 62% among all age groups of the studied patients with fatal cases.

## REFERENCES


1. Osterweil N. Case fatality rate for COVID-19 near 1.4 %, increases with age. https://www.medscape.com/viewarticle/927870.
2. Wadman M. Sex hormones signal why virus hits men harder. Science. 2020: 368(6495): 1038–1039. doi. org/10.1126/science.368.6495.1038 63.
3. Zaiets K., Padilla R. Coronavirus, diabetes, obesity and other underlying conditions: Which patients are most at risk? https://www.usatoday.com/in-depth/news/2020/04/15/coronavirus-risk-90-patients-had-underlying-conditions/2962721001/
4. Long B., Brady W.J., Koyfman A., Gottlieb M. Cardiovascular complications in COVID-19. The American Journal of Emergency Medicine. 2020. doi: https://doi.org/10.1016/j.ajem.2020.04.048
5. Omer S.B., Malani P., Del Rio C. The COVID-19 Pandemic in the US: A Clinical Update. JAMA. 2020. doi: https:// doi.org/10.1001/jama.2020.5788
6. Giuseppe Lippi, Johnny Wong, Brandon Michael Henry Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. PAIM 2020; 130(4). doi: 10.20452/pamw.15272
7. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382:727–33.
8. Jin J-M, Bai P, He W, et al. Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health 2020;8:152.
9. Wadhera RK, Wadhera P, Gaba P, et al. Variation in COVID-19 hospitalizations and deaths across New York City boroughs. JAMA 2020; 323:2192.
10. Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020; 75:1730–41.
11. World Health Organization. Coronavirus Disease 2019 (COVID-19). Situation Report – 162. https://www.who.int/docs/default-source/coronaviruse/20200630-covid-19-sitrep-162.pdf?sfvrsn=e00a5466_2. Accessed Jun, 30, 2020.
12. Huang C, Wang Y, Li X, et al Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5.
13. L. Zhuravlyova. B., O. Ogneva. A new problem: diabetes and COVID-19 doi: https://doi.org/10.37987/1997-9894.2020.5(241).214031.
14. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507- 513. doi:10.1016/S0140-6736(20)30211-7.
15. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997; 336(4):243-250. doi:10.1056/ NEJM199701233360402.


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ORIGINAL ARTICLE

# HIPPOTHERAPY IN CEREBRAL PALSY – SURVEY RESEARCH

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## ABSTRACT

**The aim:** To assess the effects of a one-year hippotherapy programme on the physical and mental functioning of children with cerebral palsy.

**Materials and methods:** The study included 15 children with cerebral palsy whose mean age was 9 years. The children participated in hippotherapy sessions at the Rehabilitation Centre in Rusinowice (one-year observation). The clinical presentation was dominated by manifestations of motor and postural abnormalities caused by central nervous system damage. A survey questionnaire was used in the study to collect information about problems associated with everyday life and functioning.

**Results:** The results obtained in this study showed that spastic CP was the most common form of the disorder, affecting 8 out of 15 children (53%). It was followed by mixed CP (40%, 6 children). Among the respondents, 67% (10 people) were already familiar with hippotherapy whereas 33% did not know this method.

**Conclusions:** There was a strong correlation between being familiar with effects of hippotherapy and the level of education of the parent/guardian. This result had a moderate influence on the frequency of hippotherapy sessions. Systematic hippotherapy sessions helped improve physical fitness and everyday functioning in children with cerebral palsy.

**KEY WORDS:** cerebral palsy, clinical problems, hippotherapy

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## INTRODUCTION

Approximately 17 million children are affected by cerebral palsy (CP) worldwide. The prevalence of CP in Poland ranges between 1 and 3 per 1,000 births, which makes CP the most common motor dysfunction, permanent dysfunction and mental disorder [1-7].

Brain damage might be caused by different factors. Those factors have been divided into prenatal factors, which are activated during prenatal development and are associated with conditions present in the mother; perinatal factors, related to the period around childbirth; and postnatal factors, which affect the newborn. The clinical presentation of the disorder includes the following:

- abnormal muscle tone: spasticity, flaccidity, stiffness;
- dyskinesia (ataxia, dystonia, athetosis, choreoathetosis);
- delays in the development of psychomotor abilities and reflexes;
- pareses and paralyses;
- concomitant symptoms: seizures; articulation, chewing, swallowing, vision abnormalities; mental retardation.

Detailed descriptions of symptoms found in adults, which differ from those seen in children, allowed for developing a classification of CP forms. The Hagberg cerebral palsy classification, describing clinical presentation and topography, is the most commonly used method [8-12]. Different CP forms include the following:

I. Spastic (pyramidal) form
II. Ataxic (cerebellar) syndromes
III. Dyskinetic (extrapyramidal) form

The Gross Motor Function Classification System (GMFCS) is used to classify functioning as well as the possibilities of planning the rehabilitation process and the ability to participate in society. The GMFCS determines the level of motor disability; more specifically, it is a gross motor function classification system. The GMFCS is divided into five physical ability levels in CP patients and presents age-dependent differences (Table I) [1, 24].

Other classification systems used to assess physical performance in children with CP include Bimanual Fine Motor Function (BFMF) and Manual Ability Classification System (MACS). The following three elements have to be present in order for a child to develop normally: ability to automatically control body position, support and uprighting mechanisms and free character of phase movements.

**Table I.** GMFCS classification based on [24].

| | |
|---|---|
| I | Walking without restrictions |
| II | Walking with restrictions |
| III | Walking with hand-held mobility devices |
| IV | Cannot walk but able to use a wheelchair |
| V | Cannot walk; transported by a caregiver |

## USE OF HIPPOTHERAPY IN CP

Hippotherapy is aimed first of all at improving and learning motor patterns, including balance, motor stimulation (sensory integration), respiratory stimulation, mouth motor function stimulation, and influencing emotions and cognitive functions of the child [16-25].

Motor pattern improvement using a horse is effective and possible due to the fact that the movements of the animal are transferred to the patient. The resultant force acting on the child provides for example motor balance, which is necessary to maintain balance while sitting on a walking horse. Rotational, forward, backward, upward, downward and side-to-side movements are provoked. Close contact with a horse provides sensations that help experience a connection between the child and the animal [2-4, 7]. The process of preparing the horse for a hippotherapy session alone, when the child can feel its warmth and breath, hear the sounds made by the animal, groom and pet it, is also therapeutic. The child feels a duty towards and responsibility for a living being. Children with neurological or mental impairment are more likely to connect with the horse than with the carer. Contrary to appearances, horses are similar to people; however, they have no expectations and give no orders. Consequently, being close to them can improve self-esteem in the child. Moreover, horses understand humans well through non-verbal communication. Sitting on a horse lets the child experience their surroundings from a new perspective and notice things that are often not visible when standing on the ground. Hippotherapy improves spatial orientation, concentration, memory and attention during activities [2-4, 7,8]. Bringing the child joy is a very important aim of hippotherapy. There is no better therapy for patients than therapy that brings positive emotions and so much joy [2-4, 7].

# THE AIM

The aim of the study was to assess the efficacy of hippotherapy used as an addition to main physical therapy methods in children with CP and to prove its efficacy with respect to motor functions, mental wellbeing, cognitive functions and emotions. Moreover, the study aimed to determine which health problem improved the most following hippotherapy.

# MATERIALS AND METHODS

The study used a survey questionnaire completed by a group of parents of 15 children participating in hippotherapy sessions (one-year observation) at St. Raphael the Archangel's Rehabilitation Centre in Rusinowice (Zielona st 23). The questionnaire consisted of 18 questions, which asked about personal information such as sex, age, place of residence (rural or urban area), age of the child ażŻnd the level of education of the parent or legal guardian. Next, the questionnaire focused on hippotherapy as a rehabilitation method (examples: Were you familiar with hippotherapy as a method used in children before? Who told you about the possibility of using hippotherapy in your child?). The next part of the questionnaire asked about the description and frequency of hippotherapy sessions (How many times a week does your child participate in hippotherapy sessions? What type of rehabilitation does your child use apart from hippotherapy?) and about the presence of non-motor abnormalities in CP (Does your child have non-motor abnormalities and if so, what are they? Have you noticed an improvement in your child's behavioural problems after hippotherapy? Have you noticed an improvement in communication with your child? Have you noticed an improvement in concentration in your child? Have you noticed that hippotherapy sessions bring joy to your child?). The last part of the questionnaire asked about the kind of effects hippotherapy had on motor functions (Have you noticed an improvement in gait function in your child after hippotherapy? Have you noticed an improvement in muscle tone in your child after hippotherapy? Have you noticed an improvement in balance in your child after hippotherapy? Have you noticed an improvement in body posture and ability to maintain body posture in your child after hippotherapy?).

## STUDY GROUP CHARACTERISTICS

A group of 15 parents or legal guardians were invited to allow for collecting information about children with CP. The table II presents sociodemographic data of the study group.

Women constituted 67% (10 people) of respondents and men constituted 33% (5 people). The place of residence was reported as an urban area by 60% of respondents (9 people) and rural area by 40% (6 people). The level of education was reported as follows: vocational school 20% (3 people), secondary school 40% (6 people) and university 40% (6 people).

The mean age of children with CP participating in hippotherapy was 9.1 years and the median was Me=9 years (Fig. 1).

**Table II.** Study group characteristics

| Data | | Number [n] | Proportion [%] |
|---|---|---|---|
| Sex | Female | 10 | 67 |
| | Male | 5 | 33 |
| **Total** | | **15** | **100** |
| Place of residence | Urban area | 9 | 60 |
| | Rural area | 6 | 40 |
| **Total** | | **15** | **100** |
| Education | Primary school | 0 | 0 |
| | Vocational school | 3 | 20 |
| | Secondary school | 6 | 40 |
| | University | 6 | 40 |
| **Total** | | **15** | **100** |

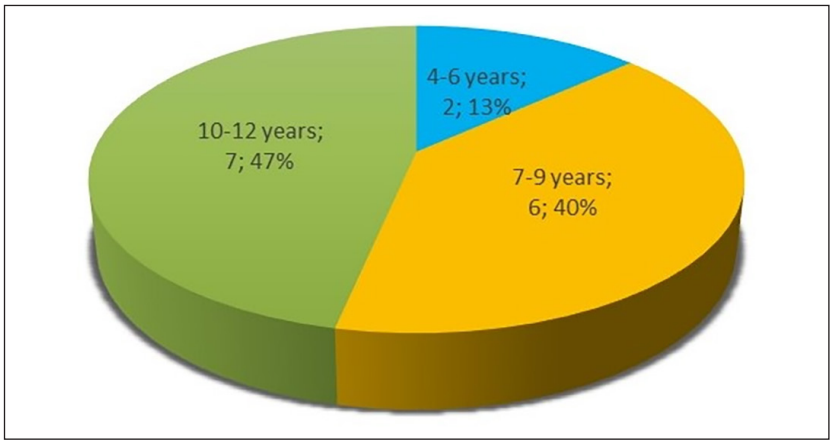


**Fig. 1.** Age structure of children with CP (n=15).

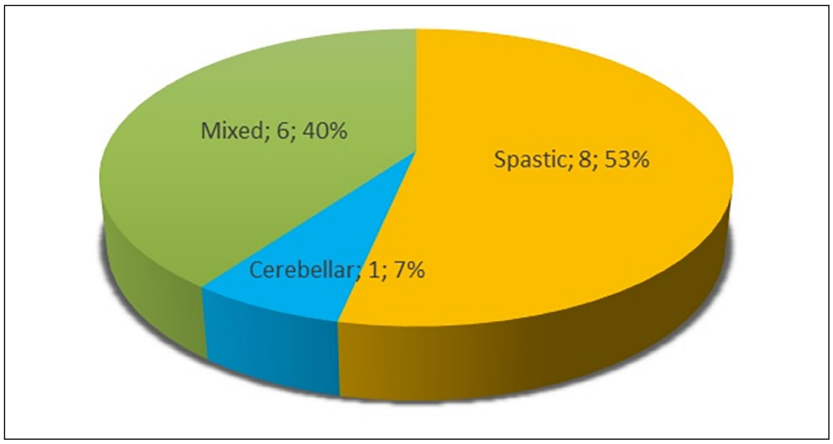


**Fig. 2.** Forms of CP present in children (n=15).

The largest age group (47%, 7 people) consisted of children aged 10 to 12 years; children aged 7 to 9 years constituted 40% of the study group (6 people) and children aged 4 to 6 years made up 13% (2 people).

## RESEARCH PROBLEMS

1. Does hippotherapy considerably improve motor functions, balance and overall body posture in children with CP?
2. Does hippotherapy influence the mental and intellectual development of the child?
3. Are children happy to participate in hippotherapy sessions, which also means they are happy to have sessions with a horse?
4. Does hippotherapy in children with CP have the desired effect in the form of visible improvements in motor, intellectual and cognitive abnormalities?
5. Is hippotherapy a popular method of rehabilitation used in children with CP?

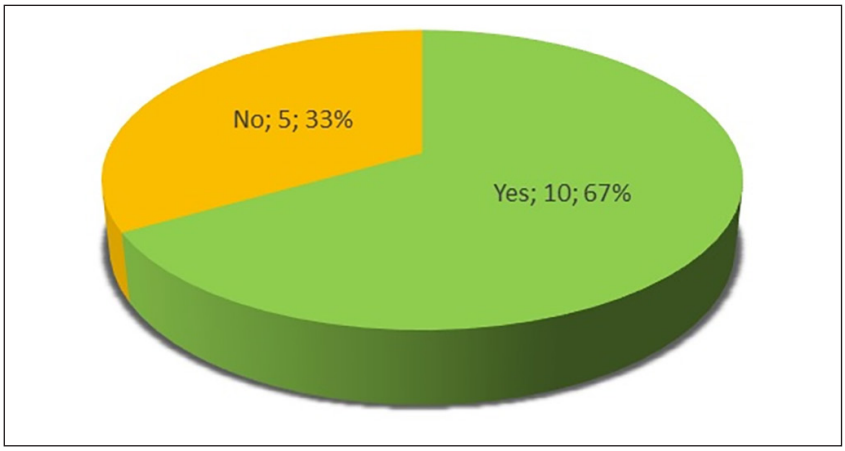


**Fig. 3.** Familiarity with hippotherapy used in children (n=15).

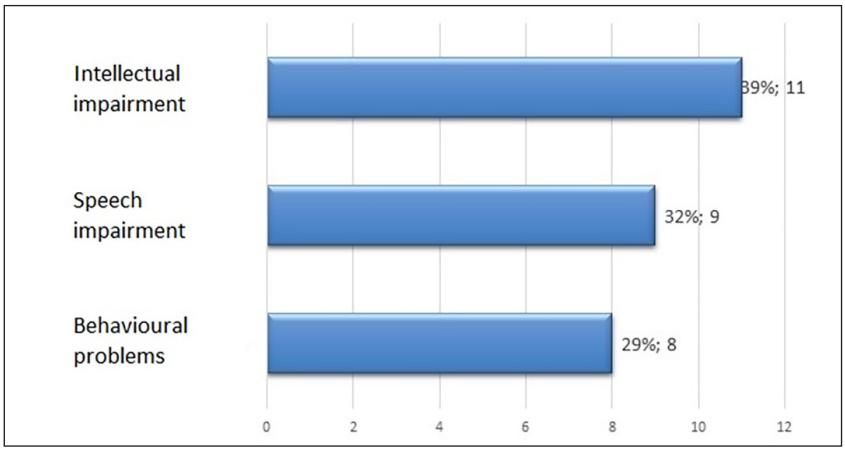


**Fig. 4.** Non-motor abnormalities in children with CP (n=28).

## STATISTICAL ANALYSIS

The results collected in the study were statistically analysed using an MS Excel spreadsheet and the Statistica software. Non-parametric and parametric statistical tests were used to verify the hypotheses. The values of the parameters analysed in the study, which were measured on a nominal scale, were characterised using the number (n) and proportion (%) of respondents.

With multiple-answer questions, the number of answers provided by respondents and filtered data were marked with the letter n.

A chi-squared test of independence was used to compare the structure, which helped determine the presence of a correlation between two variables. Moreover, the level of association was measured with Cramer's V symmetric measures. If the value of those measures is 0–0.3, the association is weak; if the value is 0.3–0.7, the association is moderate; and if the value is 0.7–1, the association is strong. The significance level (maximum acceptable risk of error) was set at $\alpha = 0.05$.

## RESULTS

The first question asked respondents about the form of CP present in their child (Fig. 2).

Spastic CP was present in 53% (8 people), cerebellar CP in 7% (1 person) and mixed CP in 40% (6 people) of the study population.

The next question asked about being familiar with hippotherapy used in rehabilitation in children (Fig. 3).

In the study, 67% of respondents (10 people) were already familiar with hippotherapy as a rehabilitation method for children before it was used in their own child and 33% (5 people) were not familiar with it.

An analysis of correlation between the level of education and being familiar with effects of hippotherapy in the past showed a strong correlation between those two variables. This means that level of education considerably influenced knowledge about effects of hippotherapy (Table III).

Next, respondents were asked who had told them about the possibility of using hippotherapy in their child. The answers included a specialist (27%, 4 people), a physiotherapist (27%, 4 people) and other sources (46%, 7 people), namely school (71%, 5 people) and the media (29%, 2 people).

The next question asked how many times a week the child participated in hippotherapy sessions. The answers were as follows: one to two times a week in 60% of respondents (9 people), 3 to 4 times a week in

**Table III.** Level of education of parent/guardian and familiarity with effects of hippotherapy (n=15).

| Familiarity | Yes | | No | | Total | |
|---|---|---|---|---|---|---|
| Education | n | [%] | [n] | [%] | [n] | [%] |
| Vocational school | 1 | 10 | 2 | 40 | 3 | 100 |
| Secondary school | 3 | 30 | 3 | 60 | 6 | 100 |
| University | 6 | 60 | 0 | 0 | 6 | 100 |
| Total | 10 | 100 | 5 | 100 | 15 | 100 |
| α = 0.05; chi-squared = 4.21; Cramer's V: 0.71 | | | | | | |

**Table IV.** Level of education of parent/guardian and frequency of hippotherapy sessions per week (n=15).

| Frequency | 1-2 times | | 3-4 times | | >4 times | | Total | |
|---|---|---|---|---|---|---|---|---|
| Education | n | % | n | % | n | % | n | % |
| Vocational school | 2 | 22 | 1 | 20 | 0 | 0 | 3 | 100 |
| Secondary school | 3 | 33 | 3 | 60 | 0 | 0 | 6 | 100 |
| University | 4 | 45 | 1 | 20 | 1 | 100 | 6 | 100 |
| Total | 9 | 100 | 5 | 100 | 1 | 100 | 15 | 100 |
| α = 0.05; chi-squared = 2.7; Cramer's V: 0.42 | | | | | | | | |

33% of respondents (5 people) and more than 4 times a week in 7% of respondents (1 person). (Table IV)

An analysis of correlation between the level of education of respondents and the number of hippotherapy sessions per week showed a moderate correlation between the two variables. This means that the level of education of the parent/guardian moderately influenced the frequency of their child's participation in hippotherapy sessions.

The next question asked respondents about types of rehabilitation used in their child apart form hippotherapy. Respondents could choose more than one answer to this question.

Sensory integration therapy was reported by 33% of respondents (12 people), occupational therapy by 31% (11 people).

The next question asked about the presence of non-motor abnormalities in the child. Respondents could choose more than one answer to this question.

Apart from motor abnormalities, children with CP often had intellectual impairment (39%, 11 people), speech impairment (32%, 9 people) and behavioural problems (29%, 8 people) (Fig. 4).

The next question asked respondents whether they had noticed any gait function improvements in their child following hippotherapy.

Gait function improvements were definitely noticed after hippotherapy by 53% of respondents (8 people) while 47% (7 people) selected the "probably yes" option (Fig. 5).

Next, respondents were asked about any muscle tone improvements in their child after hippotherapy. Muscle tone improvements were definitely noticed after hippotherapy by 47% of respondents (7 people) while 53% (8 people) selected the "probably yes" option.

Next, respondents were asked about any balance improvements in their child after hippotherapy. Balance improvements were definitely noticed after hippotherapy by 60% of respondents (9 people) while 40% (6 people) selected the "probably yes" option.

The next question asked about any body posture improvements in the child after hippotherapy.

Body posture improvements were definitely noticed after hippotherapy by 47% of respondents (7 people) while 53% (8 people) selected the "probably yes" option (Fig. 6).

The next question asked about any improvements in behavioural problems after hippotherapy. Improvements in behavioural problems were definitely noticed after hippotherapy by 60% of respondents (9 people) while 40% (6 people) selected the "probably yes" option.

The next question asked about any improvements with respect to communication with the child after hippotherapy. Communication improvements were definitely noticed after hippotherapy by 53% of respondents (8 people) while 47% (7 people) selected the "probably yes" option.

The next question asked about any improvements in the child's concentration after hippotherapy. Concentration improvements were definitely noticed after hippotherapy by 73% of respondents (11 people) while 27% (4 people) selected the "probably yes" option.

The last question asked respondents whether hippotherapy sessions brought joy to their child. Joy due to hippotherapy was definitely noticed by 73% of respondents (11 people) while 27% (4 people) selected the "probably yes" option.

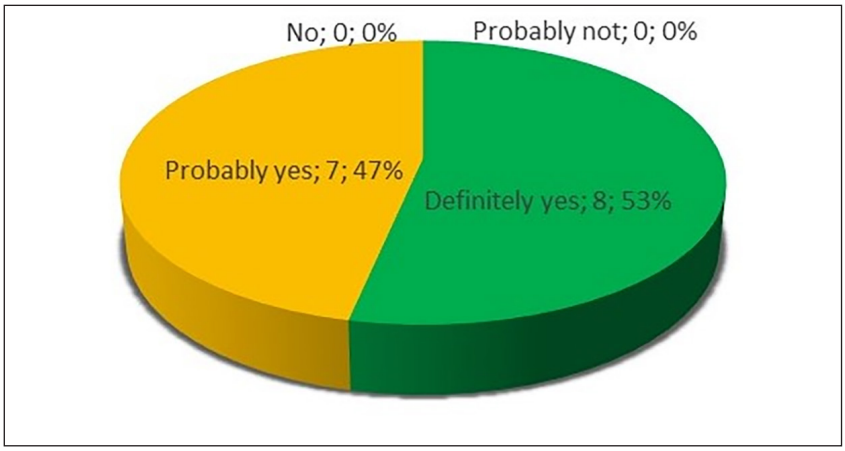


**Fig. 5.** Gait function improvement after hippotherapy (n=15).

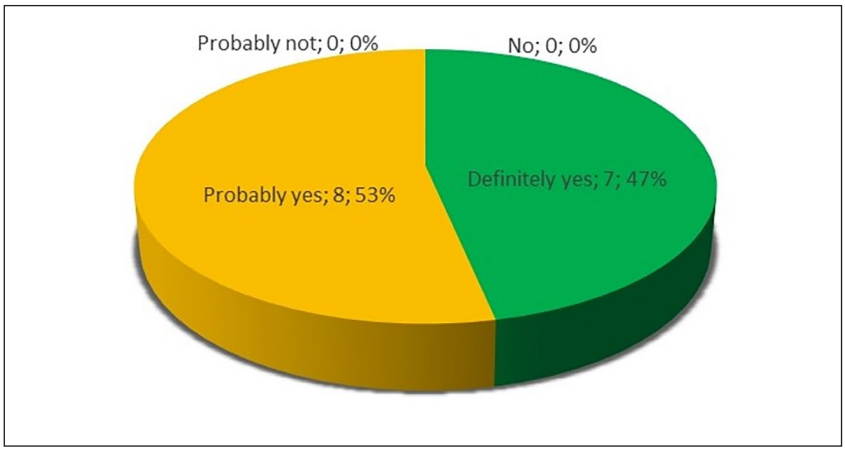


**Fig. 6.** Body posture improvement after hippotherapy (n=15).

With respect to sessions taking place 1–2 times a week, 22% of respondents (2 people) believed hippotherapy definitely improved gait function and 78% (7 people) selected the "probably yes" option (Fig. 7).

22% of respondents (2 people) said that hippotherapy sessions definitely improved muscle tone in the child and 78% (7 people) selected the "probably yes" option. Moreover, 44% of respondents who reported hippotherapy sessions 1–2 times a week (4 people) believed hippotherapy definitely improved balance and 56% (5 people) selected the "probably yes" option.

With respect to sessions taking place 3–4 times a week, 100% of respondents believed hippotherapy definitely improved gait function.

80% of respondents (4 people) said that hippotherapy definitely improved muscle tone in the child and 20% (1 person) selected the "probably yes" option. Moreover, 80% of respondents who reported hippotherapy sessions 3–4 times a week (4 people) believed hippotherapy definitely improved balance and 20% (1 person) selected the "probably yes" option. According to 60% (3 people), hippotherapy definitely improved body posture while 40% (2 people) selected the "probably yes" option.

All respondents (100%; 1 person) who reported hippotherapy sessions more than 4 times a week believed hippotherapy definitely improved gait function, muscle tone, balance and body posture in their child.

In the group where hippotherapy sessions took place 1–2 times a week, 56% of respondents (5 people) declared that hippotherapy definitely improved behavioural problems in the child and 44% (4 people) selected the "probably yes" option. 44% (4 people) believed that hippotherapy definitely improved communication with the child and 56% (5 people) selected the "probably yes" option for this question. Moreover, 56% of those who reported hippotherapy sessions 1–2 times a week (5 people) said that hippotherapy definitely improved concentration and 44% (4 people) selected the "probably yes" option. According to 89% (8 people), hippotherapy definitely improved the level of joy in the child and 11% (1 person) selected the "probably yes" option.

In the group where hippotherapy sessions took place 3–4 times a week, 60% of respondents (3 people) declared that hippotherapy definitely improved behavioural problems in the child and 40% (2 people) selected the "probably yes" option. 60% (3 people) believed that hippotherapy definitely improved communication with the child and 40% (2 people) selected the "probably yes" option for this question. Moreover, 100% of those who reported hippotherapy sessions 3–4 times a week (5

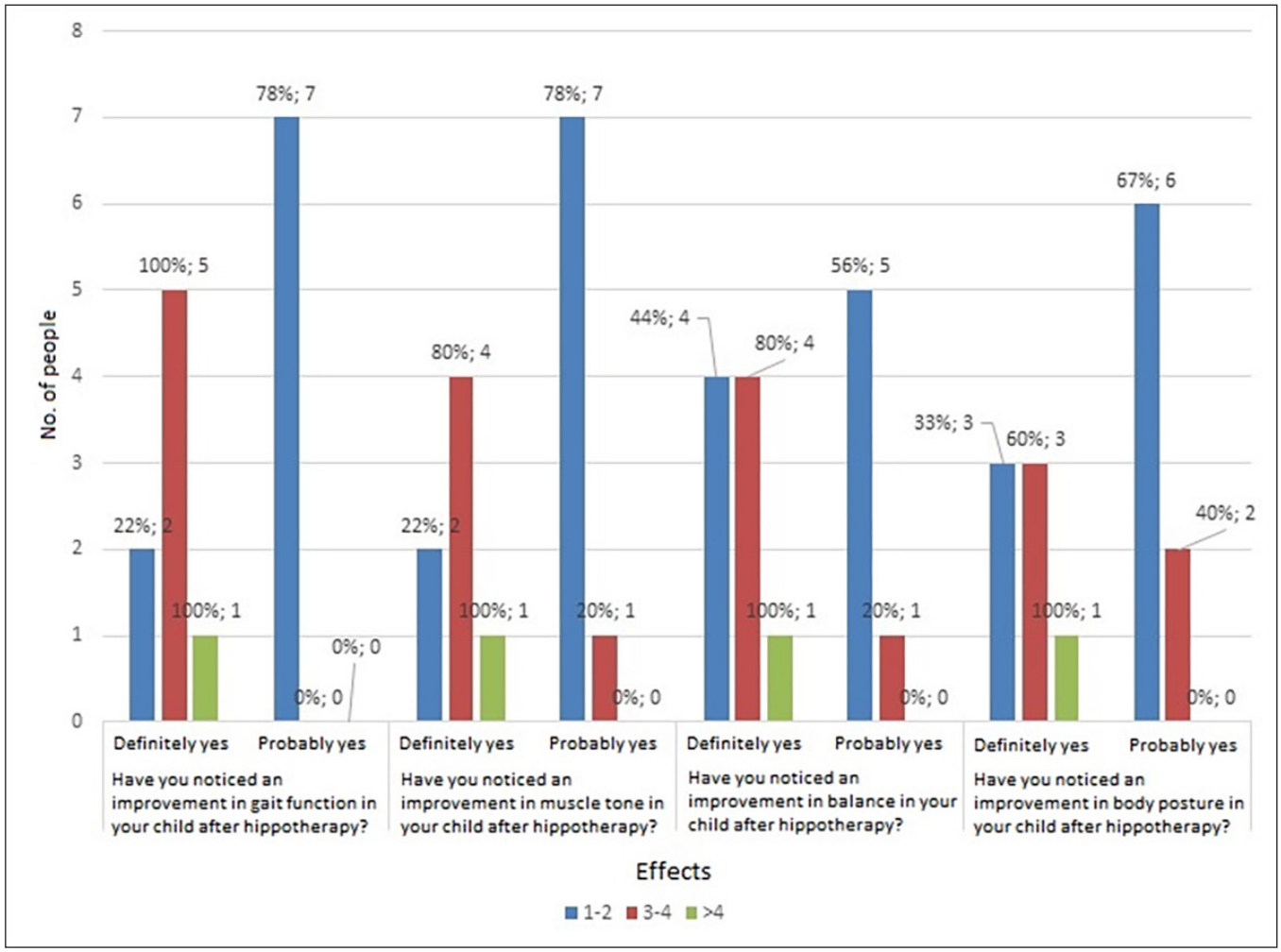


**Fig. 7.** Frequency of hippotherapy sessions and effects with respect to gait function, muscle tone, balance and body posture (n=15).

people) said that hippotherapy definitely improved concentration. According to 100% (5 people), hippotherapy definitely improved the level of joy in the child.

In the group where hippotherapy sessions took place more than 4 times a week, 100% of respondents (1 person) declared that hippotherapy definitely improved behavioural problems in the child. 100% (1 person) believed that hippotherapy definitely improved communication with the child and 0% (0 people) selected the "probably yes" option for this question. Moreover, 100% of those who reported hippotherapy sessions more than 4 times a week (1 person) said that hippotherapy definitely improved concentration. According to 100%, hippotherapy definitely improved the level of joy in the child.

The proportion of parents/guardians who reported that they definitely noticed improvements in gait function in their child after hippotherapy was 62% (5 people) for children with spastic CP and 38% (3 people) for children with mixed CP.

The proportion of parents/guardians who reported that they definitely noticed improvements in muscle tone in their child after hippotherapy was 71% (5 people) for children with spastic CP, 0% (0 people) for children with cerebellar CP and 29% (2 people) for children with mixed CP (Fig. 9).

The proportion of parents/guardians who reported that they definitely noticed improvements in balance in their child after hippotherapy was 67% (6 people) for children with spastic CP, 0% (0 people) for children with cerebellar CP and 33% (3 people) for children with mixed CP.

The proportion of parents/guardians of children with spastic CP who reported that they definitely noticed improvements in body posture in their child after hippotherapy was 86%.

The proportion of parents/guardians who reported that they definitely noticed improvements in behavioural problems in their child after hippotherapy was 56% (5 people) for children with spastic CP, 11% (1 person) for children with cerebellar CP and 33% (3 people) for children with mixed CP.

The proportion of parents/guardians of children with spastic CP who reported that they definitely noticed improvements in communication with the child after hippotherapy was 62%.

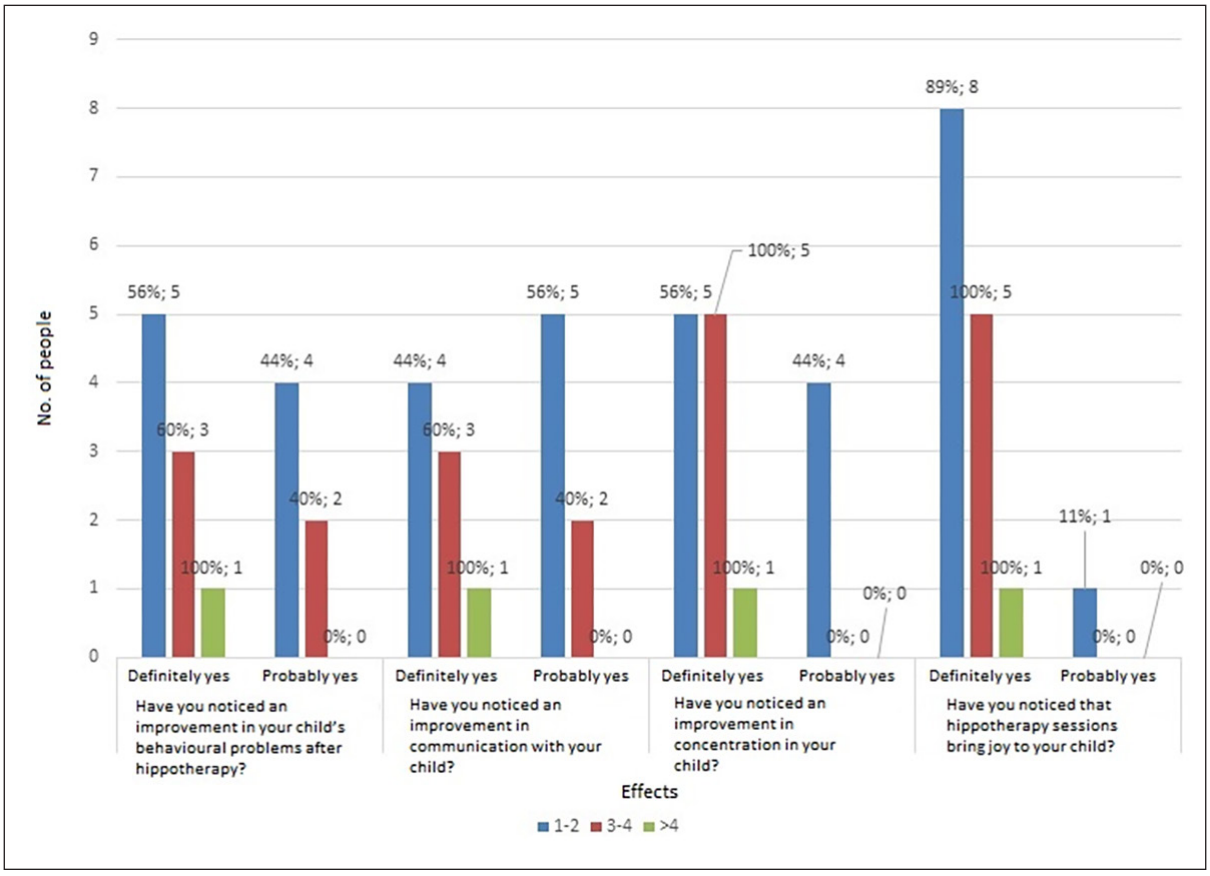


**Fig. 8.** Frequency of hippotherapy sessions and effects with respect to behavioural problems, improved communication, concentration and joy (n=15).

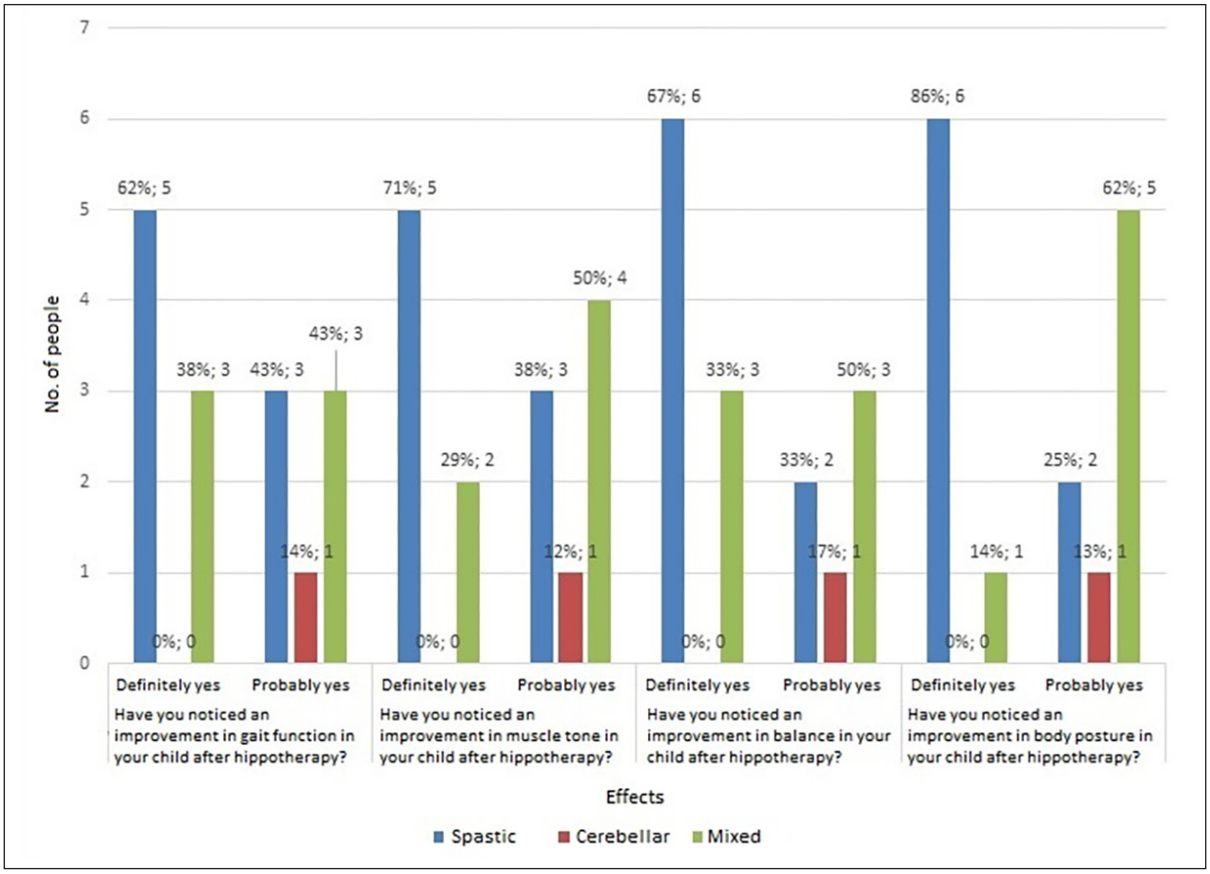


**Fig. 9.** Form of CP and effects of hippotherapy with respect to gait function, muscle tone, balance and body posture (n=15).

The proportion of parents/guardians who reported that they definitely noticed improvements in concentration in their child after hippotherapy was 55% (6 people) for children with spastic CP, 9% (1 person) for children with cerebellar CP and 36% (4 people) for children with mixed CP.

The proportion of parents/guardians who reported that they definitely noticed improvements in the level of joy in their child after hippotherapy was 57% (8 people) for children with spastic CP, 7% (1 person) for children with cerebellar CP and 36% (5 people) for children with mixed CP.

## DISCUSSION

The results obtained in this study showed that spastic CP was the most common form of the disorder, affecting 8 out of 15 children (53%). It was followed by mixed CP (40%, 6 children). Among the respondents, 67% (10 people) were already familiar with hippotherapy whereas 33% did not know this method. There was a strong correlation between being familiar with effects of hippotherapy and the level of education of the parent/guardian. This result had a moderate influence on the frequency of hippotherapy sessions. Most respondents answered that their child participated in hippotherapy sessions 1 to 2 times a week (60%, 9 people).

When asked about other types of rehabilitation apart from hippotherapy, respondents usually listed sensory integration therapy (33%, 12 people) and occupational therapy (31%, 11 people). The study confirmed considerable efficacy of hippotherapy as an excellent method of rehabilitation, particularly motor rehabilitation, which is associated with abnormal muscle tone found in children with CP. This is a close correlation with so-called perceptive-intellectual functions [24]. Motor functions influence speech in children. Moreover, when asked about improvements in communication with the child and concentration after hippotherapy, the vast majority of parents/guardians reported such improvements (53%, 8 people ). Consequently, questions concerning improvements in gait, balance, muscle tone and body posture in children participating in hippotherapy provide confirmation of the efficacy of this method as well as clear answers to the study hypotheses. Finally, the study allowed for concluding that children experience joy when participating in hippotherapy (73%, 11 people). Having contact with an animal and being able to communicate with it makes patients very happy, which is particularly important for any therapy aimed at children.

## CONCLUSIONS

1. Hippotherapy sessions helped achieve a considerable improvement in motor abilities in terms of gait, balance, body posture and muscle tone.
2. Improved muscle tone facilitates communication between children and their surroundings.
3. Children with CP showed improved concentration, which translated into more effective learning.
4. Hippotherapy is one of the most pleasant forms of rehabilitation and, more importantly, is enjoyable for children.

There was a strong correlation between being familiar with effects of hippotherapy and the level of education of the parent/guardian. This result had a moderate influence on the frequency of hippotherapy sessions.

## REFERENCES


1. Gajewska E. Nowe definicje i skale funkcjonalne stosowane w mózgowym porażeniu dziecięcym. Neurol Dziec. 2009;35:67-71 (in Polish).
2. Martin-ValeroR, Vega-Ballon J, Perez-Cabezas V. Benefits of hippotherapy in children with cerebral palsy: A narrative review. Eur J Paediatr Neurol 2018;22(6):1150-1160.
3. Dong-Wook R, Soon Shin J, Soohyeon K. Effects of hippotherapy on Gross Motor Function and Functional Performance of Children with Celebral Palsy. Yonsei Med J. 2014;55(6):1736-1742.
4. Hauser G. Wpływ terapeutycznej jazdy konnej na poprawę funkcjonowania społecznego dzieci i młodzieży ze specjalnymi potrzebami. Przegl Hipoterapeut. 2008;2(8): 22-25 (in Polish).
5. Moraes AG, Copetti F, Angelo VR, Chiavoloni LL, David AC. The effects of hippotherapy on postural balance and functional ability in children with cerebral palsy. J Phys Ther Sci. 2016;28(8):2220-2226.
6. Palisano R, Rosenbaum PL, Walter S, Russell D. Gross Motor Function Classification System for Cerebral Palsy. Development Med Child Neurol. 2008;39(4):214-223.
7. Bojarczuk J. Hipoterapia. Wydawnictwo SBM 2016.
8. Gulati S, Sondhi V. Cerebral Palsy: An Overview. Indian J Pediatr. 2018 Nov;85(11):1006-1016.
9. Shin JW, Song GB. The effects of neck and trunk stabilization exercises on upper limb and visuoperceptual function in children with cerebral palsy. J Phys Ther Sci. 2016 Nov; 28(11): 3232-3235.
10. Ha SY, Sung YH. Effects of Vojta approach on diaphragm movement in children with spastic cerebral palsy. J Exerc Rehabil. 2018 Dec;14(6):1005-1009.

11. Williams SA, McFadden LM, Blackmore AM, et al. Do adolescents with cerebral palsy meet recommendations for healthy weight and physical activity behaviours? Disabil Rehabil. 2020 May;42(9):1227-1232.
12. Salazar AP, Pagnussat AS, Pereira GA, et al. Neuromuscular electrical stimulation to improve gross motor function in children with cerebral palsy: a meta-analysis. Braz J Phys Ther. 2019;23:1413-1425.
13. Novak I. Commentary on Development of a Pediatric Goal-Centered Upper Limb Spasticity Home Exercise Therapy Program. Phys Occup Ther Pediatr. 2019;39(2):136-138.
14. Saleh M, Almasri NA, Malkawi SH, Abu-Dahab S. Associations between impairments and activity limitations components of the international classification of functioning and the gross motor function and subtypes of children with cerebral palsy. J Phys Ther Sci. 2019 Apr;31(4):299-305.
15. Ryan JL, Wright FV, Levac DE. Exploring physiotherapists' use of motor learning strategies in gait-based interventions for children with cerebral palsy. Phys Occup Ther Pediatr. 2019 Jun 3:1-14.
16. Kaya Kara O, Livanelioglu A, Yardimci BN, Soylu AR. The effects of functional progressive strength and power training in children with unilateral cerebral palsy. Pediatr Phys Ther. 2019 Jul;31(3):286-295.
17. Hwang J, Lee JA, You JSH. Multiple relationships between Tardieu, Kinematic data, and Wolf Motor Function Test with children with cerebral palsy. NeuroRehabilitation. 2019;44(2):191-197.
18. van Balen LC, Dijkstra LJ, Dirks T et al. Early intervention and postural adjustments during reaching in infants at risk of cerebral palsy. Pediatr Phys Ther. 2019 Apr;31(2):175-183.
19. Toovey R, Spittle AJ, Nicolaou A, et al; Training Two-Wheel Bike Skills in children with cerebral palsy: a practice survey of therapists in Australia. Phys Occup Ther Pediatr. 2019 Mar;18:1-18.
20. Das SP, Ganesh GS. Evidence-based approach to physical therapy in cerebral palsy. Indian J Orthop. 2019 Jan-Feb;53(1):20-34.
21. Farr WJ, Green D, Bremner S, at al. Feasibility of a randomised controlled trial to evaluate home-based virtual reality therapy in children with cerebral palsy. Disabil Rehabil. 2019 May;25:1-13.
22. Hsu CW, Kang YN, Tseng SH. Effects of therapeutic exercise intensity on cerebral palsy outcomes: a systematic review with meta-regression of randomized clinical trials. Front Neurol. 2019 Jun 21;10:657-659.
23. Lee H, Kim EK, Son DB et al. The role of regular physical therapy on spasticity in children with cerebral palsy. Ann Rehabil Med. 2019 Jun;43(3):289-296.
24. Kuliński W. Metody stosowane w fizjoterapii. In: Kuliński W (ed.). Fizjoterapia w pediatrii. Wydawnictwo Lekarskie PZWL, Warszawa, 2012.
25. Kryszczyńska J. Inne metody stosowane w rehabilitacji dzieci z mózgowym porażeniem dziecięcym In: Kuliński W (ed.). Fizjoterapia w pediatrii. Wydawnictwo Lekarskie PZWL. Warszawa 2012.

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**Conflict of interest:**
*The Authors declare no conflict of interest.*

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ORIGINAL ARTICLE

# THE EFFECT OF COVID-19 INFECTION ON THE INCIDENCE OF THE RENAL ABNORMALITY FOR THE PATIENT ADMITTED IN TO THE COMMUNICABLE DISEASE UNITE AT AL-HAKEEM HOSPITAL

DOI: 10.36740/WLek202305103

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JABIR IBN HAYYAN MEDICAL UNIVERSITY, NAJAF, IRAQ

## ABSTRACT

**The aim**: To predict the effect of COVID-19 virus on the incidence of the renal damage.

**Materials and methods:** A case-control study was designed and one hundred and twenty individual had been included, 60 were healthy volunteer without COVID disease and another 60 suffer from viral infection particularly COVID-19 (there diagnosis was based on the PCR results: the real time type of the PCR) and shows a clinical manifestation of renal abnormality. Both of the healthy and COVID individuals were further divided to males and females in order to predict the effect of the gender that might be related to correlation of renal with a COVID disease. Data and the result obtained from the blood sample was analyzed for measurement of the uric acid, urea, creatinine at Jabr Ibn Hayyan Medical University, Faculty of Medicine and the results obtained was statistically analyzed using SPSS software version 20.

**Results**: data showed that about half of the result obtained showed the renal damage and the other is unrelated to the viral infection. Male are more exposed to the renal abnormalities caused by the viral infection than the females, no correlation were seen between the difference of the gender in relation to the viral infection and so in relation to the renal damage.

**Conclusions**: COVID-19 is one of the main prognostic factor that could induce an irreversible renal damage. This damage might be varied between acute to a chronic result that might ends with renal failure and death of the patient.

**KEY WORDS:** COVID, uric acid, urea, creatinine, renal damage

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## INTRODUCTION

COVID is a viral disease that shows many complications and unpredictable consequences, and one of its effect is the increasing of the incidence of the renal damage whether acute or chronic that may ends with a permanent renal damage and failure [1]. As it understood from the name, this disease mostly attack the respiratory system and may affect many other organs or even the RBCs, and so many of the death reasons reported as a complications or even a consequences of this disease [2]. The study of biochemical changes that recorded with this disease help the medical staff whether in hospitals or even private sector. The number of cases was exaggerated and the severity of it increase to a degree that it converted from a few case to the number to epidemic and even to a pandemic with increase the morbidity and increase the mortality. Many clinical and review articles reported on the history of this disease and the recording the biochemical parameters of this disease. These parameters play an important role in the follow-up and treatment of the disease [3]. Many cases reported in the isolation hospitals and special intensive or even reparatory care unites during their stay in this unites was completely informative about the date of incidence, progress of the disease, response of to the treatment [4, 5]. Blood sample is one of the diagnostic options beside the clinical manifestations, CT scan, US and many other diagnostic strategies. These tests may include urea, uric acid, creatinine, clotting time, D-dimer, blood count (the complete one), platelet, and many other parameters [6]. The specific diagnosis of this virus is gene mapping and the sequencing of the gene of this virus occur by many techniques like PCR, and gene sequencer and WBC counting, C reactive proteins but here we focus on the effect of this disease on the biochemical changes of the other organs. Aside from that in this research there parameter help us to diagnosis whether this disease is viral only or progressed in to secondary bacterial infection. But we should accept the truth that this disease is highly depend

on the WBC count (especially the lymphocyte and even the neutrophil and the ratio that could be calculated between the first to the second one) science there regarded as inflammatory markers and give us a clear picture about what is the degree of the damage or the inflammation of induced by this disease [7].

## THE AIM

The aim of this study is to answer the question: could be the COVID-19 a serious risk factor of the incidence of renal impairment.

## MATERIALS AND METHODS

A case-control study was designed and one hundred and twenty individual had been included in this study, sixty of them were healthy volunteer without COVID disease and another sixty suffer from viral infection particularly COVID-19 (there diagnosis was based on the PCR results: the real-time type of the PCR) and shows a clinical manifestation of renal abnormality (blood in urine, difficult in urination, pain in the lower part of the abdomen, and even some times fever with other signs of UTI) or even a laboratory analysis that indicated the incidence of UTI. Both of the healthy and COVID individuals were further divided to males and females in order to predict the effect of the gender that might be related to correlation of renal with a COVID disease. All of these patients were examined in the Al-Hakeem hospital in the communicable disease unit and in the COVID-19 isolation sector for the time from June to September 2021. Data and the result obtained from the blood sample was analyzed for measurement of the uric acid, urea, creatinine at Jabr Ibn Hayyan Medical University, Faculty of Medicine and the obtained results was statistically analyzed using SPSS software version 20. The t-test w used to the mean between two group regarding the urea, creatinine a uric acid values in those of female and male to predict the effect of theses parameter on the in diagnosis the renal functions in both male and female whether in healthy or patient one. It depend on the mean of the variation of theses three parameters and its comparison between each to groups mentioned.

## RESULTS

A total of the one hundred and twenty persons was included and they were 60 male and another 60 female. The data showed the difference of the urea, creatinine and uric acid in those of COVID compared with the healthy one. Table I shows the differences in the level of the creatinine, urea, and uric acid between the female patient and the control group, and there is a significant difference between those COVID women and those the control one in the urea level but not in the uric acid or creatinine concentration. Data in this research indicated that the incidence of COVID disease is not a risk factor for the occurrence of the renal abnormalities in these women (Table I).

Table II shows the differences in the level of the creatinine, urea and uric acid between the male patient and the control group, and there is a significant difference between those patient and those the control one in the uric acid level, urea or creatinine concentration.

Table III shows the differences in the level of the creatinine, urea and uric acid between the female patient and male patients of COVID-19, and there is a significant difference in the uric acid, but not it in urea or creatinine concentration.

## DISCUSSION

Corona virus nowadays is one of the most complicated disease, especially in the last two years. Most of the researches indicated that its complications is unpredictable: sometimes it induce a renal abnormalities and even a renal failure, but another articles showed that it had no effect on the renal function, some authors showed that it induce hepatitis or even NASH (nonalcoholic steatosis hepatitis) and may even progressed in to irreversible hepatic failure, but another data revealed no risk of this virus on the incidence of the hepatic function. Furthermore, it may induce a respiratory failure and required an admission in to hospital under a permanent ventilator and other cases shows that this virus induce thrombosis that may ends with CVAs [8, 9]. This unexpected results has a numerous opportunities to take inconsideration the best methods to control of this disease and to keep a big interest about best guideline for the treatment with best result expected. It showed that although the virus generally induce a hepatic problems, but still it has no effect in the renal function of the females, although there might be a little increment of the urea level in female but it does not give as a complete evidence that this it induce renal problems in female (table I), but on the other hand our data proved the effect of this disease on the renal function of the male patients (table II), while this research showed no difference between male and female regarding creatinine and urea levels , this might be due to a low sample size (table III). Here we have to disuse this controversy of the result or more accurately we had to focus on the effect of this disease on the renal function which is a corner stone of this research. Many of researches revealed that COVID-19 induce a renal damage in more than fifty percent of the total data collected, this is in accordance with our results that showed that thirty male showed a renal abnormality of the total sixty COVID patient [10] but it is not in accordance with other results

**Table I.** Differences in the level of the creatinine, urea and uric acid between the female patient and the control group.

| Parameter | Group | N | Mean | Std. Deviation | T-test | P-value |
|---|---|---|---|---|---|---|
| Creatinine (mg/dl) | female patients | 30 | 1.183 | 0.3914 | 0.922 | 0.24 |
| | female control | 30 | 0.91 | 1.576 | | |
| Urea (mg/dl) | female patients | 30 | 67.43 | 23.535 | 8.268 | 0.0001 |
| | female control | 30 | 29.5 | 8.803 | | |
| Uric acid (mg/dl) | female patients | 30 | 4.783 | 1.9384 | 1.271 | 0.209 |
| | female control | 30 | 4.253 | 1.2091 | | |

**Table II.** Differences in the level of the creatinine, urea and uric acid between the male patient and the control group.

| Parameter | Group | N | Mean | Std. Deviation | T-test | P-value |
|---|---|---|---|---|---|---|
| Creatinine (mg/dl) | male patients | 30 | 1.215 | 0.3524 | 4.98 | 0.151 |
| | male control | 30 | 0.743 | 0.3812 | | |
| Urea (mg/dl) | male patients | 30 | 70.47 | 35.731 | 6.531 | 0.001 |
| | male control | 30 | 26.03 | 10.575 | | |
| Uric acid (mg/dl) | male patients | 30 | 6.743 | 0.9153 | 5.053 | 0.0343 |
| | male control | 30 | 5.297 | 1.2735 | | |

**Table III.** Differences in the level of the creatinine, urea and uric acid between the female patient and male patients of COVID-19.

| Parameter | Group | N | Mean | Std. Deviation | T-test | P-value |
|---|---|---|---|---|---|---|
| Creatinine (mg/dl) | male patients | 30 | 1.215 | 0.3524 | 0.335 | 0.74 |
| | female patients | 30 | 1.183 | 0.3914 | | |
| Urea (mg/dl) | male patients | 30 | 70.47 | 35.731 | 0.388 | 0.699 |
| | female patients | 30 | 67.43 | 23.535 | | |
| Uric acid (mg/dl) | male patients | 30 | 6.743 | 0.9153 | 5.008 | 0.0196 |
| | female patients | 30 | 4.783 | 1.9384 | | |

that showed less than thirty percent of the hospitalized patient had renal damage as a results of the virus attach and some cases may even ends with death complication of the kidney [11]. Renal damage may be attributed with the cytokine storm by the hyper inflammatory responses that may induce a clinical illness in the beginning of the viral infection [12], this may even induce a not preferred prognosis and increase the chance of the mortality, and it might produce the a renal functional defect particularly in the tubular par or even a glomerular one [13]. COVID may induce acute or even chronic kidney injury or its failure with a sudden impairment of the renal function which may even not last more than seven days and that why it may induce a death of the COVID patient not due to the virus itself but due to its renal complications [14], and this renal damage might be diagnosed by increased the level of creatinine or impaired the output of the renal system or both of them which might due to pre-renal or renal reason or even the post renal causes. Many results revealed that this virus might also induce glomerulonephritis or a necrosis of the glomeruli that is regarded as renal damage [15, 16]. Our data prove the fact that this virus is one of the most common prognostic factor or, an even a remarkable risk factor, of the incidence of the renal damage that might require an emergency admition and follow-up of the patient from that moment of detection of the virus to the last day of the asmition and even a continuous follow-up of the patient after the leaving the hospital, and it is a critical issue that the viral infection might be long life and could ends with uncontrolled mortality that required a global interest about its reasons and its un-preferred complications.

## CONCLUSIONS

COVID-19 is one of the main prognostic factor that could induce an irreversible renal damage one of these indication is the elevated the level of urea, creatinine and even uric acid and this increment could be of the evidence of the deterioration of the renal function. So many data had been reported and still reporting indication the sever effect of this virus on the renal function but it could be mentioned in more details in other studies that may be taken in the future particularly those related to complete renal damage.

## REFERENCES


1. Ketenci S, Saraçoğlu İ, Duranay R et al. Retrospective analysis of biochemical markers in COVID-19 intensive care unit patients. The Egyptian Journal of Bronchology. 2022;16(1):27. doi: 10.1186/s43168-022-00129-7.
2. Li Q, Guan X, Wu P et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382(13):1199-1207. doi: 10.1056/NEJMoa2001316.
3. Liu Y, Du X, Chen J et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81(1):e6-e12. doi: 10.1016/j.jinf.2020.04.002.
4. Henry BM, de Oliveira MHS, Benoit S et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58(7):1021-1028. doi: 10.1515/cclm-2020-0369.
5. Bekdas M, Goksugur SB, Sarac EG et al. Neutrophil/lymphocyte and C-reactive protein/mean platelet volume ratios in differentiating between viral and bacterial pneumonias and diagnosing early complications in children. Saudi Med J. 2014;35(5):442-447.
6. İlhan M, İlhan G, Gök AF et al. Evaluation of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and red blood cell distribution width-platelet ratio as early predictor of acute pancreatitis in pregnancy. J Matern Fetal Neonatal Med. 2016;29(9):1476-1480. doi: 10.3109/14767058.2015.1051026.
7. Yazar FM, Bakacak M, Emre A et al. Predictive role of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios for diagnosis of acute appendicitis during pregnancy. Kaohsiung J Med Sci. 2015;31(11):591-596. doi: 10.1016/j.kjms.2015.10.005.
8. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet. 2022;399(10334):1513-1536. doi: 10.1016/S0140-6736(21)02796-3.
9. Yanez ND, Weiss NS, Romand JA et al. COVID-19 mortality risk for older men and women. BMC Public Health. 2020;20(1):1742. doi: 10.1186/s12889-020-09826-8.
10. Coronavirus: Kidney Damage Caused by COVID-19. Johns Hopkins Medicine. 2022, p.301.
11. Devresse A, Belkhir L, Vo B et al. COVID-19 Infection in Kidney Transplant Recipients: A Single-Center Case Series of 22 Cases From Belgium. Kidney Med. 2020;2(4):459-466. doi: 10.1016/j.xkme.2020.06.001
12. Wadman M, Couzin-Frankel J, Kaiser J et al. A rampage through the body. Science. 2020;368(6489):356-360. doi: 10.1126/science.368.6489.356.
13. Bhaskar S, Sinha A, Banach M et al. Cytokine Storm in COVID-19-Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. Front Immunol. 2020;11:1648. doi: 10.3389/fimmu.2020.01648.
14. Satturwar S, Fowkes M, Farver C et al. Postmortem Findings Associated With SARS-CoV-2: Systematic Review and Meta-analysis. Am J Surg Pathol. 2021;45(5):587-603. doi: 10.1097/PAS.0000000000001650.
15. Webb S, Dobb G. ARF, ATN or AKI? It's now acute kidney injury. Anaesth Intensive Care. 2007;35(6):843-844. doi: 10.1177/0310057X0703500601.
16. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019;394(10212):1949-1964. doi: 10.1016/S0140-6736(19)32563-2.



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*The Authors declare no conflict of interest.*

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ORIGINAL ARTICLE

# THE ROLE OF BIOMARKER MACROPHAGE MIGRATION INHIBITORY FACTOR IN CARDIAC REMODELING PREDICTION IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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## ABSTRACT

**The aim:** To estimate the role of macrophage migration inhibitory factor and soluble ST2 in predicting the left ventricle remodeling six months after ST-segment elevation myocardial infarction.

**Materials and methods:** The study involved 134 ST-segment elevation myocardial infarction patients. Occurrence of post-percutaneous coronary (PCI) intervention epicardial blood flow of TIMI <3 or myocardial blush grade 0-1 along with ST resolution <70% within 2 hours after PCI was qualified as the no-reflow condition. Left ventricle remodeling was defined after 6-months as an increase in left ventricle end-diastolic volume and/or end-systolic volume by more than 10%.

**Results:** A logistic regression formula was evaluated. Included biomarkers were macrophage migration inhibitory factor and sST2, left ventricle ejection fraction: Y=exp(-39.06+0.82EF+0.096ST2+0.0028MIF) / (1+exp(-39.06+0.82EF+0.096ST2+0.0028MIF)). The estimated range is from 0 to 1 point. Less than 0.5 determines an adverse outcome, and more than 0.5 is a good prognosis. This equation, with sensitivity of 77 % and specificity of 85%, could predict the development of adverse left ventricle remodeling six months after a coronary event (AUC=0.864, CI 0.673 to 0.966, p<0.05).

**Conclusions:** A combination of biomarkers gives a significant predicting result in the formation of adverse left ventricular remodeling after ST-segment elevation myocardial infarction.

**KEY WORDS:** inflammation, prognosis, biomarkers, coronary event

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## INTRODUCTION

A sharp decrease in the contractile capacity of instigated cardiomyocytes in ST-segment elevation myocardial infarction (STEMI) leads to changes in the heart architecture [1]. Left ventricle remodeling (LVR) refers to alterations in ventricular function involving both the infarcted and non-infarcted zones leading to a progressive increase in systolic and diastolic LV volumes. Adverse LVR after STEMI treated with primary percutaneous coronary intervention (PCI) is the main determinant for the long-term outcomes. In STEMI, to reduce the area of necrosis and scar formation, inflammation and the neurohumoral system play significant roles [2]. In routine clinical practice, a series of biomarkers use in helping to assess the prognosis in STEMI patients. These are high-sensitive C-reactive protein (C-RP) and N-terminal pro-brain natriuretic peptide, a biomarker of inflammation and hemodynamic stress [3,4]. However, the search for a universal biomarker that can predict the maximum number of possible complications in the early period of the disease continues. The soluble isoform of suppression tumorigenicity 2 (sST2) has a combination of such properties. The level of sST2 increases because of myocardial damage that occurs after STEMI onset, and it is linked with myocardial fibrosis formation. [5-7]. However, the role of sST2 in the development of adverse LVR is not clear. Known that the no-reflow phenomenon takes a role in adverse cardiac remodeling as much as myocardial ischemia due to insufficient myocardial perfusion [8]. Based on the knowledge, we suggest one promising biomarker in this field, macrophage migration inhibitory factor (MIF). MIF functions as a pleiotropic protein, participating in inflammatory and immune responses [9-11].

## THE AIM

The aim of the study was to estimate the role of MIF and sST2 in predicting the LVR six months after STEMI.

## MATERIALS AND METHODS

The hypothesis of the study is that level of biomarker MIF, sST2 or their combination can help us to determine STEMI patients with high risk of adverse LVR and could help in the decision process regarding the treatment strategy to reduce probability of heart failure formation.

The study involved 134 STEMI patients. Primary PCI was performed in the Department of Interventional Cardiology of the V. T. Zaitseva Institute of General and Emergency Surgery of the National Academy of Medical Sciences of Ukraine 12 hours after the index event. 24-48 hours after the PCI patients have transferred to the emergency department of the L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine. STEMI diagnosis based on European Society of Cardiology guidelines (2017) [12]. The study was approved by the local ethics committee (Protocol №13 of December 19, 2019). All patients signed informed consent before the enrollment procedure.

### PERCUTANEOUS CORONARY INTERVENTION

Within 12 h after the first symptoms, primary PCI was performed. There are two types of stents: bare-metal and drug-eluting stents (Resolute Integrity (Medtronic, USA), Integrity (Boston Scientific, USA, respectively)). Coronary angiography was undertaken on an Integris Allura digital X-ray system (Philips Healthcare, Best, The Netherlands). Several projections of coronary arteries have been recorded during coronary angiography. Ultravist-370 (Bayer Pharma GmbH, Germany) was used to increase contrast. All patients received standard treatment [12].

Using serial electrocardiography in 12 leads obtained before and 60-90 minutes after primary PCI evaluation of ST-segment dynamics was performed [13].

### REAL-TIME MYOCARDIAL PERFUSION IMAGING

We used real-time myocardial perfusion imaging with Myocardial Blush Grade (MBG) determination to measure myocardial perfusion [14, 15]. The MBG was scored during angiographic analysis using the Van't Hof method [16]. MBG graded as 0, 1, 2, and 3 that corresponded to the following criteria: a lack of myocardial blush or contrast density, minimal myocardial blush or contrast density, myocardial blush or contrast density with impaired clearing, and unchanged myocardial blush or contrast density, respectively [17]. Occurrence of post-PCI epicardial blood flow of TIMI <3 or MBG 0-1 along with STR <70% within 2 hours after PCI was qualified as the no-reflow condition.

### DETERMINATION OF RISK FACTORS AND COMORBIDITIES

The trained investigator measured anthropometric parameters during the interview and assessed anamnesis vitae by questionnaire. Body mass index (kg/m2) calculated. Hypercholesterolemia diagnosed according to the guidelines of the European society of cardiology for dyslipidemia [18], hypertension [19], chronic heart failure following the recommendations of the European Society of Cardiology [20].

A combined primary endpoint was determined as all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, chronic heart failure decompensation with or without hospitalization, unscheduled revascularization. Patients had excluded if they had a prior history of ischemic events.

### TRANSTHORACIC ECHOCARDIOGRAPHY AND DOPPLER

Transthoracic Doppler echocardiography with Toshiba TUS-A500 (Aplio 500, Japan) was performed 24-48 hours after PCI and after a 6-months follow-up. LV end-diastolic and end-systolic volume (LVEDV and LVESV, relatively), LV myocardial mass (LVM), LV ejection fraction (LVEF), and left atrial volume (LAV) determined by Simpson's biplane method. To assess the diastolic function of the left ventricle by pulse Doppler mode diastolic transmitral velocity (E / A) from the beginning to the late period, the ratio of peak mitral inflow rate to an early diastolic velocity of the mitral ring (E / e ') used. Right ventricular function was assessed as TAPSE [21]. LV remodeling was defined after 6-months as an increase in LVEDV and/or ESV by more than 10%.

### SAMPLE SIZE CALCULATION

The sample size was calculated through the prospective design of the study, providing the design effect of 1.0, confidence intervals of 95%, and the error of 5% [22].

### BLOOD SAMPLES

Blood samples for biomarker analysis have collected before PCI and 24 hours after. Peak troponin I (TnI) levels were measured every six hours for 24 h after hos-

**Table I.** Parameters of echocardiography in studied patients

| Parameters | Period | Group with LV remodeling n=47 | Group without LV remodeling n=86 | p* |
|---|---|---|---|---|
| Heart rate, per minute | At admission | 77,28±13,14 | 80,40±18,46 | 0,527 |
| | 6 months after | 67.49±1074 | 66.26±10.19 | 0,8403 |
| | p | 0.00004* | 0.000006* | |
| SBP, mm Hg | At admission | 141,43±22,73 | 130,64±32,72 | 0,072 |
| | 6 months after | 131.34±14.99 | 125.54±14.66 | 0,0787 |
| | p | 0.009* | 0.1457 | |
| DBP, mm Hg | At admission | 84,21±13,54 | 78,35±14,84 | 0,038* |
| | 6 months after | 81.49±8.66 | 78.43±9.68 | 0,0641 |
| | p | 0.170 | 0.7080 | |
| LV EDV, ml | At admission | 115,77±24,40 | 135,37±32,23 | 0,001* |
| | 6 months after | 148.71±40.57 | 129.77±34.05 | 0,0123* |
| | p | 0.000001* | 0.3167 | |
| Index EDV | At admission | 58,24±10,98 | 69,74±16,18 | 0,0002* |
| | 6 months after | 73.79±16.77 | 67.15±17.11 | 0,0624 |
| | p | 0.000001* | 0.3780 | |
| LV ESV, ml | At admission | 53,43±21,08 | 67,33±21,63 | 0,001* |
| | 6 months after | 76.28±26.74 | 64.24±22.88 | 0,0102* |
| | p | 0.000002* | 0.3053 | |
| Index ESV | At admission | 26,83±9,83 | 34,62±10,87 | 0,0002* |
| | 6 months after | 38.13±11.73 | 33.17±11.17 | 0,0401* |
| | p | 0.000001* | 0.3167 | |
| Stroke volume, ml | At admission | 31,41±6,45 | 35,12±9,93 | 0,079 |
| | 6 months after | 35.59±9.57 | 33.98±8.10 | 0,2859 |
| | p | 0.004* | 0.7107 | |
| LV EDD, cm | At admission | 4,97±0,43 | 5,25±0,51 | 0,006* |
| | 6 months after | 5.45±0.55 | 5.17±0.56 | 0,0125* |
| | p | 0.000001* | 0.4227 | |
| Index EDD | At admission | 2,51±0,26 | 2,71±0,32 | 0,002* |
| | 6 months after | 2.75±0.30 | 2.68±0.34 | 0,2991 |
| | p | 0.0002* | 0.7862 | |
| ESD, cm | At admission | 3,54±0,54 | 3,91±0,52 | 0,001* |
| | 6 months after | 4.09±0.56 | 3.82±0.56 | 0,0200 |
| | p | 0.000003* | 0.3492 | |
| Index ESD | At admission | 1,79±0,29 | 2,02±0,29 | 0,0005* |
| | 6 months after | 2.07±0.28 | 1.98±0.30 | 0,1596 |
| | p | 0.00003* | 0.4992 | |
| IVS, cm | At admission | 1,22±0,18 | 1,16±0,22 | 0,019* |
| | 6 months after | 1.18±0.16 | 1.16±0.16 | 0,4729 |
| | p | 0.2336 | 0.6724 | |
| LV posterior wall, cm | At admission | 1,16±0,15 | 1,11±0,16 | 0,116 |
| | 6 months after | 1.17±0.12 | 1.12±0.12 | 0,1699 |
| | p | 0.9540 | 0.5985 | |
| RWT | At admission | 0,48±0,07 | 0,43±0,07 | 0,001* |
| | 6 months after | 0.43±0.06 | 0.52±0.43 | 0,4908 |

**Table I.** (cont.)

| | | | | |
|---|---|---|---|---|
| | p | 0.001* | 0.3555 | |
| LA1, cm | At admission | 3,61±0,41 | 3,62±0,41 | 0,997 |
| | 6 months after | 3.86±0.43 | 3.67±0.42 | 0,0470* |
| | p | 0.003* | 0.4752 | |
| LA2, cm | At admission | 3,92±0,48 | 4,02±0,59 | 0,445 |
| | 6 months after | 4.23±0.41 | 4.09±0.52 | 0,1567 |
| | p | 0.0005* | 0.4509 | |
| LA index | At admission | 1,98±0,24 | 2,07±0,29 | 0,168 |
| | 6 months after | 2.14±0.23 | 2.11±0.28 | 0,3970 |
| | p | 0.001* | 0.3245 | |
| LA volume, ml | At admission | 27,65±9,63 | 28,71±10,86 | 0,779 |
| | 6 months after | 33.89±9.92 | 29.79±10.09 | 0,0515 |
| | p | 0.001* | 0.4320 | |
| LA volume, index | At admission | 13,82±4,10 | 14,69±5,24 | 0,594 |
| | 6 months after | 16.91±4.30 | 15.33±5.11 | 0,0807 |
| | p | 0.0003* | 0.3631 | |
| LV EF, % | At admission | 51,61±9,28 | 48,36±7,93 | 0,075 |
| | 6 months after | 47.69±6.54 | 50.34±5.90 | 0,0365* |
| | p | 0.036* | 0.1358 | |
| E/A | At admission | 1,07±0,39 | 1,10±0,37 | 0,795 |
| | 6 months after | 1.17±0.46 | 1.01±0.39 | 0,1554 |
| | p | 0.7129 | 0.2799 | |
| LV mass, g | At admission | 218,87±66,07 | 225,92±84,97 | 0,802 |
| | 6 months after | 217.88±62.32 | 194.85±75.15 | 0,0759 |
| | p | 0.6582 | 0.0720 | |
| LV mass index, g/м2 | At admission | 107,74±35,45 | 112,14±45,88 | 0,770 |
| | 6 months after | 109.62±34.02 | 100.62±38.31 | |
| | p | 0.9367 | 0.1246 | 0,1222 |

* - p <0.05; SBP – systolic blood pressure; DBP – diastolic blood pressure; LV – left ventricle; EDV – end-diastolic volume, ESV – end-systolic volume; EDD – end-diastolic dimension; ESD – end-systolic dimension; IVS – interventricular septum; RWT – relative wall thickness; LA – left atrium; EF – ejection fraction.

pitalization. Determination of the level of biomarkers performed by enzyme-linked immunosorbent assay following the recommendations of manufacturers using kits «Human MIF ELISA» (RayBio, USA), «Presage ST2 Assay» (Critical Diagnostics, CA, USA), «Troponin I-ELISA» (Xema, Russia) and CRP-ELISA (Xema, Russia).

For statistical analysis of the obtained results, we used the software package "Statistica" version 10.0 (Stat Soft Inc, USA). Data has been given as the arithmetic mean ± standard deviation (M ± SD) or median and the quartile interval between the 25th and 75th percentiles (Q3 – Q1) (Me [LQ; UQ]) depending on the type of distribution. The Mann – Whitney U-test was used to estimate intergroup quantitative differences. Spearman's Rank-Order Correlation used to identify the correlation between the parameters. The logistic regression analysis has been used to predict LV remodeling. Value determination, sensitivity, and specificity were performed according to the ROC analysis. The differences were considered statistically significant at p <0.05.

## RESULTS

In our study, most patients were male (73.3%), average age is 60,64±10,42 years. Among concomitant diseases, hypertension was in 76.7% of cases, type 2 diabetes mellitus in 28.6% of patients, history of ischemic heart disease — in 42,5%, unstable angina in 18,3% and obesity — in 23.3%. Distribution according to localization of myocardial infarction was equal, 47,5% is anterior and 52,5% posterior wall. In 67,5% patients the left anterior descending artery was injured, 61,7% – right coronary artery, other were circumflex artery and main left coronary artery, 32,5 and 6,7%, relatively. Among all 134

**Table II.** Parameters of echocardiography in studied patients with or without "no-reflow"

| | | MBG 0-1, pST<70% (n=32) | MBG 2-3, pST>70% (n=61) | p |
|---|---|---|---|---|
| LV EDV | At admission | 132,75±32,16 | 126,15±27,39 | 0,7514 |
| | 6 months after | 141,38±35,44 | 143,39±34,57 | 0,7297 |
| | p | 0,4472 | 0,009* | |
| Index EDV | At admission | 65,12±15,19 | 64,54±14,56 | 0,8673 |
| | 6 months after | 71,94±12,94 | 73,48±15,34 | 0,7199 |
| | p | 0,1207 | 0,0057* | |
| LV ESV | At admission | 64,45±23,97 | 59,95±21,72 | 0,3484 |
| | 6 months after | 69,95±25,49 | 73,62±23,66 | 0,4359 |
| | p | 0,5092 | 0,0050* | |
| Index ESV | At admission | 32,76±10,35 | 30,68±11,21 | 0,4190 |
| | 6 months after | 34,83±10,22 | 38,08±11,08 | 0,3052 |
| | p | 0,5167 | 0,0022* | |
| LV EDD | At admission | 5,24±0,51 | 5,13±0,44 | 0,9360 |
| | 6 months after | 5,37±0,57 | 5,39±0,51 | 0,8310 |
| | p | 0,4732 | 0,0115* | |
| Index EDD | At admission | 2.62±0,26 | 2,62±0,30 | 0,9832 |
| | 6 months after | 2,77±0,25 | 2,80±0,29 | 0,7353 |
| | p | 0,0654 | 0,0053* | |
| ESV | At admission | 3,89±0,54 | 3,71±0,54 | 0,2642 |
| | 6 months after | 3,98±0,57 | 4,05±0,51 | 0,4318 |
| | p | 0,6383 | 0,0026* | |
| Index ESV | At admission | 1,97±0,26 | 1,90±0,32 | 0,3529 |
| | 6 months after | 2,04±0,21 | 2,11±0,27 | 0,3543 |
| | p | 0,3564 | 0,0015* | |
| LA volume, index | At admission | 14,82±9,07 | 13,93±4,52 | 0,3047 |
| | 6 months after | 20,70±10,97 | 16,86±5,08 | 0,4430 |
| | p | 0,0977 | 0,004* | |
| LV EF, % | At admission | 45,42±7,32 | 50,03±8,86 | 0,4921 |
| | 6 months after | 48,17±8,30 | 48,39±5,69 | 0,9803 |
| | p | 0,2939 | 0,3099 | |
| E/A | At admission | 0,96±0,42 | 1,08±0,36 | 0,3914 |
| | 6 months after | 1,17±0,50 | 1,17±0,43 | 0,7053 |
| | p | 0,2364 | 0,3498 | |
| RV TAPSE | At admission | 22,00±4,00 | 21,23±2,85 | 0,6749 |
| | 6 months after | 23,62±4,25 | 21,69±2,42 | 0,1015 |
| | p | 0,6015 | 0,6398 | |
| E/e'. | At admission | 11,61±6,04 | 11,95±5,60 | 0,3914 |
| | 6 months after | 13,06±6,35 | 14,70±6,04 | 0,4033 |
| | p | 0,7823 | 0,3611 | |

LV – left ventricle; EDV – end-diastolic volume, ESV – end-systolic volume; EDD – end-diastolic dimension; ESD – end-systolic dimension; IVS – interventricular septum; TAPSE – tricuspid annular plane systolic excursion; LA – left atrium; EF – ejection fraction.

patients enrolled in the present study, 99,9 % of patients completed the follow-up. After a 6-months follow-up, 28 (20,9%) patients reached a combined primary endpoint.

All patients were split into two groups according to developing LVR, 35% developed adverse cardiac remodeling (Table I). Hemodynamic parameters did not

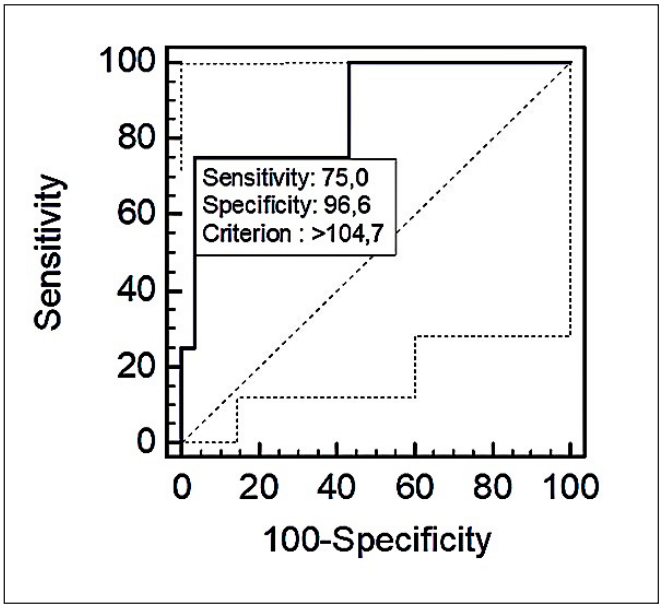


**Fig. 1.** Level of sST2 biomarker as a predictor of left ventricle ejection fraction deterioration (ROC-analysis).

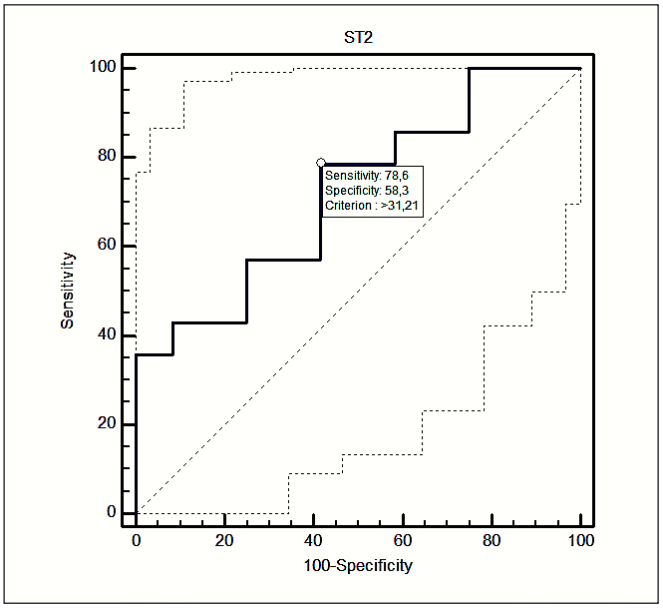


**Fig. 2.** Level of sST2 biomarker as a predictor of left ventricle remodeling after STEMI (ROC-analysis).

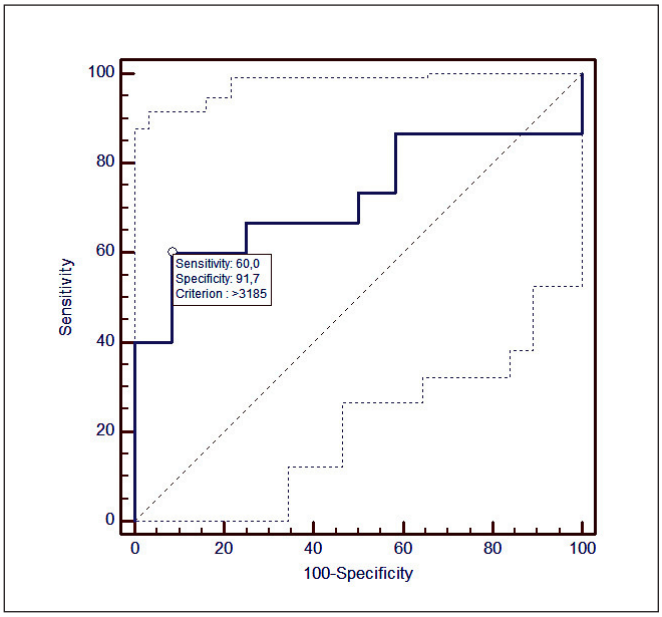


**Fig. 3.** Level of MIF biomarker as a predictor of left ventricle remodeling after STEMI (ROC-analysis).

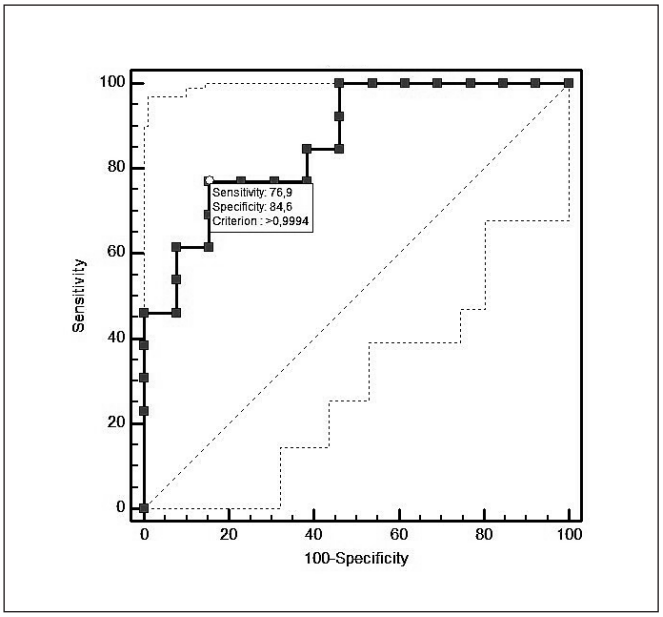


**Fig. 4.** ROC-curve of the formula that predicts left ventricle remodeling after STEMI.

vary significantly. In the LVR group, EDV was lower initially, but 6-months later, the indicator was significantly higher. The EDV index did not differ significantly after six months, although, at admission was higher in the group without LVR. ESV and its index were also initially lower at admission at the end of the 6th month of observation, and the parameter significantly increased. Stroke volume remained unchanged in both groups. At admission, RWT in the group of adverse LVR was higher than in another group. RWT 6-months after did not differ significantly. LV end-diastolic and end-systolic diameters (EDD) in the first group were initially lower in comparison to the second group but six months after this parameter changed significantly in the group of adverse remodeling. Their indexes did not show crucial changes. In the remodeling group, the left atrium size significantly increased six months after and worsened within the group over time. LVEF parameters deteriorated in the group of adverse remodeling after six months and reached statistical importance among two groups only after the observation period. LV mass and its index did not significantly.

We also divided studied patients according to MBG and compared groups with insufficient and normal MBG. Upon admission, echocardiography parameters

did not differ significantly in both groups, with and without "no-reflow" phenomenon. However, six months after the index event, in the "no-reflow" group, a significant increase in ESV and EDV was noted, while the LV EF remained unchanged (Table II).

A ROC analysis curves served to determine the optimal cut-off point of sST2 and MIF biomarkers for identifying patients with very high risk of adverse cardiac remodeling formation. ROC analysis showed that the serum level of sST2 > 104.7 ng/ml with a sensitivity (Sen) of 75%, a specificity (Spe) of 97% (area under curve (AUC) = 0.875, 95% confidential interval (CI) – 0.766–0.945, p = 0.0001) (Fig 1) could prognosticate reduced LVEF.

After that we tested both biomarkers If they have a predictive power in LVR six months after the event. ROC analysis demonstrated that the sST2 (Fig 2) and MIF (Figure 3) have a predictive potential for LVR. The cut-off for sST2 was > 31.21 ng/ml (Sen – 80%, Spe – 60%, AUC – 0.720, 95% CI – 0.511 – 0.877, p=0.0305), for MIF more than 3185 pg/ml (Sen – 60%, Spe – 92%, AUC – 0.722, 95% CI – 0.518 – 0.876, p=0.0318).

The multivariate Cox regression analysis was conducted. The results were assessing the independent predictive value of following parameters for late cardiac remodeling revealed that biomarker MIF (odd ratio (OR)=1,0028, p=0.0289) before revascularization, sST2 (OR=1,1008, CI 1,0032 to 1,2079, p=0.04), and the ejection fraction of LV (OR=2,2712, CI 1,0787 to 4,7818, p=0.03) were independent predictors of LVR in patients who underwent PCI after STEMI.

Although, these results were significant, but CI was not satisfactory. We combined these parameters, and a logistic regression formula was evaluated. Included parameters were MIF, sST2 and LVEF:

Y=exp(39.06+0.82EF+0.096ST2+0.0028MIF)/(1+exp(39.06+0.82EF+0.096ST2+0.0028MIF))

This equation, with Sen of 77 % and Spe of 85% predicts the development of adverse LVR six months after the coronary event (AUC=0.864, CI 0.673 to 0.966, z statistic=5.17, p=0.0001) (Fig 4).

The estimated range is from 0 to 1 point. Less than 0.5 determines the adverse outcome formation, and more than 0.5 corresponds to a good prognosis.

## DISCUSSION

On the one hand, post-myocardial infarction remodeling should be considered an adaptive process, on the other hand, too many studies have shown that an increase in the ESV index and a decrease in ejection fraction are valuable predictors of heart failure development and all-cause mortality. The magnitude of adverse remodeling is related to the infarct size and insufficient myocardial perfusion, the "no-reflow" phenomenon. In our study, ESV and EDV significantly changed. However, in the remodeling group, they were lower than in patients of the second group at admission. The statistical difference between the two-group estimated six months after the event to be significant. Accordingly, it is not worth focusing on these indicators in the early period of the disease. That is why the issue of the search for the ideal biomarker is so sharp. An ideal biomarker should have high Sen, which will diagnose as early as possible, and high Spe, which will exclude a non-cardiac origin of the marker and must have prognostic properties.

We evaluated the role of two biomarkers in predicting the development of adverse LVR six months after STEMI. The biomarker MIF was compared with sST2 since the latter is more discovered in the heart failure development in patients after acute myocardial infarction. ST2 is a cardiac biomarker associated with stress and the fibrosis process, with significant dynamics in patients with myocardial infarction or acute heart failure. Because of its lack of cardiac specificity, it had been ruled out as a diagnostic tool for myocardial infarction, but other studies have shown promising results on its prognostic value related to mortality and heart failure development [23]. Our result showed that sST2 predicted a decrease in LV EF in the acute phase. However, the biomarker had low specificity in predicting LVR six months after the event.

In turn, the MIF biomarker looked more promising. MIF, a pleiotropic protein with inflammatory properties, has already been proven in STEMI patients to predict infarct size and adverse outcomes.

We observed that high levels of MIF in the first hours of the disease indicated the state of cardiac function in the long term and the prognosis in patients with STEMI. This relationship was probably obtained due to the direct involvement of MIF in the inflammatory response, regulation of cardiac remodeling, and formation of fibrosis after myocardial infarction. The severity of the inflammatory response and fibrosis induced after infarction are important determinants of the severity of LVR and the progression of heart failure. [24, 25].

With the development of ischemia is accompanied by myocardial necrosis, MIF promotes the accumulation of macrophages in necrotic tissue, enhances the inflammatory response, and induces the production of other inflammatory factors, such as C-RP, interleukin-6, which exacerbates myocardial damage [26, 27]. There is evidence, MIF can also affect interstitial fibrosis in non-infarct areas after myocardial infarction [28], which allows us to consider this biomarker important in predicting adverse LVR.

Biomarker MIF did not show high sensitivity, and sST2 did not have high specificity. So, we attempted to combine them to improve the accuracy of the prognosis. Analysis of logistic regression equation

with continuous predictor applying derivatives helps choose optimal thresholds that provide maximally effective discriminative functions with priority sensitivity or specificity.

### RESEARCH LIMITATIONS

A small sample size of patients and a short follow-up period were the main limitations of this study.

## CONCLUSIONS

In our study, we have shown that the biomarkers MIF and sST2 exhibit prognostic properties in adverse cardiac remodeling formation. However, a combination of biomarkers gives a more significant predicting result in the formation of adverse left ventricular remodeling after STEMI. To implement these results in routine clinical practice future investigations needed.

### REFERENCES


1. Van der Bijl P, Abou R, Goedemans L et al. Left ventricular remodeling after ST-segment elevation myocardial infarction: sex differences and prognosis. ESC Heart Fail. 2020;7(2):474-481.
2. Bernhagen J. Protective cardiac conditioning by an atypical cytokine. Clin Sci (Lond). 2019;133(8):933-937.
3. Clerico A, Passino C. Predictive Value of NT-pro BNP in Patients with Acute Myocardial Infarction. Clin Chem. 2017;63(5):1045-1046.
4. Zhang X, Wang S, Fang S et al. Prognostic Role of High Sensitivity C-Reactive Protein in Patients with Acute Myocardial Infarction. Front Cardiovasc Med. 2021; 8:659446.
5. Barnett O, Polyetayeva K, Halkevych M et al. Novel marker of myocardial remodeling ST2 and the influence of aldosterone antagonist in patients with heart failure caused by hypertension and ischemic heart disease, Journal of Hypertension. 2018;36:163.
6. Park S, Kim IC, Kim H et al. Ability of soluble ST2 to predict left ventricular remodeling in patients with acute coronary syndrome. Heart Vessels. 2022;37(2):173-183.
7. Homsak E, Gruson D. Soluble ST2: A complex and diverse role in several diseases. Clin Chim Acta. 2020; 507:75-87.
8. Refaat H, Tantawy A, Gamal AS et al. Novel predictors and adverse long-term outcomes of No-reflow phenomenon in patients with acute ST elevation myocardial infarction undergoing primary percutaneous coronary intervention. Indian Heart J. 2021;73(1):35-43.
9. Chan W, White DA, Wang XY et al. Macrophage migration inhibitory factor for the early prediction of infarct size. J Am Heart Assoc. 2013;2(5): e000226.
10. Voss S, Krüger S, Scherschel K et al. Macrophage Migration Inhibitory Factor Expression Increases during Myocardial Infarction and Supports Pro-Inflammatory Signaling in Cardiac Fibroblasts. Biomolecules. 2019;9(2):38.
11. Takahashi M, Nishihira J, Shimpo M et al. Macrophage migration inhibitory factor as a redox-sensitive cytokine in cardiac myocytes. Cardiovascular Research. 2001;52(3):438–445.
12. Ibanez B, James S, Agewall S et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology. Eur Heart J. 2018;39(2):119-177.
13. Lønborg J, Kelbæk H, Holmvang L et al. ST peak during primary percutaneous coronary intervention predicts final infarct size, left ventricular function, and clinical outcome. J Electrocardiol. 2012;45(6):708-16.
14. Brener SJ, Dizon JM, Mehran R et al. Complementary prognostic utility of myocardial blush grade and ST-segment resolution after primary percutaneous coronary intervention: Analysis from the HORIZONS-AMI trial. American Heart Journal. 2013;166(4):676-683.
15. Yusuf J, Das D, Mukhopadhyay S et al. Correlation of QRS duration with myocardial blush grade as a marker of myocardial reperfusion in primary percutaneous coronary intervention. Indian Heart Journal. 2018;70(3):359-364.
16. Henriques JP, Zijlstra F, van 't Hof AW et al. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. Circulation. 2003;107(16):2115-9.
17. Shakiba M, Salari A, Mirbolouk F et al. Clinical, Laboratory, and Procedural Predictors of No-Reflow in Patients Undergoing Primary Percutaneous Coronary Intervention. J Tehran Heart Cent. 2020;15(2):50-56.
18. Mach F, Baigent C, Catapano AL et al. ESC Scientific Document Group, 2019 ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidemias of the European Society of Cardiology and European Atherosclerosis Society. Eur Heart J. 2020;41(1):111–188.
19. Williams B, Mancia G, Spiering W et al. ESC Scientific Document Group, 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Eur Heart J. 2018;39(33):3021–3104.
20. Ponikowski P, Voors A, Anker S et al. ESC Scientific Document Group, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology Developed with the special contribution of the Heart Failure Association of the ESC. Eur Heart J. 2016;37(27):2129–2200.

21. Lang R, Badano L, Mor-Avi V et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiography. 2015;28(1):139.
22. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med. 2013;35(2):121-126.
23. Galli A, Lombardi F. Postinfarct Left Ventricular Remodeling: A Prevailing Cause of Heart Failure. Cardiol Res Pract. 2016;2016:2579832.
24. Luedike P, Alatzides G, Papathanasiou M et al. Circulating macrophage migration inhibitory factor in patients with heart failure. Cytokine. 2018; 110:104-109.
25. Mao S, Liang Y, Chen P et al. In-depth proteomics approach reveals novel biomarkers of cardiac remodeling after myocardial infarction: An exploratory analysis. J Cell Mol Med. 2020;24(17):10042-10051.
26. Petyunina O, Kopytsya M, Berezin A. Macrophage Inhibitory Factor Predicted Late Cardiac Remodeling in Acute Myocardial Infarction Patients Underwent Successful Percutaneous Coronary Intervention. Prensa Med Argent. 2019; 105:6-160.
27. Prabhu S, Frangogiannis N. The Biological Basis for Cardiac Repair After Myocardial Infarction: From Inflammation to Fibrosis. Circ Res. 2016;119(1):91112.
28. Ruze A, Chen BD, Liu F et al. Macrophage migration inhibitory factor plays an essential role in ischemic preconditioning-mediated cardioprotection. Clin Sci (Lond). 2019;133(5):665-680.

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ORIGINAL ARTICLE

# EFFECTIVENESS OF THE MAGNESIUM APPLICATION IN OBSTETRICAL PRACTICE

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## ABSTRACT

**The aim:** Conducting an evaluation of the effectiveness and safety of the use of magnesium in pregnant women.

**Materials and methods:** A comprehensive examination of 60 pregnant women was conducted, of which 30 were taking a magnesium preparation in a daily dose of 2473.72 mg of magnesium citrate and 40 mg of pyridoxine hydrochloride (the main group) and 30 pregnant women who were not taking a magnesium preparation (comparison group). The analysis of the clinical course of the first half of the pregnancy with the determination the frequency and structure of complications, blood pressure levels, indicators of ultrasound, general and biochemical blood tests, urinalysis, lipid status and carbohydrarate metabolism.

**Results:** The main complications of the first half of pregnancy were: threatening miscarriage, abortion in progress, early gestosis, anemia, respiratory viral infection, exacerbation of extragenital pathology, hypertension. During the analysis of carbohydrate and lipid metabolism increased atherogenic potential. Analyzing the results of ultrasound studies reliably earlier comes down the local hypertonus.

**Conclusions:** The correction of chronic magnesium deficiency, performed by the drug magnesium has allowed to reduce cases of threat of abortion, the abortion that was started, the symptoms of early preeclampsia, anemia of pregnant women, symptoms of respiratory viral infection, reduces the number of bed-days in the case of hospitalization. The use of magnesium helped to normalize blood pressure, carbohydrate and lipid metabolism, reduces hypertonus of the myometrium.

**KEY WORDS:** magnesium deliciency, pregnancy complication, magnesium

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## INTRODUCTION

The problem of maintaining reproductive health, reducing obstetric and perinatal complications, taking into account the complex demographic situation that has developed in Ukraine over the last 10-15 years, goes beyond the medical sector and is of national importance [2,4,5]. Among the many factors that support the life of the body of the pregnant and the fetus, micronutrients that are necessary for the normal growth and functioning of cells, tissues, organs and systems, prevention of infections, metabolism of the main classes of nutrients, hormones, mediators and other biologists are of great importance [6,12]. In the structure of the pathology of the elemental status of women, magnesium deficiency occupies a leading position, the individual prevalence of magnesium deficiency in the female population is 1.3 times higher than in the male population. Magnesium functions as a cofactor in more than 300 known enzymatic reactions, which can explain its effect on carbohydrate and lipid metabolism, myometrial function, and nerve tissue. The daily requirement for magnesium for women is 280-300 mg, and during pregnancy and lactation increases by 20-30% - up to 340-355 mg. Although magnesium is quite common in nature, its deficiency is observed in the population of 16-42%, clinical manifestations are much more frequent [3, 9, 15].

Magnesium deficiency is of particular importance in obstetric and gynecological practice. Hypomagnesemia during pregnancy is caused by a significant need for this element, as well as increased renal excretion. An important role belongs to the state of magnesium deficiency in the genesis of pregnancy miscarriage. In conditions of low magnesium concentration, pathological activation of calcium-dependent contractile reactions in the myometrium occurs and the risk of pregnancy termination increases, especially in the II-III trimeste. In addition, hypomagnesemia promotes the development of increased excitability of the CNS, which provokes the central mechanisms of spastic reaction of the uterus.

In addition, concomitant hypertension disrupts the blood supply to the fetoplacental complex, increases the blood content of vaso-constrictor factors (renin, angiotensin II, prostaglandin F, serotonin), which increases the risk of miscarriage [7,8].

Antiplatelet effect of magnesium on platelets and directly on the vascular wall has been established as it reduces the imbalance between the synthesis of the prostacyclin of the vascular wall and thromboxane. There was also a decrease in the synthesis and release of catecholamines from the depot. All this improves perfusion in tissues, in particular in the chorion [1, 4, 11, 13].

A fundamental mechanism of the physiological effects of magnesium is its role as a natural calcium antagonist. At the same time magnesium competes with calcium not only in the structure of membrane channels but also at all levels of the cellular system, suppressing various reactions initiated by calcium. This mechanism provides anti-angina, anti-arrhythmic and antihypertensive effects of magnesium. Due to its antagonism with calcium, magnesium is able to influence the processes of oxidative phosphorylation in the mitochondria, resulting in increased ATP synthesis and reduced cellular oxygen demand (Table I) [1-4].

During pregnancy, due to hormonal changes occurring in the body of a woman, there is a tendency to the formation of hypomagnesemia. This is also due to the increase in 2-3 times the consumption of magnesium, which in turn is due to the growth and development of the fetus.

Hight micronutrient activity is determined by their mutual influence on each other's metabolism, as well as synergism and potentiation of biological effects. An example of this interaction is the tandem of magnesium and vitamin B6. Pyridoxine is involved in the synthesis of neurotransmitters and many enzymes, has neuro-, cardio-, hepatotropic, as well as hematopoietic effects, promotes energy reserves, maintains skin health, digestive tract, immune system. Vitamin B6 improves the absorption of magnesium in the digestive tract, serves as a conductor for it inside the cell, increases the permeability of cell membranes for magnesium and potassium ions, transfers them as an endogenous substance.

Magnesium drug therapy plays a significant role during pregnancy, childbirth, postpartum rehabilitation, and for the prevention of gestational diabetes and obesity. When carrying out magnesium therapy, it should be borne in mind that the endothelial and antiplatelet effect of magnesium preparations is short-lived and ends after their excretion. Therefore, long-term maintenance of oral forms of magnesium preparations during pregnancy is required [1,4-6].

## THE AIM

Conducting an evaluation of the effectiveness and safety of the use of magnesium in pregnant women.

## MATERIALS AND METHODS

In the first half of pregnancy, 60 pregnant women aged 29-38 years (mean age 28±1.9 years) were observed in the Department of Gynecology KNP "Maternity Clinical House №1" in Lviv for six months of 2021 during the first half of pregnancy in the period from 13 weeks to 21 weeks+6 days. All patients were referred to a hospital or treated independently with lower abdominal pain (22 women) and a combination of pain with blood flow (8 women).

The patients were divided into two groups according to the features of treatment. The main group of observation included 30 pregnant women who, in order to prevent obstetric and perinatal complications, used a pharmaceutical preparation, which is an organic combination of magnesium citrate 618.43 mg and pyridoxine hydrochloride 10 mg. The drug was used at a daily dose of 2473.72 mg of magnesium citrate and 40 mg of pyridoxine hydrochloride. The daily dose was divided into 2 doses. Shelf life – during the first half of pregnancy. In addition, atients in the main group received micronized progesterone, vitamin E.

Patients of the comparison group (30 women) received in the complex treatment preparations of micronized progesterone, vitamin E, multivitamin complex for pregnant women.

The distribution of pregnant women into groups was carried out in accordance with the principle of randomization. Before forming observation groups, all pregnant women were asked to sign informed consent to participate in a clinical trial.

Diagnosis of magnesium deficiency was performed by the method of colorimetric result from venous blood at Synevo Medical Laboratory. Considering the speed of execution within 2 days and the relative inexpensiveness of the method, all women were determined to determine magnesium levels.

During the analysis of anamnestic data, the age categories of pregnant women, extragenital and ingenious pathology, reproductive function, clinical course of the first half of pregnancy were systematized determination of frequency and structure of complications. Blood pressure, ultrasound, general blood and urine tests, lipid (total cholesterol, B-lipoproteins, triglycerides, low-density lipoproteins, high density lipoproteins) metabolism were performed. The studies were performed by standart methods. The ultrasound examination focused on the presence of local myometrium hypertension in combination with subjective pain, the study was performed with an abdominal ultrasound sensor. Cervicometry, performed by a vaginal sensor (after 18 weeks of pregnancy), aimed to detect structural changes in the cervix, such as shortening of less than 30 mm, opening the inner eye.

**Table I.** Clinical manifestations of magnesium deficiency

| Violation | Clinical manifestations |
|---|---|
| Increase of nervous excitability of a muscle cell | The redundancy of reduction processes in relation to the processes of relaxation (convulsions of extremities) |
| Increase of cardiomyocyte excitability | Disorders of the heart rhythm (tachycardia, extrasystole, heartache during physical activity) |
| Increasing the excitability of vascular smooth muscle cells | Sudden changes in blood pressure, headache, fatigue, apathy, increased risk of bronchospastic conditions |
| Imbalance in neuropeptides | Irritability, anxiety, bouts of fear, tearfulness, sometimes depression |
| Disorders of blood supply in the vessels of the brain | Frequent headaches, dizziness |
| Damage to neurons | Memory impairment, ability and concentration |
| Disorders of circadian melatonin synthesis processes and processes of excitation and inhibition in the nervous system | Insomnia, daytime sleepiness, night terrors, "broken" in the morning |
| Disruption of energy production and use processes | Muscle weakness, nervous exhaustion, general fatigue, chronic fatigue syndrome |

The average length of stay in the gynecological hospital is 14±5,3 days.

Statistical data processing was performed using Statistica 6.0 for WINDOWS v8.0.550 (StatSoft, USA). The comparison group and the main group were evaluated for subordination to the normal law of distribution according to the Pearson test. The significance of the difference of the mean values was determined by calculating the Student's t-test. The difference between the values compared was considered significant at $p<0,05$ [7].

## RESULTS

In the study, we did not find any significant differences between the pregnant women in the compared age groups (the mean age in the main group was 28±1.9; in the comparison group 29±2.2; p=0.08). In the structure of somatic pathology of the examined pregnant women, diseases of the cardiovascular system (19.2%), digestive tract (15.7%), respiratory organs (14.3%), kidneys(10.7%), endocrinopathy took the main place (11.2%), varicose veins of the lower extremities (7.5%). Analyzing the history of patients from both the main and the comparison group with approximately the same frequency (p 0.05) were noted: pathology of the cervix (17.3%), adenomyosis (21.2%), miscarriage (27.3%), intrauterine infection (19.3%), preterm birth (34.2%).

This allowed us to consider the groups representative and to exclude the possible effects of pregnancy factors other than our therapy. During the evaluation of the clinical effectiveness of treatment and prevention measures, the absence of allergic reactions and the individual intolerance of the drug magnesium were ascertained.

The concentration of magnesium in serum from 12 to 17 mg/l (1-1.4 mEq/l, or 0.5-0.7 mmol/l) indicates a deficiency of magnesium; below 12 mg/l (1mEq/l, or 0.5 mmol/l) for severe magnesium deficiency.

Analysis of the course of the first half of pregnancy in the surveyed women is presented in table II.

To accept the distribution between the specified checks as conforming to one law, according to the χ2-Pearson criterion, it was determined that the practical value of the level $\chi2pr=1.327$, and the tabular value at the selection volumes n=30 and the number of degrees of freedom equal to 6, the value of $\chi2=14.1$, at levels significance $p<0.05$.

Since $\chi2_{pr} < \chi2$, the sample data obey one distribution law at a given level of significance. According to Student's t-test, the difference in mean values between the comparison group and the main group is probably not reliable ($t_{pr} = 1.943$, $p>0.05$).

The criteria for diagnosing the threat of termination of pregnancy were: complaints about the pulling nature of the pain in the abdomen; ultrasound signs of local uterine hypertension, and in the case of abortion, the presence of a retrochoric hematoma, sometimes the attachment of minor blood flow from the genital tract. Hypomagnesemia is an independent and proven risk factor for early preeclampsia. According to our data, early preeclampsia developed in 3 (10.0%) women of the comparison group. A similar pattern was characteristic of other complications of the first half of pregnancy. Thus, anemia (13.3%), respiratory viral infection (10.0%), exacerbation of extragenital pathology (3.3%) were diagnosed in pregnant women more often than in the main group.

The regularities established by us testify to the negative impact of hypomagnesemia on the clinical course

of the first half of gestation, especially regarding the high incidence of non-pregnancy and reproductive losses (Table 2).

While evaluating the course of the first half of pregnancy in women in the main group, there was a tendency to reduce the incidence of complications in pregnant women compared. Thus, the number of cases of threat of abortion was 1.5 times lower; started abortion - 1.5 times and symptoms of early preeclampsia - 1.5 times; anemia of pregnant women – 2 times; adherence of symptoms of respiratory viral infection – 3 times. Important is the fact that there were no reproductive losses in this contingent of women during the first half of pregnancy. The use of therapeutic and prophylactic measures with the use of the drug magnesium reduced the number of bed-days in pregnant women during hospitalization with the threat of abortion to 9.4±1.1 days, and in the manifestations of early preeclampsia – to 7.8±1.2 days. Therefore, in our opinion, reducing the incidence of complications during the first half of pregnancy will contribute to its physiological course in the future and will have a positive effect on the condition of the pregnant, fetus and newborn.

Indicators of blood pressure in the examined pregnant women are presented in table III. Analysis of the level of blood pressure showed that in 12 (40.0%) pregnant women with hypomagnesemia revealed the 1st degree of hypertension. Assessment of the level of blood pressure on the background of therapy with the drug magnesium revealed normalization of indicators, while in pregnant women who did not use there indicators remained significantly higher (table III).

Indicators of carbohydrate and lipid metabolism in the examined pregnant women are presented in table IV.

During the analysis of carbohydrate and lipid metabolism in pregnant women prior to therapy, the level of total cholesterol, β-lipoproteins, triglycerides and LDL was at the upper limit of the reference values. Changes in the lipid spectrum of the blood toward increasing the concentration of total cholesterol in LDL and triglycerides is physiological for pregnancy. However, in the case of pronounced increase in lipids in the blood, the processes of atherogenesis are accelerated, and lipolytic action on insulin receptors increases the insulin resistance that already exists with magnesium deficiency [9,10]. As a result of therapy with magnesium, positive changes in blood lipid spectrum were recorded in pregnant women of the main group, as evidenced a decrease in the level of total cholesterol, β-lipoproteins – by 1.2 times, LDL – by 1.1 times ($p<0.05$) (table IV).

During an ultrasound examination on the day of hospitalization, it was revealed that fetal OPS (occipital-parietal size) corresponded to the pregnancy period in both study groups.

The main sonographic sign of the threat of pregnancy termination was thickening of the myometrium, which was more often located at the place of attachment of the chorion to the wall of the uterus. Ultrasound in the dynamics was performed in both study groups after 1 week of treatment and before discharge (preferably on day 14). The results obtained are shown in table V.

Table V shows that in the main group significantly earlier there is a decrease in local hypertension, and since the first control ultrasound (a week from the start of treatment). This clinical effect is achieved due to the synergistic effect of the drug magnesium and micronized progesterone on myometrium.

Thus, the use of magnesium in the first half of pregnancy helped reduce the incidence of hypomagnesemia, reduce the number of complications of pregnancy, normalization of carbohydrate and lipid metabolism. The conducted clinical studies revealed no organic and systemic disorders in women.

## DISCUSSION

The current situation in Ukraine (martial law, environmental problems, violations of living conditions and food quality) has led to significant changes in the course of pregnancy. Irrational and poor-quality nutrition of a pregnant woman can harm both herself during the period of greatest stress on the body and the fetus. In the future, the refusal of breastfeeding or its impossibility for any reason further increases the negative metabolic changes in the body of a newborn child, which lay the already disturbed foundation of health for the next life.

Nutritional deficiencies do not depend on the season and place of residence, and 70-80% of pregnant women have polyhypovitaminosis [11]. Such a situation should be prevented by determining a woman's micronutrient status even before pregnancy, during the period of pre-gravid preparation, and by correcting it. According to current WHO recommendations, it is mandatory for women to receive iron and folic acid, starting from the stage of preparation for pregnancy and during its entire course. As for other trace elements and vitamins, their use in this contingent of women should be justified by evidence of their deficiency [12].

Calcium (Ca) and vitamin D, as well as iodine, are often lacking today, especially in endemic regions, which requires their appointment in the form of mineral-vitamin complexes or individual trace elements [13].

At the same time, another one of the most important macronutrients — the fourth cation in quantity and the second most physiologically important trace element in the human body after potassium — remains overlooked, namely magnesium (Mg). It acts as a cofactor

**Table II.** Complications of the first half of pregnancy in the surveyed women

| Complication | Comparison group, n=30 | | Main group, n=30 | | Statistical analysis | |
|---|---|---|---|---|---|---|
| | abs | % | abs | % | Pearson's Chi2 | Significance level |
| The threat of termination of pregnancy | 9 | 30,0 | 6 | 23,3 | 1,92 | 0,04 |
| Abortion started | 6 | 20,0 | 5 | 16,7 | 1,95 | 0,04 |
| Unintended termination of pregnancy | 3 | 10,0 | 5 | 16,7 | 1,96 | 0,03 |
| Early preeclampsia | 3 | 10,0 | 3 | 10,0 | 1,96 | 0,03 |
| Anemia of pregnant women | 4 | 13,3 | 3 | 10,0 | 1,97 | 0,02 |
| Respiratory viral infection | 3 | 10,0 | 4 | 13,3 | 1,97 | 0,02 |
| Exacerbation of extragenital pathology | 2 | 6,7 | 3 | 10,0 | 1,98 | 0,01 |

Note: Difference is significant in comparison group ($p<0,05$).

**Table III.** Indicators of blood pressure in the examined pregnant women

| Indicator | Comparison group, n =30 | | Main group, n=30 | | Statistical analysis | |
|---|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Pear-son's $Chi^2$ | Significance level p |
| Systolic blood pressure, mm Hg.Art. | 150,2±1,2 | 135,5±0,7 | 145,7±1,8 | 124,8±0,8 | 2,83 | 0,03 |
| Diastolic blood pressure, mm Hg. Art | 98,7±0,8 | 85,7±0,7 | 91,3±0,4 | 91,3±0,4 | 2,69 | 0,04 |

**Table IV.** Indicators of carbohydrate and lipid metabolism in the examined pregnant women

| Indicator | Comparison group, n =30 | | Main group, n=30 | | Statistical analysis | |
|---|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Pear-son's Chi2 | Significance level p |
| Glucose, mmol/l | 4,3±0,25 | 4,2±0,24 | 4,2±0,06 | 4,1±0,07 | 1,94 | 0,03 |
| Total choles-terol, mmol/l | 6,02±0,1 | 5,97±0,09 | 6,08±0,09 | 5,02±0,07 | 1,94 | 0,03 |
| β-lipopro-teins, units/l | 63,15±0,92* | 54,21±0,88 | 63,13±0,82 | 50,44±0,62 | 1,34 | 0,02 |
| Triglycerides, mmol/l | 2,78± 0,02 | 2,61± 0,03 | 2,77±0,03 | 2,26± 0,22 | 1,97 | 0,02 |
| LDL, mmol/l | 64,81±0,96 | 60,35±0,72 | 64,75±0,82 | 58,10±0,7 | 1,30 | 0,04 |
| HDL, mmol/l | 1,26±0,05 | 1,31±0,08 | 1,25±0,07 | 1,32±0,05 | 1,98 | 0,01 |

Note: * - $p<0,05$.

**Table V.** Ultrasonographic characteristics in the dynamics of treatment

| Ultrasonographic characteristics | Comparison group, n =30 | | Main group, n=30 | | Statistical analysis | |
|---|---|---|---|---|---|---|
| | One week later | Two weeks later | One week later | Two weeks later | Pear-son's $Chi^2$ | Significance level p |
| Local hypertonic of the myometrium | 22 (73,3) | 7 (23,3) | 12 (40,0) | 5 (16,7) | 1,51 | 0,03 |
| Structural changes of the cervix uterus | 4 (13,3) | 1(3,3) | 3 (10,0) | 1 (3,3) | 1,50 | 0,03 |

in more than 600 enzymatic reactions and is necessary for the synthesis of nucleic acids and proteins. Magnesium contributes to the formation and hydrolysis of ATP, plays an important role in the processes of glycolysis, in the citrate cycle. With the participation of Mg, cholinesterase is activated, cholesterol synthesis and esterification takes place, it regulates the secretion of parathyroid hormone and neuromuscular conduction, participates in the functioning of muscle tissue and osteogenesis. At the same time, extracellular Mg affects

the heart rhythm, its deficiency can lead to ventricular tachycardia and sudden death. Hypomagnesemia is often accompanied by increased excitability of the central nervous system, and hypermagnesemia by its depression [14].

The physiological daily need for Mg for adults is 280-300 mg, and during pregnancy and lactation it increases by 20-30% to 340-355 mg.

The main sources of dietary Mg are legumes and cereals, spinach, as well as nuts and chocolate. However, these products also contain a large amount of such elements as Ca, sodium and phosphorus (P), which prevent sufficient absorption of Mg. According to various researchers, Mg deficiency in the population reaches 14.5%, among pregnant women this figure is 16-43% [15].

There are primary and secondary Mg deficiency. Primary, or latent, Mg deficiency is associated with gene mutations that lead to disturbances in its transmembrane exchange. Secondary deficiency of Mg in the body can be caused by various diseases (gastroenteritis, nephrotic syndrome, hypercorticism, etc.), taking drugs (diuretics, cytostatics, estrogen-containing drugs), as well as living conditions (chronic stress, physical overload, hypodynamia, pregnancy and lactation) [16].

It should be noted that many women at the onset of pregnancy already have a certain deficiency of Mg, which is confirmed by research conducted in Germany. Thus, in 56.4% of people aged 14-18 years, in 38.3% - 19-24 years, and in 26.5% - 25-34 years, the level of serum Mg did not meet the recommendations of the German Nutrition Society [17].

Thus, the periods of pregnancy and lactation are recognized as risk factors for the development of hypomagnesemia, since it is at this time that the mother's and the fetus's bodies consume most of the micro- and macroelements, including and Mg. During pregnancy, the need for Mg increases 1.5-2 times, which is largely due to the formation and functioning of the placenta, intrauterine growth and development of the fetus, as well as an increase in estrogen and aldosterone levels [4, 10].

In addition to the needs of the mother and fetus in Mg and its insufficient intake with food, pregnant women have increased excretion of the mineral with urine; according to L. Spätling et al. (2017) — by 20% [11]. This can be explained by a 40% increase in cardiac stroke volume due to pregnancy, which leads to increased renal filtration and inadequate Mg reabsorption [17].

Thus, Mg deficiency in pregnant women can lead to the development of placental dysfunction, preeclampsia due to uterine artery spasm, fetal growth retardation syndrome; the relative deficiency of Mg2+ ions causes the threat of termination of pregnancy, the development of a pathological preliminary period, uncoordinated labor activity, a violation of the state of the connective tissue, and the development of isthmic-cervical insufficiency (ICI) [16].

Placental cells contain the maximum number of mitochondria, the deficiency of Mg in which negatively affects their functioning [4, 12]. Thus, it has been proven that hypomagnesemia in the mother leads to impaired placental function and, as a result, fetal growth retardation and fetal distress [13, 14]. Mg deficiency in pregnant women can lead to an increase in intrauterine death of the fetus, a decrease in its body weight and size. Magnesium has an antioxidant effect, activates the production of nitric oxide and prostacyclin, thus preventing the development of vascular endothelium pathology. It is a disaggregant and moderate anticoagulant [17, 18]. Increased urinary Mg excretion during pregnancy can also cause an increase in blood pressure [18].

Modern views on the use of Mg in obstetrics and gynecology practice are based on the need to determine its deficiency at the stage of pre-gravid preparation, correct this deficiency with the help of adequate therapy and continue taking Mg drugs throughout pregnancy, taking into account the multitude of its effects in the body of the woman and the fetus, and as well as its insufficient entry into the body with food products.

Specialists of the German Society for Magnesium Research (Society for Magnesium Research e.V.) recommend the use of Mg preparations throughout pregnancy, as they have a good safety profile, a low frequency of side effects and are economically available [18]. According to them, a pregnant woman should receive Mg in a dose of 240-480 mg (10-20 mmol) daily. Reception should be started as early as possible, continue throughout the entire period of gestation and during lactation. Treatment should not be stopped even before childbirth, since the inhibitory effect of these drugs on the onset of labor is unproven. The only contraindication for taking Mg drugs is severe renal failure [18].

## CONCLUSIONS

1. The correction of chronic magnesium deficiency, performed by the drug magnesium has allowed to reduce by 1.5 times the number of cases of threat of abortion, by 1.2 times – the abortion that was started, by 1.5 times – by the symptoms of early preeclampsia, by 2 times – anemia of pregnant women, 3 times – symptoms of respiratory viral infection, 1.5 times to reduce the number of bed-days in the case of hospitalization ($p<0.05$).

2. The use of magnesium helped to normalize blood pressure, carbohydrate and lipid metabolism.
3. Correction of magnesium deficiency with the drug magnesium antistress in the complex treatment of patients with the risk of pregnanacy termination (in combination with the preparations of micronized progesterone) leads to a reliable ($p<0.05$) faster reduction of local hypertonic of the myometrium.
4. Effective correction of magnesium deficiency during pregnancy is provided by the modern oral magnesium drug, which combines a combination of magnesium citrate with pyridoxine, which has high bioavailability, maximum absorption in the intestines and the passage of magnesium into cells, sufficient efficiency, low reactogenicity, and is completely safe for application in midwifery practice.

## REFERENCES


1. Fanni D, Gerosa C, Nurchi V.M. et al. The Role of Magnesium in Pregnancy and in Fetal Programming of Adult Diseases. Biol Trace Elem Res. 2021 Oct;199(10):3647-3657. doi: 10.1007/s12011-020-02513-0.
2. Zoroddu M.A, Aaseth J, Crisponi G et al. The essential metals for humans: a brief overview. J Inorg Biochem. 2019;195:120–129. doi: 10.1016/j.jinorgbio.2019.03.01
3. Magee L.A., De Silva D.A., Sawchuck D. et al. No. 376-magnesium sulphate for fetal neuroprotection. J Obstet Gynaecol Can. 2019;41:505–522. doi: 10.1016/j.jogc.2018.09.018.
4. Poppe T, Thompson B, Boardman J.P. et al. Effect of antenatal magnesium sulphate on MRI biomarkers of white matter development at term equivalent age: The MagNUM Study. EBioMedicine. 2022 Apr;78:103923. doi: 10.1016/j.ebiom.2022.103923.
5. Lu A, Ye Y, Hu J et al. Case Series: Video-Assisted Minimally Invasive Cardiac Surgery During Pregnancy. Front Med (Lausanne). 2021 Dec 22;8:781690. doi: 10.3389/fmed.2021.781690.
6. Conde-Agudelo A, Romero R, Jung EJ, Garcia Sánchez ÁJ. Management of clinical chorioamnionitis: an evidence-based approach. Am J Obstet Gynecol. 2020 Dec;223(6):848-869. doi: 10.1016/j.ajog.2020.09.044.
7. Ichizuka K, Toyokawa S, Ikenoue T. Risk factors for cerebral palsy in neonates due to placental abruption. J Obstet Gynaecol Res. 2021 Jan;47(1):159-166. doi: 10.1111/jog.14447.
8. Lee H.H, Yeh C.C, Yang S.T. Tocolytic Treatment for the Prevention of Preterm Birth from a Taiwanese Perspective: A Survey of Taiwanese Obstetric Specialists. Int J Environ Res Public Health. 2022 Apr 1;19(7):4222. doi: 10.3390/ijerph19074222.
9. Stelzl P, Kehl S, Oppelt et al. Do obstetric units adhere to the evidence-based national guideline? A Germany-wide survey on the current practice of initial tocolysis. Eur J Obstet Gynecol Reprod Biol. 2022 Mar;270:133-138. doi: 10.1016/j.ejogrb.2022.01.006.
10. Shen H.S, Chang W.C, Chen Y.L. Chinese Herbal Medicines Have Potentially Beneficial Effects on the Perinatal Outcomes of Pregnant Women. Front Pharmacol. 2022 Jun 6;13:831690. doi: 10.3389/fphar.2022.831690. eCollection 2022.
11. Eddy K.E., Vogel J.P., Zahroh R.I. et al. Factors affecting use of magnesium sulphate for pre-eclampsia or eclampsia: a qualitative evidence synthesis. BJOG An International Journal of Obsteyrics & Gynaecology. 2022 Feb 129 (12). doi:10.1111/1471-0528.16913
12. Alabintei O.M, Abasi I.J, Alabrah P.W. The Use of Magnesium Sulphate in the Management of Severe Preeclampsia and eclampsia in Bayelsa State, Nigeria Journal of Gynaecology and Women's Health. 2021 April 21(3): 001-0010. doi: 10.19080/JGWH.2021.21.556063
13. Sara Young, Michelle J. Wang et al. Intrapartum magnesium sulfate exposure and obstetric hemorrhage risk. The Journal of Maternal-Fetal & Neonatal Medicine, 2022, 35:25, 10036-10043, doi: 10.1080/14767058.2022.2086796
14. Nosenko O. M. & Khancha F. O. Magnesium in the prevention of gestational complications in women with pregnancy induced in the art cycle. Reproductive Endocrinology, 2020 (56), 80–87. doi:10.18370/2309-4117.2020.56.80-87
15. Jin, S., Sha, L., Dong, J., et al. Effects of Nutritional Strategies on Glucose Homeostasis in Gestational Diabetes Mellitus: A Systematic Review and Network Meta-Analysis. Diabetes Res 2020 (2020): 6062478. doi: 10.1155/2020/6062478
16. Fartushok T. Covid-19: topical issues of clinic activities during a pandemic. Georgian medical newsthis link is disabled, 2020;306: 122–132
17. Medication Errors in Labor and Delivery: Reducing Maternal and Fetal Harm. Pennsylvania Patient Safety Advisory 6 Suppl. 2020;1:1–6. http://patientsafety.pa.gov/ADVISORIES/documents/2009sup1_01.pdf
18. Jayaram, Pradeep M., Mohan et al. Antenatal magnesium sulfate for fetal neuroprotection: a critical appraisal and systematic review of clinical practice guidelines. Journal of Perinatal Medicine, 2019,(47)3:262-269. doi:10.1515/jpm-2018-0174



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ORIGINAL ARTICLE

# MULTIFACTOR REGRESSION MODEL FOR PREDICTION OF CHRONIC RHINOSINUSITIS RECURRENCE

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## ABSTRACT

**The aim:** To propose an approach to forecasting the risk of chronic rhinosinusitis recurrence based on multivariate regression analysis for effective diagnosis and carrying out treatment and preventive measures.

**Materials and methods:** 104 patients aged 18 to 80, including 58 women and 46 men, diagnosed with chronic rhinosinusitis were examined.

**Results:** To build a multifactorial regression model for predicting the recurrence of chronic rhinosinusitis, probable factors of the occurrence of the disease were selected. 14 possible factors were analyzed using multivariate regression analysis. 13 risk factors were selected for predicting recurrence of chronic rhinosinusitis with a significance level of less than 0.05. Histograms of the residual deviations of predicting the recurrence of chronic rhinosinusitis were obtained, which are distributed symmetrically, and a normal-probability straight line is presented, on which there are no systematic deviations. The given results confirm the statistical hypothesis that the residual deviations correspond to the normal distribution law. Residual deviations relative to the predicted values are scattered chaotically, which indicates the absence of dependence on the predicted values of the risk of recurrence of chronic rhinosinusitis. The value of the coefficient of determination was calculated, which is 0.988, which gives grounds to claim that 98.8% of the factors are taken into account in the model for predicting the recurrence of chronic rhinosinusitis and its high reliability and acceptability in general.

**Conclusions:** The proposed model makes it possible to predict in advance potential complications and the possibility of recurrence of the studied disease.

**KEY WORDS:** chronic rhinosinusitis, prognosis, multivariate regression analysis, recurrence

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## INTRODUCTION

Patients with various forms of chronic rhinosinusitis (ChRS) are the dominant part of patients with ENT pathology who are currently seen as outpatients by family doctors and otolaryngologists. Chronic rhinosinusitis is a broad concept that includes a number of diagnoses. It is defined as "infection of the sinuses and Schneiderian membrane lasting more than 3 months (or 12 weeks) per year." In most cases, this category of patients in the period of exacerbation of the disease requires not only hospitalization with intensive conservative therapy, but also quite often – surgical intervention.

In particular, among the entire population of the United States, chronic rhinosinusitis is currently diagnosed in 15.5% and for many years it has been considered the second most common among all chronic pathologies [1-3]. According to other data, from 5% to 15% of the population in different countries suffers from chronic rhinosinusitis in its various forms [4-6]. It is worth noting that from year to year this problem ceases to be only medical, but becomes social and financial – it causes a long-term decrease and loss of working capacity of patients, leads to significant material burdens on the patient and the state [7, 8].

In the structure of sinusitis, 56-73% are lesions of the maxillary sinus due to its large volume, high natural anastomosis and close contact with the roots of the teeth (premolars of the upper jaw) [9]. At the same time, the frequency of chronic sinusitis of the maxillary sinus is 5 times higher than for the example of the frontal sinus [10].

Despite modern surgical methods of treatment, postoperative complications and recurrences of the disease requiring reoperation are still observed in 18% of patients during long-term observation [11].

That is why the issue of predicting potential relapses of chronic rhinosinusitis depending on its form of manifestations remains open and relevant. The creation of appropriate prognostic mathematical models will make it possible to timely and reliably diagnose the occurrence of complex forms of CRS and their relapses, and may also be one of the options for solving the current problem of effective treatment of ENT diseases.

At present day, the examples of effective application of multivariate regression analysis in medicine

are the works of Musiienko V. et al.; Musiienko V. et al.[12, 13].

Prognostic factors of recurrence of polyps in chronic rhinosinusitis are also considered in the work of Junqin Bai et al. [14], and early postoperative endoscopic evaluation with eosinophilic chronic rhinosinusitis was carried out in the work of Kosuke Akiyama, Yasushi Samukawa, Hiroshi Hoshikawa[15].

## THE AIM

The aim of the work is to propose an approach to forecasting the risk of recurrence of chronic rhinosinusitis in patients based on multivariate regression analysis for timely, convenient and accurate diagnosis while carrying out effective treatment and preventive measures in ENT departments (otolaryngology departments).

## MATERIALS AND METHODS

We examined 104 patients aged 18 to 80, including 58 women and 46 men, with a diagnosis of chronic rhinosinusitis, who were undergoing inpatient treatment in the otolaryngology department of the Ternopil Regional Hospital under Ternopil Regional Council. The average age of the patients was 45 years, and the duration of the disease varied within 5-8 years.

All patients signed an informed consent to participate in the study. After receiving the opinion of the ethics commission at Ivan Horbachevsky Ternopil National Medical University (minutes No.63 dated March 16, 2020), the study was conducted in compliance with all moral and ethical principles, taking into account the Helsinki Declaration of the World Medical Association on Biomedical Research (World Medical Association Declaration of Helsinki).

All patients underwent a comprehensive clinical and laboratory examination, which included an examination, anamnesis collection, complete blood count with formula, biochemical blood analysis, and radiological examination (radiography of the paranasal sinuses, CT or MRI of the head).

According to a specially developed questionnaire for predicting the level of recurrence of CRS, all patients were surveyed, which included 15 risk factors for the development of ChRS: age, gender, environmental living (working) conditions, nasal septum deviation, presence of an allergic component, carious or damaged teeth (upper premolars), nasal or facial skeleton injuries, the presence of leukocytosis (according to the leukocyte formula), the ESR level, the presence of diagnosed diabetes, the level of glycemia, the degree of bronchial asthma, radiological signs, smoking, and the incidence of SARS during the last 12 months, and their gradation was established from numerical values.

Construction of a prognostic model of the risk of ChRS recurrence was carried out using multivariate regression analysis. The statistical processing of the obtained research results was carried out using the statistical package Statistica 10.0 and the table editor Microsoft Excel 2019.

## RESULTS

The method of multivariate regression analysis for predicting the recurrence of ChRS, taking into account the most informative factors and variants of their severity, makes it possible to create a mathematical model for predicting this disease. The use of this method makes it possible to predict the possibility of recurrence, which helps in the development of effective methods of treatment, prevention of the development and progression of the pathology.

104 patients diagnosed with various forms of ChRS were examined using a specially developed questionnaire to predict the recurrence of ChRS, the average age of the examined was 45 years. The gender component was 58 women and 46 men.

Probable factors of the occurrence of chronic rhinosinusitis were selected to build a multifactorial regression model for predicting the recurrence of ChRS. With the help of multivariate regression analysis, 14 possible factors for the occurrence of ChRS were analyzed: age, gender, environmental living (working) conditions, nasal septum deviation, an allergic component in the anamnesis, the presence of carious or damaged teeth (upper premolars), leukocytes, white blood components, erythrocyte sedimentation rate (ESR), presence of diabetes, glycemic level, radiological signs, smoking, respiratory diseases during the last 12 months.

To assess the significance of the influence of factor characteristics, a stepwise multivariate regression analysis was performed in Statistica 10.0 program. First, a correlation matrix was obtained, in which the absence of pairwise correlation coefficients greater than 0.7 was established. Thus, the presence of multicollinear factors of ChRS recurrence gives reason to use all 14 above-mentioned factors to build a regression model. The next stage was the calculation of the regression coefficients "b" (Beta), which reflect for each selected factor the relationship regarding the impact on the development of ChRS recurrence in the examined patients. The result of obtaining significant factors for predicting ChRS recurrence when performing multivariate regression analysis in Statistica 10.0 program is shown in fig. 1.

**Table I.** Significant risk factors for ChRS recurrence.

| Name of factors | Conventional designations of factors in the mathematical forecasting model | Factor ranges and names of their possible variants | Numerical values of factor ranges |
|---|---|---|---|
| Age | X1 | 18-25 | 0 |
| | | 25-44 | 1 |
| | | 44-60 | 2 |
| | | 60-75 | 3 |
| | | 75-90 | 4 |
| Gender | X2 | M | 1 |
| | | F | 2 |
| Ecological living (Working) conditions | X3 | Maternity leave/ Does not work/ Pensioner/ Disabled of II-III grade | 1 |
| | | Nurse/ Doctor | 2 |
| | | Student/ Educator/ Junior researcher/ Teacher/ Lecturer/ Librarian/ Accountant/ Leading specialist/ Manager/ Engineer/ Private entrepreneur/Operator | 3 |
| | | Barista/ Waiter/ Make-up artist/ Salesman/ Cook/ Cleaner/ Watchman/ Driver/ Plant worker/ Warehouse administrator/ Foreman/ Tractor driver/ Police inspector/ Storekeeper/ Carpenter/ Crane operator | 4 |
| Nasal Septum Deviation | X4 | 1/3 of nasal meatus | 1 |
| | | 2/3 of nasal meatus | 2 |
| | | Completely | 3 |
| | | S-shaped | 4 |
| Allergic component | X5 | No | 0 |
| | | Yes | 1 |
| Carious (damaged) teeth (premolars) | X6 | 1 tooth | 1 |
| | | 2 teeth | 2 |
| | | 3 teeth | 3 |
| Components of white blood | X7 | Normocytosis | 0 |
| | | Eosinophilic leukocytosis | 1 |
| | | Basophilic leukocytosis | 2 |
| | | Monocytic leukocytosis | 3 |
| | | Neutrophil leukocytosis | 4 |
| | | Lymphocytic leukocytosis | 5 |
| ESR level | X8 | Norm | 0 |
| | | Increased | 1 |
| Presence of diabetes | X9 | Absent | 0 |
| | | Diabetes of I type | 1 |
| | | Diabetes of II type | 2 |
| Glycemic level | X10 | Nrml 3.3-5.5 mMol/L | 0 |
| | | Light 6.7-8.2 mMol/L | 1 |
| | | Medium 8.3-11.0 mMol/L | 2 |
| | | Severe more than 11.0 mMol/L | 3 |
| X-ray signs (CT, MRI) | X11 | Swelling of the mucous membrane | 1 |
| | | Fluid level | 2 |
| | | Cyst | 3 |
| | | Foreign body/ Mycetoma | 4 |
| | | Tumor process/ Osteoma/ Polyps | 5 |
| Smoking | X12 | No | 0 |
| | | Yes | 1 |
| Flu infection | X13 | Wasn't sick | 0 |
| | | 1-2 times a year | 1 |
| | | 3-4 times a year or more | 2 |

| N=104 | Regression Summary for Dependent Variable: ChRS Relapse (1<br>R= ,99400574 R?= ,98804741 Adjusted R?= ,98616723<br>F(14,89)=525,51 p<0,0000 Std.Error of estimate: ,40044<br>b* | Std.Err. of b* | b | Std.Err. of b | t(89) | p-value |
|---|---|---|---|---|---|---|
| **Intercept** | | | -2,91301 | 0,355570 | -8,19251 | 0,000000 |
| Age | 0,286032 | 0,013298 | 0,05931 | 0,002757 | 21,50998 | 0,000000 |
| Sex | 0,158368 | 0,016660 | 1,08613 | 0,114256 | 9,50611 | 0,000000 |
| Working conditions | 0,343985 | 0,012426 | 0,96458 | 0,034844 | 27,68301 | 0,000000 |
| NSD (Nasal Septum Deviation) | 0,280321 | 0,012876 | 1,03899 | 0,047724 | 21,77088 | 0,000000 |
| Allergy comp | 0,055126 | 0,012623 | 1,11596 | 0,255547 | 4,36696 | 0,000034 |
| Dental caries | 0,205421 | 0,012738 | 1,07302 | 0,066535 | 16,12717 | 0,000000 |
| Leukocytes | -0,018909 | 0,013065 | -0,02989 | 0,020649 | -1,44738 | 0,151305 |
| White blood comp | 0,618464 | 0,012851 | 1,03299 | 0,021465 | 48,12483 | 0,000000 |
| ESR | 0,115017 | 0,012578 | 0,03974 | 0,004346 | 9,14421 | 0,000000 |
| Diabetes | 0,069331 | 0,013077 | 1,08076 | 0,203845 | 5,30188 | 0,000001 |
| Glucose | 0,102867 | 0,014082 | 0,38112 | 0,052174 | 7,30475 | 0,000000 |
| X-ray, CT, MRI | 0,362615 | 0,013245 | 1,01183 | 0,036958 | 27,37774 | 0,000000 |
| Smoking | 0,146888 | 0,015665 | 1,16471 | 0,124214 | 9,37666 | 0,000000 |
| Flu infection | 0,148020 | 0,012187 | 0,91877 | 0,075648 | 12,14527 | 0,000000 |

**Fig. 1.** The result of obtaining significant factors for predicting ChRS recurrence when performing multivariate regression analysis in Statistica 10.0 program.

| N=104 | Regression Summary for Dependent Variable: ChRS Relapse (1<br>R= ,99386421 R?= ,98776607 Adjusted R?= ,98599894<br>F(13,90)=558,97 p<0,0000 Std.Error of estimate: ,40287<br>b* | Std.Err. of b* | b | Std.Err. of b | t(90) | p-value |
|---|---|---|---|---|---|---|
| **Intercept** | | | -3,02163 | 0,349667 | -8,64147 | 0,000000 |
| Age | 0,285824 | 0,013378 | 0,05927 | 0,002774 | 21,36604 | 0,000000 |
| Sex | 0,162198 | 0,016548 | 1,11240 | 0,113489 | 9,80177 | 0,000000 |
| Working conditions | 0,345134 | 0,012476 | 0,96780 | 0,034983 | 27,66464 | 0,000000 |
| NSD (Nasal Septum Deviation) | 0,277670 | 0,012822 | 1,02917 | 0,047525 | 21,65524 | 0,000000 |
| Allergy comp | 0,055010 | 0,012700 | 1,11361 | 0,257092 | 4,33158 | 0,000038 |
| Dental caries | 0,200789 | 0,012404 | 1,04883 | 0,064791 | 16,18783 | 0,000000 |
| White blood comp | 0,617377 | 0,012907 | 1,03118 | 0,021558 | 47,83240 | 0,000000 |
| ESR | 0,112440 | 0,012527 | 0,03885 | 0,004328 | 8,97582 | 0,000000 |
| Diabetes | 0,068969 | 0,013153 | 1,07513 | 0,205044 | 5,24341 | 0,000001 |
| Glucose | 0,097594 | 0,013685 | 0,36158 | 0,050704 | 7,13131 | 0,000000 |
| X-ray, CT, MRI | 0,362671 | 0,013325 | 1,01199 | 0,037182 | 27,21704 | 0,000000 |
| Smoking | 0,146406 | 0,015757 | 1,16090 | 0,124939 | 9,29170 | 0,000000 |
| Flu infection | 0,148273 | 0,012260 | 0,92034 | 0,076099 | 12,09392 | 0,000000 |

**Fig. 2.** The result of obtaining significant factors for predicting recurrence of ChRS in Statistica 10.0 program without taking into account leukocytes.

The risk factor "Leukocytes" with a significance level of p=0.15 was excluded from further analysis. Since the significance levels of thirteen risk factors were less than 0.05, they were included in the mathematical model for predicting ChRS recurrence.

After constructing the correlation matrix excluding leukocytes, there were also no multicollinear factors, as there were no pairwise correlation coefficients greater than 0.7. Therefore, all 13 factors, except leukocytes, were used to construct a multivariate regression model. The result of obtaining significant factors for predicting recurrence of ChRS without taking into account leukocytes is shown in fig. 2.

So, among the 14 analyzed factors in Statistica 10.0 program (fig. 1), the 13 most significant risk factors that have the greatest influence on the development

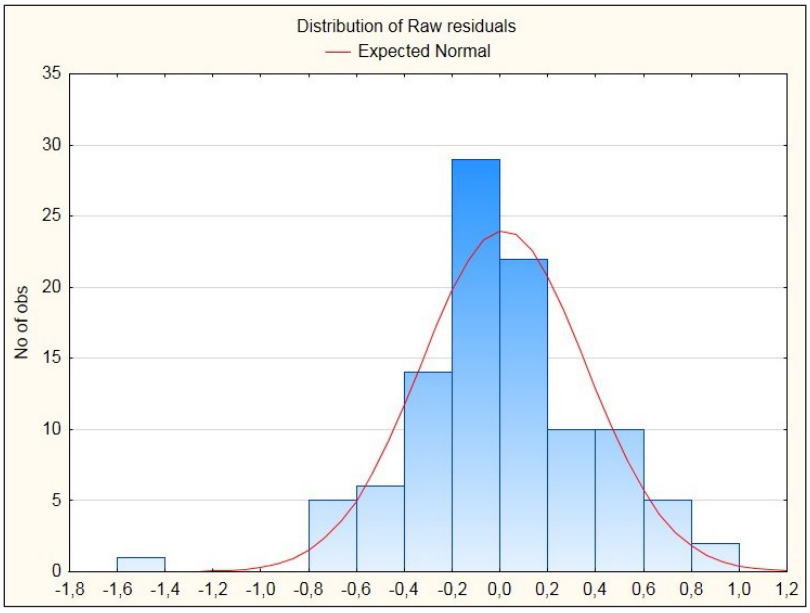


**Fig. 3.** Histogram of the residual deviations of the multivariate regression model for predicting ChRS recurrence.

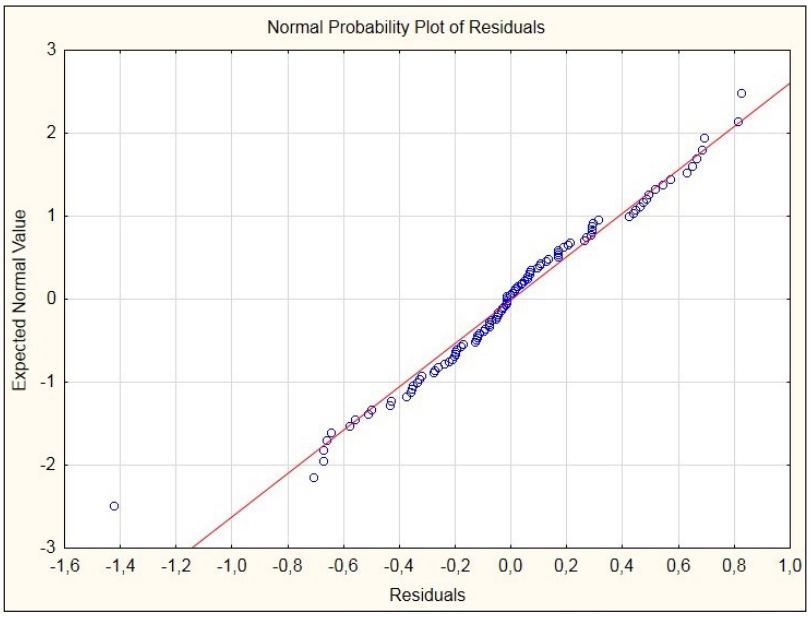


**Fig. 4.** Normal-probability graph of the residual deviations of the multivariate regression model for predicting ChRS recurrence.

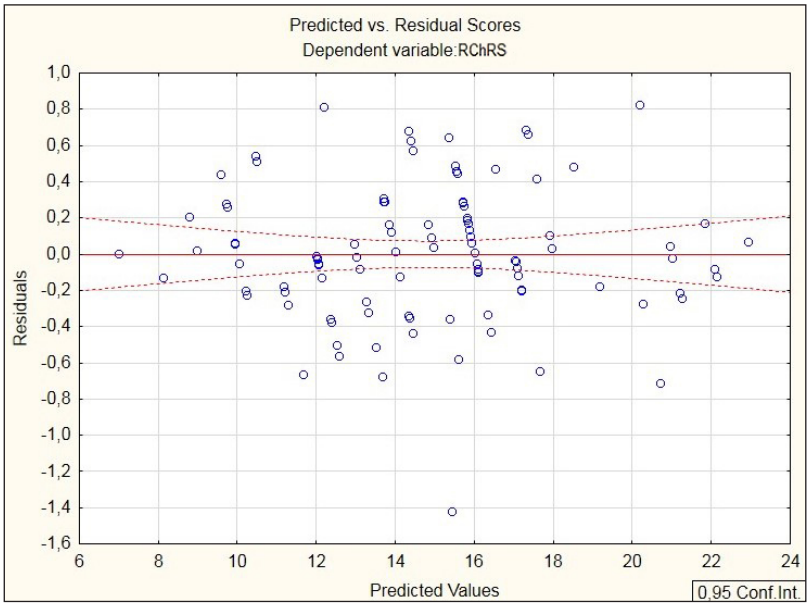


**Fig. 5.** Scatter diagram of the residual deviations of the multivariate regression model for predicting ChRS recurrence.

| Effect | Analysis of Variance; DV:RChRS | | | | |
|---|---|---|---|---|---|
| | Sums of Squares | df | Mean Squares | F | p-value |
| Regress. | 1179,719 | 14 | 84,26565 | 525,5060 | 0,00 |
| Residual | 14,271 | 89 | 0,16035 | | |
| Total | 1193,990 | | | | |

**Fig. 6.** Analysis of the coefficient of determination of the multivariate regression model for predicting ChRS recurrence.

of recurrence of this pathology were selected: X1 – age; X2 – gender; X3 – ecological living (working) conditions; X4 – nasal septum deviation; X5 – allergic component in anamnesis; X6 – presence of carious or damaged teeth (upper premolars); X7 – components of white blood; X8 – erythrocyte sedimentation rate; X9 – presence of diabetes; X10 – glycemic level; X11 – X-ray signs; X12 – smoking; X13 – respiratory diseases during the last 12 months. Significant risk factors for CRS recurrence are listed in Table I.

Based on the results of the multivariate regression analysis of predicting the level of recurrence of ChRS, which are shown in fig. 2, we build a mathematical model for determining the risk ratio of ChRS recurrence (RRChRSR):

RRCRSR = X1*0.059+X2*1.112+X3*0.968+X4*1.029 +X5*1.114+X6*1.049+ +X7*1.031+X8*0.039+X9*1.07 5+X10*0.362+X11*1.012+X12*1.161+X13*0.92-3.022,

where RRChRSR is the risk ratio of ChRS recurrence;

X1-X13 – selected risk factors for ChRS recurrence with regression coefficients;

3.022 is a constant.

To assess the quality of the regression model, it was necessary to analyze the residual deviations, in particular to obtain their histogram (Fig. 3). As can be seen from the obtained histogram, the residual deviations are distributed symmetrically, approaching the normal distribution curve of the residuals, therefore the statistical hypothesis that their distribution conforms to the normal distribution law is not rejected.

In order to additionally confirm residual deviations from the normal distribution law, a normal-probability graph was constructed (Fig. 4). Analyzing its data, we note the absence of systematic deviations from the normal-probability straight line. This makes it possible to conclude that the residual deviations are distributed according to the normal distribution law.

To check the dependence of the residual deviations on the predicted values, we construct a scatter diagram (Fig. 5).

Based on the obtained results, we note that the residuals relative to the predicted values are scattered chaotically, which indicates the absence of dependence on the predicted values of the risk of ChRS recurrence. Histogram and normal-probability graph confirm the residual deviations corresponding to the normal distribution law. Therefore, the obtained model for predicting the risk of recurrence of ChRS is qualitative and adequate.

The next step was to assess the acceptability of the model as a whole, for which we conduct an ANOVA analysis (Fig. 6). Analyzing the obtained data, we can conclude about the high level of acceptability of the model for predicting the risk of ChRS relapse in general using ANOVA analysis, since the level of significance is $p<0.001$, and the model itself will work better than a simple forecast using average values.

For an additional assessment of the quality of the mathematical model of RRChRSR, the Nigelkirk coefficient of determination ($R^2$) was analyzed, which shows what part of the factors is taken into account during forecasting. It is considered as a universal measure of the relationship of one random variable with others. The coefficient of determination varies from 0 to 1. The closer its value is to "1", the better the multivariate regression model. The coefficient of determination in the proposed mathematical model of the RRChRSR is $R^2$=0.987 (in Statistica 10.0 program R?= .98776607 (Fig. 2)). So, in our case, 98.7% of the factors are taken into account in the model for predicting the risk of ChRS recurrence.

The coefficient of determination indicates how well the obtained observations confirm the mathematical model.

## DISCUSSION

The use of the mathematical model proposed by us, which takes into account possible risk factors for the development of ChRS recurrence, provides the possibility of early prediction of potential complications and the probability of disease relapse. This, in turn, contributes to early diagnosis and the choice of more effective and less harmful methods of ChRS treatment.

The results of our research closely similar European studies conducted earlier. For example, you can take the SNOT-22 questionnaire, which includes 22 questions, each of which is evaluated on a 5-point scale (from 0 to 5 points depending on the degree of manifestation of symptoms), which helps to assess the quality of life and complaints of patients with ChRS [16]. Traditionally, the most pronounced symptoms of the disease are impaired nasal breathing, discharge from the nasal cavity, impaired perception of smells, pain in the face [17].

One of the modern methods of ChRS treatment is functional endoscopic sinus surgery (FESS), which is based on the principles of maximum preservation of the functional anatomy of the nasal cavity. This contributes not only to faster recovery, reducing the number of postoperative complications, but also to improving the quality of life of patients during the entire postoperative period [18]. Functional endoscopic sinus surgery (FESS) is currently the most effective treatment for drug-refractory chronic sinusitis, with symptomatic improvement reported in approximately 90% of patients [19]. However, despite the high efficiency of FESS, postoperative complications and disease recurrences requiring reoperation are still observed in 18% of patients during long-term follow-up [11]. Therefore, the application of the mathematical model developed by us creates the possibility of reducing the number of ChRS recurrences, and the development of postoperative therapy algorithms, based on the results of the formula, will be based on the further prevention of the development of the progression of the disease.

Based on the obtained results, including the joint influence of socio-economic and medical-biological factors in patients with ENT diseases, it will be possible to use a mathematical model for the design of an information-diagnostic system for evaluating and predicting ChRS recurrences. In the following studies, it is necessary to conduct ROC analysis to determine the sensitivity, specificity, and accuracy of the proposed mathematical model for predicting ChRS recurrences.

## CONCLUSIONS

1. The proposed mathematical model, which takes into account risk factors for the development of ChRS recurrence, makes it possible to predict potential complications and the possibility of recurrences of the disease in advance.
2. This model will make it possible to reduce the number of ChRS recurrences and to develop algorithms for postoperative therapy with the aim of further prevention of disease progression.
3. In the future, the obtained results can be used to design an information-diagnostic system for evaluating and predicting the recurrence of ChRS, which develops as a result of the joint influence of a number of socio-economic and medical-biological factors in patients with ENT diseases.

## REFERENCES


1. Beule A. Epidemiology of chronic rhinosinusitis, selected risk factors, comorbidities, and economic burden. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2015; 14:11.
2. Hirsch AG, Yan XS, Sundaresan AS et al. Five-year risk of incident disease following a diagnosis of chronic rhinosinusitis. Allergy. 2015; 70: 1613-21.
3. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. Vital Health Stat. 2009;10242: 1-157.
4. Jarvis D, Newson R, Lotvall J et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012;67(1): 91-8.
5. Kim YS, Kim NH, Seong SY et al. Prevalence and risk factors of chronic rhinosinusitis in Korea. Am J Rhinol Allergy. 2011;25(3):117-21.
6. Hamilos DL. Chronic rhinosinusitis: Epidemiology and medical management. J Allergy Clin Immunol. 2011;128(4):693-707. doi: 10.1016/j.jaci.2011.08.004.
7. Wahid NW, Smith R, Clark A et al. The Socioeconomic Cost of Chronic Rhino-sinusitis Study. Rhinology. 2020. doi: 10.4193/ rhin19.424.
8. Lourijsen ES, Fokkens WJ, Reitsma S. Direct and indirect costs of Dutch adult patients with Chronic Rhinosinusitis with nasal polyps. Rhinology. 2020;58(3):213-17. doi: 10.4193/rhin19.468.
9. Ovchinnikov AYu, Ponyakina MA, Kolbanova IH. Sinusitis: clinical and epidemiological analysis. Consillium medicum. 2005;7:10.
10. Sakovich AR. Sinusitis: clinical and epidemiological analysis. Military medicine. 2009; 3.
11. Hopkins C, Philpott C, Crowe S et al. Identifying the most important outcomes for systematic reviews of interventions for rhinosinusitis in adults: working with Patients, Public and Practitioners. Rhinology. 2016; 54(1):20-6. doi: 10.4193/Rhin15.199.
12. Musiienko V, Sverstiuk A, Lepyavko A et al. Prediction factors for the risk of diffuse non-toxic goiter development in type 2 diabetic patients. Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiegothis link is disabled. 2022;50(296): 94–98.
13. Musiienko V, Marushchak M, Sverstuik A et al. Prediction Factors For The Risk Of Hypothyroidism Development In Type 2 Diabetic Patients. PharmacologyOnLine. 2021; 3: 585-594.

14. Junqin Bai, Huang JH, Price CPE et al. Prognostic factors for polyp recurrence in chronic rhinosinusitis with nasal polyps. Journal of Allergy and Clinical Immunology. 2022. doi: 10.1016/j.jaci.2022.02.029.
15. Akiyama K, Samukawa Ya, Hoshikawa H. Early postoperative endoscopic score can predict the long-term endoscopic outcomes in eosinophilic chronic rhinosinusitis (ECRS) patients, Brazilian Journal of Otorhinolaryngology. 2022. doi: 10.1016/j.bjorl.2021.12.003.
16. Abdalla S, Alreefy H, Hopkins C. Prevalence of sinonasal outcome test (SNOT-22) symptoms in patients undergoing surgery for chronic rhinosinusitis in the England and Wales National prospective audit. Clin Otolaryngol. 2012;37(4):276-82.
17. Dietz de Loos D, Hopkins C, Fokkens W. Symptoms of chronic rhinosinusitis with and without nasal polyps. Clin Transl Allergy. 2013;3:02.
18. Mandal S, Sharma A. Effect on Quality Of Life of Patients Before and After Functional Endoscopic Sinus Surgery. Indian J Otolaryngol Head Neck Surg. 2019; 71(3): 2065-2071. doi: 10.1007/s12070-018-1471-8.
19. Tan BK, Chandra RK. Postoperative prevention and treatment of complications after sinus surgery. Otolaryngol Clin North Am. 2010; 43(4): 769-79. doi: 10.1016/j.otc.2010.04.004.

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ORIGINAL ARTICLE

# MICROBIOLOGICAL FEATURES OF *STAPHYLOCOCCUS* ASSOCIATED WITH COMPLICATIONS OF DENTAL IMPLANTATION

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## ABSTRACT

**The aim:** To describe microbiological features of the *Staphylococcus spp*. involved in complications of dental implantation.

**Materials and methods:** The main method was bacteriological. Indentification of the obtained isolates was done using commercially available test kits. Adhesive properties were evaluated using Brillis technique. Biofilm-forming ability was studied according to Christensen et al. Antimicrobial susceptibility testing was done following EUCAST recomendations.

**Results:** There were 26 smears taken from the peri-implant area and gingival pockets of 12 patients. We obtained 38 isolates. Most of the patients were positive for Streptococcus spp. – 94% and Staphylococcus spp. – 90%. Among the representatives of Staphylococcus spp., the initial share of clinical isolates was S. aureus (34.21%) with inherent coagulase-positive properties. Coagulase-negative pathogens accounted for 65.79% of *Staphylococcus spp*., among them *S. epidermidis*, *S. hominis*, *S. warneri* were the main. All obtained isolates had typical properties, but appearance of small colonial variants of S. aureus was also recorded. Antimicrobial susceptibility testing was performed in 100% of cases. Among 13 isolates of *S. aureus* there were 2 cultures resistant to cefoxitin, i. e. methicillin-resistant by phenotype. Clinical isolates of *S. aureus*, colonizing peri-implant tissues in infectious-inflammatory complications of dental implantation, also had high adhesive and biofilm-forming properties. Clinical isolates of S. epidermidis an average ability to form biofilms.

**Conclusions:** There is a prooved direct correlation between biofilm-forming ability and adhesive properties in highly biofilm-forming clinical isolates involved in the occurrence of purulent-inflammatory complications in peri-implant site.

**KEY WORDS:** dental implantation, biofilm, adhesiveness, infectious complications

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## INTRODUCTION

According to the current data, more than 70% of stomatological patients require dental orthopedic care. Dental implantation is performed in almost of 20% of the patients. Although significant success of the procedure, the frequency of complications associated with surgery and occur in early postoperative period or in the long-term after implantation remains high [1-3].

Dental implantation allows to expand indications for using of fixed or removable orthopedic constructions, sometimes becoming an irreplaceable method of rehabilitation of stomatological patients [4, 5]. Along with high restoration of masticatory efficiency and aesthetics, the widespread application of odontoimplantation is accompanied by increasing amount of complications occuring on different stages of the procedure.

Inflammatory complications after the surgical stage of dental implantation occur in 1-5% of patients [3, 6]. Complications after odontoimplantation arise due to the immune response to the installed implant, however, probably a key role belongs to microbial factor. The etiological role of a defenite of microorganisms remains unexplored, but there is a link between infectious and inflammatory processes with opportunistic oral microbiota and disturbances in normobiosis because of poor hygiene on the patient`s side and and inadequate compliance with the principles of aseptic measures during implantation [2, 7, 8].

A complex approach of prevention and treatment of complications associated with odontoimplantation comprises both, parenteral and topical application of antimicrobial agents [8, 9]. An important medical problem that deprave curative and preventive efforts is infectious origin followed by inflammation process in the site of odontoimplantation. A subsistence of pathogens resistant to the major antimicrobial agents many times increases the frequency of theraputical failure at the initial stages of treatment and significantly boosts the risk of infectious inflammatory complications The situation is facilitated by the ability of microbes to pro-

duce exopolysaccharide matrix with the formation of a «biofilm» providing unimpeded persistence of infection and elimination failures [3, 5, 9].

## THE AIM

The study was aimed to determine the etiological structure of complications associated with dental implantation; to study the biological (morphological, tinctorial, cultural, adhesive, biofilm-forming) properties of the *Staphylococcus spp.* assosiated with odontoimplantation complications and its sensitivity to antimicrobial agents.

## MATERIALS AND METHODS

The study was conducted in the scientific laboratory of the department of microbiology, virology, immunology, and epidemiology. It was planned and designed in accordance with Helsinki Declaration. Patients have signed the Patient Informed Consent Form. Previously, the study was approved by the Bioethics Committee of the University (№8, 17.10.2018) [10].

The collection of clinical samples was performed in chair-side manner. For the selection of aerobic and facultative anaerobic microbiota biopsy specimens of the oral mucosa from the area of the installed implant and peri-implant pocket were taken by a sterile thin cotton swab and its seepage. Obtained samples ex tempore were brought in microbiological examination.

Primary inoculation of the specimens was carried out after its threefold double dilution in 1 ml of sterile saline with subsequent inoculation in standard set of culture mediums. The cultivation was done under aerobic conditions and in the presence of 5% – 10% $CO_2$. For selective isolation of *Staphylococcus spp.* mannitol-salt agar (bioMerieux, France) was used. Columbian agar with 5% sheep blood (bioMerieux, France) was used for non-selective cultivation and assessment of hemolytic activity. Standard kit also included selective agar for *Enterococcus* (bioMerieux, France), MacConkey agar (BioMerieux, France) and Sabouraud dextrose agar with chloramphenicol (Hi-Media, India). Inoculated Petri dishes were incubated in thermostat during 24-72 hours under 37$^0$C [11].

Smear from obtained colonies underwent microscopical examination for assessment of their tinctorial and morphological properties. Cultural properties of microorganisms were evaluated by the peculiarities of the growth on culture mediums, followed by the selection of pure cultures.

Colonies of *Staphylococcus spp.* was tested for ability to coagulate rabbit plasma (BioLife, Italy) and exhibit catalase activity (10% hydrogen peroxide). Identification of *Staphylococcus spp.* was performed using STAPHYtest 16 (ErbaLachema, Czech Republic) containing follows indicators of biochemical activity: urease, arginine, ornithine, β- galactosidase, β- glucuronidase, esculin, nitrates, phosphatase, galactose, sucrose, trehalose, mannitol, xylose, maltose, mannose, lactose.

Antimicrobial susceptibility testing was performed in accordance with EUCAST 2021, version 11.0 on Muller-Hinton agar (bioMerieux, France). The follows disks were used: benzylpenicillin 1 OD, cefoxitin 30 mcg, norfloxacin 10 mcg, ciprofloxacin 5 mcg, levofloxacin 5 mcg, moxifloxacin 5 mcg, ofloxacin 5 mcg, amikacin 30 mcg, gentamicin 10 mcg, tobramycin 10 mcg, erythromycin 15 mcg, clindamycin 2 mcg, tetracycline 30 mcg, tigecycline 15 mcg, minocycline 30 mcg, linezolid 10 mcg, rifampicin 5 mcg, trimethoprim/ sulfamethoxazole 25 mcg [12-14]. The obtained data were entered into the table of results.

To determine the adhesive properties of *Staphylococcus spp.*, the method of Brilis V. I. et al. was applied using commercially available sheep erythrocytes. The following indicators were determined: AAI – average adhesion index, that is the average number of microbial cells attached to the surface of one erythrocyte by counting at least 25 erythrocytes, considering no more than five of them in one field of view; CEP – coefficient of erythrocyte participation, that is the percentage of erythrocytes that have adhered microbes on their surface; AIM – the adhesion index of the microorganism, the average number of microbial cells on the erythrocyte, taking into account only erythrocytes involved in the adhesive process. The formula for calculating of AIM = (AAI / CEP) x100. Microbes were considered non-adhesive at AIM≤1.75, low-adhesive – from 1.76 to 2.5, medium-adhesive – from 2.51 to 4.0, high-adhesive – at AIM above 4.00 [15].

To study biofilm-producing properties of *Staphylococcus aureus*, the obtained isolates were proceeded according to Christensen et al. in microtiter plate test. Biofilms were grown in meat-peptone broth. For this purpose, an overnight culture was diluted with nutrient broth 100 times to a turbidity of 0.5 according to the McFarland standard, so the concentration was $10^6$ CFU/ml. Aliquots of bacterial suspension (0.2 ml) were inoculated into the wells of sterile flat-bottomed 96-well polystyrene tablet (Corning, USA) and overnight incubated at 37$^0$C. After incubation, liquid was removed; the wells were washed with phosphate buffer (pH 7.2 – 7.3) and stained by 1% crystal violet for 4 minutes. After washing, the microtiter plates were dried at room temperature and the level of dye absorption was evaluated on the spectrophotometer HumanReader (Germany) at

wavelength 620 nm. For negative control non-inoculated meat-peptone broth was used. Biofilm-producing ability was evaluated as optical density (OD) values, so if OD<0.120 it was assessed as low, if OD = 0.221-0.39 as average, and if OD > 0.240 as high [16-18]. The results were brought in the table.

The Microsoft Office Excel 2010® with customizations was used for statistical data processing. Normality data distribution was evaluated with the Shapiro-Wilk test. For quantitative data with non-normality distribution Median, % and its interquartile range – Me (25%; 75%) were used. The Spearmen test was used for comparison of independent samples by qualitative data. The Kruskal-Wallis test was used for multiplying comparisons of quantitative data; it was completed by the Mann-Whitney U-test. The results of the experiments were statistically significant at $p<0.05$ [19].

## RESULTS

The study involved 12 patients with purulent-inflammatory complications after dental implantation. There were 26 smears taken from the peri-implant area and gingival pockets of patients.

We obtained 38 isolates of microorganisms. Most of the patients were positive for *Streptococcus spp.* – 94% and *Staphylococcus spp.* – 90%. In contrast, gram-negative pathogens were identified much less frequently, the dominant representatives were *Pseudomonas spp., Acinetobacter spp.* and *Escherichia spp.* From all patients enrolled in the study we isolated mixed culture with two or more species. It should be noted that 3-4 component associations of opportunistic pathogens were identified in 60% of cases. The etiology of peri-implantation complications is presented in table I.

Among the representatives of *Staphylococcus spp.*, the initial share of clinical isolates was *S. aureus* (34.21%) with inherent coagulase-positive properties. Accordingly, coagulase-negative pathogens accounted for 65.79% of the total number of isolates *Staphylococcus spp.*, among them *S. epidermidis, S. hominis, S. warneri* were the main (Table II).

All obtained isolates had typical morphological, tinctorial, cultural and biochemical properties, but appearance of small colonial variants of *S. aureus* was also recorded (Fig. 1). The last were characterized by growth on blood agar after 48-72 hours of incubation without manifestations of hemolytic properties. Auxotrophy to hemin was detected using the growth factor disc test.

Antimicrobial susceptibility testing was performed in 100% of cases. All isolates were phenotypically tested for methicillin resistance. It is well-known that a test with cefoxitin 30 mcg may predict reliably presence of *mecA* or *mecC* genes, and screening for BORSA (borderline oxacillin resistant *S. aureus*) using oxacillin MIC is not recommended by the EUCAST for routine use [13, 14]. Therefore, among 13 isolates of *S. aureus* there were 2 cultures resistant to cefoxitin, i. e. methicillin-resistant by phenotype. These cultures were obtained from different patients. Such isolates also showed resistance to erythromycin, gentamicin, norfloxacin and ciprofloxacin, chloramphenicol, and trimethoprim-sulfamethoxazole. The results of the antimicrobial susceptibility testing of *Staphylococcus spp.* are given in table III. The best results were registered for the third-generation aminoglycosides, the third-generation fluoroquinolones, linezolid, rifampicin, tetracyclines and lefamulin.

In our study, there were only 61.53 (53.73-79.60) % isolates sensitive to all beta-lactams (including unprotected penicillins). At the same time, it should be mentioned that even susceptible culture may withstand an impact of oral drugs *in vivo*. Those isolates of *Staphylococcus spp.* that showed resistance to benzylpenicillin, that is due to the ability to produce penicillinases, were also resistant to phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin.

Among all, 84.62% of isolates showed susceptibility to cefoxitin. Such cultures were sensitive to penicillins in combination with beta-lactamase inhibitors (if not sensitive to benzylpenicillin), isoxazolpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin, most cephalosporins (cefaclor, cefadroxil, cefalexin, cefazolin, cefepime, cefotaxime, cefpodoxime, ceftriaxone, cefpodoxime) and carbapenems (ertapenem, imipenem, meropenem, meropenem-vaborbactam).

There were 69.23% of isolates susceptible to screening with erythromycin, so they were also sensitive to azithromycin, clarithromycin and roxithromycin. Resistant isolates were sensitive to clindamycin; however, the appearance of the D-phenomenon was recorded twice (Fig. 2).

There were 84.62% of isolates sensitive to screening with norfloxacin; resistant ones were individually tested for susceptibility to ciprofloxacin, ofloxacin, levofloxacin and moxifloxacin and showed a positive result in most cases.

The sensitivity to screening with tetracycline was 92.31%, such isolates directly were defined as susceptible to tetracycline, doxycycline, and minocycline. The only isolate that showed resistance to tetracycline was sensitive to minocycline. It is known that strains resistant to tigecycline are extremely rare, and in our study, there were no such isolates.

We found that clinical isolates of *S. aureus* colonizing peri-implantation site in case of odontoimplantation, had high adhesive properties (Fig. 3).

**Table I.** Etiological structure of purulent-inflammatory processes associated with dental implantation

| Genera | Number of isolates, n | Proportion of isolates, % |
|---|---|---|
| *Staphylococcus spp.* | 13 | 34,21 |
| *Streptococcus spp.* | 14 | 36,84 |
| *Enterococcus spp.* | 3 | 7,90 |
| *Pseudomonas spp.* | 3 | 7,90 |
| *Acinetobacter spp.* | 1 | 2,63 |
| *Escherichia spp.* | 2 | 5,26 |
| *Candida spp.* | 2 | 5,26 |
| Overall | 38 | 100 |

**Table II.** The species composition of the *Staphylococcus* genus responsible for peri-implant complications

| Species | Number of isolates, n | Proportion of isolates, % |
|---|---|---|
| *Staphylococcus aureus* | 7 | 53,85 |
| *Staphylococcus epidermidis* | 3 | 23,08 |
| *Staphylococcus hominis* | 1 | 7,69 |
| *Staphylococcus warneri* | 2 | 15,38 |
| Overall | 13 | 100 |

**Fig. 1.** Small colony variants of *Staphylococcus aureus* together with wild-type colonies on Colombian agar with 5% sheep blood, 72 h

The AIM of *S. aureus* was 4.79 (1.10). It should be noted that the AAI was 3.08 (0.99). Moreover, more than half of erythrocytes 64.8 (15.5) % contained adhered staphylococci on their surface. It was found that coagulase-negative *Staphylococcus* spp. had lower adhesive properties compared to coagulase-positive representatives. The isolate of *S. warneri* had medium adhesive properties and the highest indices among studied coagulase-negative staphylococci. AIMs for *S. epidermidis, S. hominis, S. warneri* were 1.76 (0.58), 1.76 (0.33) and 3.02 (0.64), respectively.

Clinical isolates of *S. aureus,* colonizing peri-implant tissues in infectious-inflammatory complications of dental implantation, also had high biofilm-forming properties. The degree of dye absorption by biofilms of *S. aureus* was 0.293 (0.13) OD, moreover, the indicator increased in 1.1 time a day, the optical density of biofilms reached 0.307 (0.11) on the 2-nd day of cultivation.

Clinical isolates of *S. epidermidis* on the first day of cultivation had an average ability to form biofilms, so 0.224 (0.08) OD, it increased to a high level after 48 hours of incubation and reached 0.248 (0.07) OD.

It was found that *S. warneri* showed the average biofilm-forming properties. The degree of dye absorption by their biofilms on the first day was 0.127 (0.05) OD and almost did not change after 48 hours – 0.128 (0.03) OD.

Biofilm formation and microbial adhesion depend on many variables, including, microbiological peculiarities

**Table III.** Chemotherapeutic susceptibility of *Staphylococcus spp.* obtained from patient with implication of dental implantation (disc-diffusion method, n = 13)

| № | Disc with antibiotic | Proportion of susceptible isolates, % | Growth inhibition zone – Me (95%CI), mm |
|---|---|---|---|
| | | Susceptibility to β-lactam agents | |
| 1 | Benzylpenicillin 1 IU | 30.77 | 14 (10-29) |
| 2 | Cefoxitin 30 mcg | 84.62 | 29 (28-32) |
| | | Susceptibility to fluoroquinolones | |
| 3 | Norfloxacin 10 mcg | 84.62 | 21 (18-22) |
| 4 | Ciprofloxacin 5 mcg* | 84.62 | 34 (12-36) |
| 5 | Ofloxacin 5 mcg* | 100.00 | 32 (13-36) |
| 6 | Levofloxacin 5 mcg* | 100.00 | 32 (28-34) |
| 7 | Moxifloxacin 5 mcg* | 100.00 | 32 (28-34) |
| | | Susceptibility to aminoglycosides | |
| 8 | Gentamycin 10 mcg | 92.31 | 22 (21-22) |
| 9 | Tobramycin 10 mcg | 100.00 | 22 (21-23) |
| 10 | Amikacin 30 mcg | 92.31 | 22 (21-23) |
| | | Susceptibility to macrolides | |
| 11 | Erythromycin 15 mcg | 69.23 | 22 (21-24) |
| 12 | Clindamycin 2 mcg | 84.62 | |
| | | Susceptibility to tetracyclines | |
| 13 | Tetracycline 30 mcg | 92.31 | 23 (22-24) |
| 14 | Tigecycline 15 mcg | 100.00 | 23 (23-25) |
| | | Susceptibility to oxazolidines | |
| 15 | Linezolid 10 mcg | 100.00 | 28 (28-35) |
| | | Miscellaneous agents | |
| 16 | Chloramphenicol 30 mcg | 69.23 | 21 (18-23) |
| 17 | Rifampicin 5 mcg | 100.00 | 31 (29-32) |
| 18 | Lefamulin 5 mcg | 100.00 | 27 (24-29) |
| 19 | Trimethoprim/ sulfamethoxazole 25 mcg | 69.23 | 22 (21-22) |

* Value refers to the growth retardation zone of only those isolates that were resistant to relevant screening

of the pathogen, physical and chemical properties of the surface, environmental factors, gene expression, etc. [16-18]. In addition, the study found a strong link between the ability of the dominant pathogens of peri-implantation complications to form biofilms and their adhesive properties. The presence of a direct correlation between these processes in *S aureus* isolated from patients with infectious-inflammatory complications of dental implantation has been proved. Spearman correlation coefficient for these values was +0.75, indicating a close relationship between biofilm formation and adhesion of pathogens.

Even though the most representatives of coagulase-negative staphylococci, particularly *S. epidermidis,* had low adhesion properties and medium ability to form biofilms, a direct correlation between these processes was also found. However, Spearman criterion between adhesion and biofilm formation of clinical isolates of *S. epidermidis* was slightly lower than in coagulase-positive staphylococci and was +0.65.

## DISCUSSION

Dental implantations have a significant impact on the microbial profile of the oral cavity. The results of the study confirm the data on the microbial heterogeneity of the peri-implant area in case of infectious-inflammatory complications of dental implantation. Moreover, most microbes are commensals of the oral cavity, that can cause infectious-inflammatory processes of tissues in osteo-integrated implant under certain conditions [5].

Dental implants are routinely used in dentistry; but it is important to know and consider the consequences of the microbes responsible for infectious-inflammatory

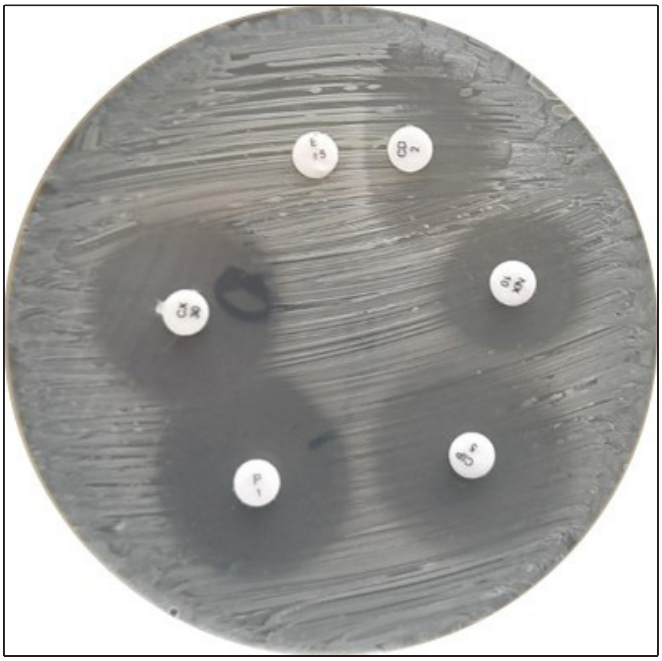

**Fig. 2.** Resistance of *Staphylococcus aureus* to clindamycin, D-phenomenon is presented. Disc-diffusion method for determination of chemotherapeutic sensitivity, 18 h of cultivation.

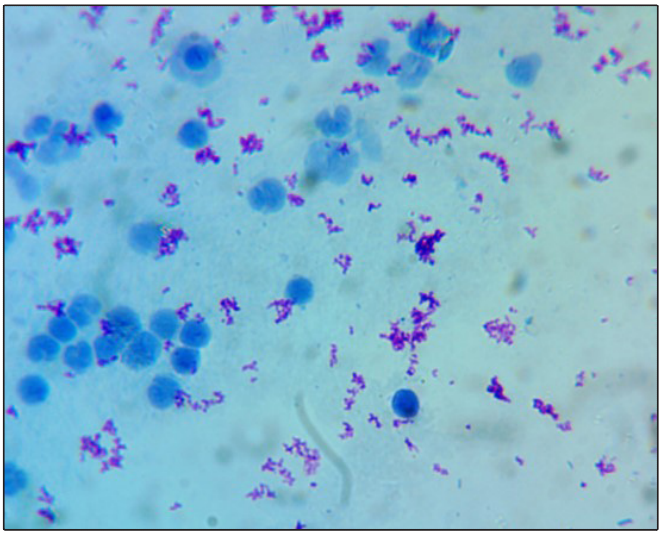

**Fig. 3.** Study of adhesion of *Staphylococcus aureus* on sheep erythrocytes according to Brillis method. Romanovsky-Giemsa staining. Magnification x40.

complications. Due to the significant prevalence of *S. aureus* in infections related to prosthetic biomaterials, particularly dental, and their occurrence in chronic and recurrent infections, this pathogen is considered as an important problem for healthcare [20]. In our study we also confirmed the role of coagulase-negative staphylococci in the pathogenesis of complications of the dental implantation. These data were relevant to the results obtained by Faustova et al. [21].

The previously published literature data indicates that *S. aureus* plays an important role in causing periodontal diseases by forming a biofilm on dental plaque. Studies suggested that

*S. aureus* exhibits a diverse range of pathogenicity. In dental patients, *S. aureus* is translocated from nasal and oral cavity, where it is highly distributed in comparison to other sites of the human body. Kim et al. suggested the cross-infection with multiple strains of *S. aureus* in the dental field, mediated either by contact of effusions, skin, and saliva between dentists and patients or by contact with *S. aureus* floating in the form of aerosols and contaminated medical instruments. The systematic use of antimicrobials is necessary to treat *S. aureus* infections. Dental patients take antibiotics to prevent postoperative primary and secondary infections, the duration of such treatment varies and comprise about 6.9 days [22]. Antibiotic resistance patterns of isolates associated with dental implantation failure were determined by using agar disk diffusion method by Kivanc et al. Analyzed isolates were resistant to 2 or 3 antimicrobials; a multi-drug resistant and methicillin-resistant isolate of Staphylococcus spp. was obtained [23]. Minkiewicz-Zochniak A. et al studied susceptibility to antimicrobials of dental isolates of *S. aureus* using the same method. Their isolates were resistant to cefoxitin 3/33 (9%), gentamycin 5/33 (15.2%), tobramycin 6/33 (18.2%), ciprofloxacin 11/33 (33.3%), levofloxacin 5/33 (15.2%), erythromycin 22/33 (66.6%), clindamycin 18/33 (54.5%), tetracycline 4/33 (12.1%), and trimethoprim/sulfamethoxazole 1/33 (3%). However, all strains were sensitive to linezolid, teicoplanin, and vancomycin. Methicillin resistance was observed in 3/33 strains (9%) [20]. In our study, among 13 isolates of *S. aureus* there were 2 cultures methicillin-resistant by phenotype. The best results were registered for the third-generation aminoglycosides, the third-generation fluoroquinolones, linezolid, rifampicin, tetracyclines and lefamulin. There were 69.23% of isolates susceptible to screening with erythromycin. There were 84.62% of isolates sensitive to screening with norfloxacin; resistant ones were individually tested for susceptibility to ciprofloxacin, ofloxacin, levofloxacin and moxifloxacin and showed a positive result in most cases. The sensitivity to screening with tetracycline was 92.31%, such isolates directly were defined as susceptible to tetracycline, doxycycline, and minocycline. We also didn't have isolates resistant to vancomycin, linezolid and teicoplanin.

In the last years, biofilms are reported to have an important role in human pathology and are responsible for a range of device-related chronic inflammatory conditions, including biofilm-related inflammation [23]. The ability to form a biofilm is associated with the capacity of the microorganism to survive under unfavourable conditions as well as on implanted biomaterials (metals and ceramics etc.). Biofilm formation by *S. aureus* and its

attachment to medical implants and host tissue leads to the establishment of chronic infection. Indeed, *S. aureus* has been recognized as the initial colonizer of dental implants [25]. A prior study reported that bacteria in biofilms found *in vivo* engage in interspecies interactions, which may be important in the establishment of functional microbial communities in vitro [22]. Our clinical isolates of *S. aureus*, colonizing peri-implant tissues in infectious-inflammatory complications of dental implantation, also had high biofilm-forming properties. Clinical isolates of *S. epidermidis* on the first day of cultivation had an average ability to form biofilms, it increased to a high level after 48 hours of incubation. It was found that *S. warneri* showed the average biofilm-forming properties and the degree of dye absorption by their biofilms did not change after 48 hours.

## CONCLUSIONS

1. The etiological structure of purulent-inflammatory complications in peri-implant area includes opportunistic pathogens. The main representatives were gram-positive facultative anaerobes, *Streptococcus spp.* and *Staphylococcus spp.*
2. Clinical isolates of *Staphylococcus spp.* showed high resistance to penicillins and episodic to cefoxitin. Emerging of methicillin-resistant isolates of *S. aureus* warns.
3. Most *Staphylococcus spp.* had high and medium adhesive properties. *S. aureus* showed the highest rates.
4. There is a direct correlation between biofilm-forming ability and adhesive properties in highly biofilm-forming clinical isolates involved in the occurrence of purulent-inflammatory complications in peri-implant site.

## REFERENCES


1. Savchuk O, Krasnov V. Ways to improve the efficacy of orthopedic treatment of patients with severe excessive tooth wear. Georgian Med News. 2021; (311):63-67.
2. Kageyama I, Maeda S, Takezawa K. Importance of anatomy in dental implant surgery. Journal of Oral Biosciences. 2021; 63 (2): 142-152. doi:10.1016/j.job.2021.01.002.
3. Romanos GE, Delgado-Ruiz R, Sculean A. Concepts for prevention of complications in implant therapy. Periodontol 2000. 2019; 81(1): 7-17. doi: 10.1111/prd.12278.
4. Wang H, Liu Y, Li W et al. Microbiota in Gingival Crevicular Fluid Before and After Mechanical Debridement With Antimicrobial Photodynamic Therapy in Peri-Implantitis. Front Cell Infect Microbiol. 2022; 11:777627. doi: 10.3389/fcimb.2021.777627.
5. Fiorellini JP, Luan KW, Chang YC et al. Peri-implant Mucosal Tissues and Inflammation: Clinical Implications. Int J Oral Maxillofac Implants. 2019;34:s25-s33. doi: 10.11607/jomi.19suppl.g2.
6. Kayabasoglu G, Nacar A, Altundag A et al. A retrospective analysis of the relationship between rhinosinusitis and sinus lift dental implantation. Head Face Med. 2014; 10: 53. doi: 10.1186/1746-160X-10-53.
7. Renvert S, Hirooka H, Polyzois I et al. Working Group 3. Diagnosis and non-surgical treatment of peri-implant diseases and maintenance care of patients with dental implants – Consensus report of working group 3. Int Dent J. 2019; 69(2): 12-17. doi: 10.1111/idj.12490.
8. Sahrmann P, Gilli F, Wiedemeier DB et al. The Microbiome of Peri-Implantitis: A Systematic Review and Meta-Analysis. Microorganisms. 2020; 8 (5): 661. doi: 10.3390/microorganisms8050661.
9. Morris S, Cerceo E. Trends, Epidemiology, and Management of Multi-Drug Resistant Gram-Negative Bacterial Infections in the Hospitalized Setting. Antibiotics (Basel). 2020; 9 (4): 196. doi: 10.3390/antibiotics9040196.
10. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013; 310 (20): 2191-4. doi: 10.1001/jama.2013.281053.
11. Carroll KC, Pfaller MA, Landry ML et al. Manual of Clinical Microbiology. 2-nd ed. ASM Press. 2019; 1: 2283.
12. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0, 2021. http://www.eucast.org. [date access 17.12.2022]
13. The European Committee on Antimicrobial Susceptibility Testing. Intrinsic resistance and unusual phenotypes. Expert rules. Version 3.3, 2021. http://www.eucast.org. [date access 17.12.2022]
14. The European Committee on Antimicrobial Susceptibility Testing. EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/ or epidemiological importance. Version 2, 2017. http://www.eucast.org. [date access 17.12.2022]
15. Semenko NM, Stepanskiy DO, Smotrova NG et al. Metody vyvchennya adheziyi mikroorhanizmiv [Investigation methods of adhesion of microorganisms]. Morphologia. 2016; 10 (4): 7–11. doi: 10.26641/1997-9665.2016.4.7-11. (in Ukrainian)
16. Águila-Arcos S, Álvarez-Rodríguez I, Garaiyurrebaso O et al. Biofilm-Forming Clinical Staphylococcus Isolates Harbor Horizontal Transfer and Antibiotic Resistance Genes. Front Microbiol. 2017; 8: 2018. doi: 10.3389/fmicb.2017.02018.
17. Høiby N, Bjarnsholt T, Moser C et al. ESCMID Study Group for Biofilms and Consulting External Expert Werner Zimmerli. ESCMID guideline for the diagnosis and treatment of biofilm infections 2014. Clin Microbiol Infect. 2015 ;21(1):S1-25. doi: 10.1016/j.cmi.2014.10.024.

18. Cruz CD, Shah S, Tammela P. Defining conditions for biofilm inhibition and eradication assays for Gram-positive clinical reference strains. BMC Microbiol. 2018; 18(1): 173. doi: 10.1186/s12866-018-1321-6.
19. Yadav SK, Singh S, Gupta R. Biomedical Statistics. A Beginner's Guide. 1st ed. Springer, Singapore. 2019. p. 342.
20. Minkiewicz-Zochniak A, Jarzynka S, Iwańska A et al. Biofilm Formation on Dental Implant Biomaterials by Staphylococcus aureus Strains Isolated from Patients with Cystic Fibrosis. Materials (Basel). 2021; 14(8): 2030. doi: 10.3390/ma14082030.
21. Nazarchuk OA, Faustova MO. Mikrobiolohichne doslidzhennya vlastyvostey hrampozytyvnykhzbudnykiv infektsiyno-zapal'nykh peryimplantatsiynykh uskladnen' [The microbiological investigation of the properties of gram-positive pathogens of infectious and inflammatory periimplantation complications]. Bulletin of Vinnytsia National Medical University. 2017: 21(2): 392-396. (in Ukrainian)
22. Bosch ME, Bertrand BP, Heim CE et al. Staphylococcus aureus ATP Synthase Promotes Biofilm Persistence by Influencing Innate Immunity. mBio. 2020; 11(5): e01581-20. doi: 10.1128/mBio.01581-20.
23. Caldara M, Belgiovine C, Secchi E, Rusconi R. Environmental, Microbiological, and Immunological Features of Bacterial Biofilms Associated with Implanted Medical Devices. Clin Microbiol Rev. 2022; 35(2): e0022120. doi: 10.1128/cmr.00221-20.
24. Kivanç AK, Güler B, Kivanç M, Kirzioglu Z. Determination of Staphylococcus species of dental plaque biofilms and their antibiotic susceptibility. Oral Health Dent Manag. 2016; 15: 8. doi:10.4172/2247-2452.C1.043.
25. Heller D, Helmerhorst EJ, Gower AC et al. Microbial Diversity in the Early In Vivo-Formed Dental Biofilm. Appl Environ Microbiol. 2016; 82(6): 1881-8. doi: 10.1128/AEM.03984-15.

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ORIGINAL ARTICLE

# COGNITIVE FUNCTIONS IN CHILDREN WITH TYPE I DIABETES

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## ABSTRACT

**The aim:** To assess the patterns and severity of cognitive impairment in children with type 1 diabetes as well as its association with disease onset and poor glycemic control.

**Materials and methods**: We assessed higher mental function and screened for psychosocial functioning in 60 children with type 1 DM and 60 age-matched control using the Modified Mini-Mental State examination and Pediatric Symptoms Checklist and its relation with age, gender, socioeconomic status, age at the onset of disease, duration of disease, HbA1c level, frequency of diabetic ketoacidosis and hypoglycemic attacks and type of treatment.

**Results**: Diabetic patients demonstrated a lower Modified Mini-Mental State examination score than controls (25.12±4.58 versus 30.08±2.95) with a highly significant difference. Furthermore, the mean Pediatric symptoms checklist score in patients was 39.08±8.18 which was much lower than that of controls 54.42±6.0 with a highly significant difference.

**Conclusions**: There is neurocognitive impairment in diabetic children compared to non-diabetics, and poor glycemic control whether hyper or hypoglycemia could affect their cognition and mental health.

**KEY WORDS:** Cognition, psychological score, Diabetes mellitus, neuronal changes

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## INTRODUCTION

Chronic medical illnesses can affect the neurodevelopment and cognitive function of the brain leading to educational, occupational, and mental health disruption from children into adulthood, as the neural development extends from the early embryonic life through adolescence [1, 2]. One of the most common chronic illnesses that affect children is type 1 diabetes mellitus (DM), it affects around 171 million people worldwide, and this number is estimated to be doubled by 2030 [3]. The incidence of type 1 diabetes in children is about 0.1 – 57.6 per 100,000 [4]. Type 1 DM has been linked to alteration of hypothalamus-pituitary-adrenal axis regulation and serotonergic neuronal changes [5]. Although the exact pathology underlying this diabetic encephalopathy is not completely understood, chronic vascular and metabolic changes may be the cause [6]. The nature and extent of brain function and structure disruption are influenced by multiple factors, including age at which diabetes began, duration, and extent of blood sugar control as both hyper- and hypoglycemia can affect brain function, comorbid conditions like hypertension, micro-, and macrovascular complications [7, 8]. In hypoglycemia, the medial temporal region in the brain especially the hippocampus may be affected leading to learning and memory function impairment [5, 9]. While a prolonged and higher level of hyperglycemia correlated with white matter volume decrement within the parietal lobe in the pediatric age group [10]. As a consequence, children with Type 1 DM have somewhat lower cognitive performance across most cognitive domains; principally intelligence, memory, executive function, attention, and psychomotor speed [11-13]. Hypoglycemia is defined by a blood glucose level of 3 mmol/l or less, warning signs such as tremor, weakness, confusion, poor attention followed by a disturbing level of consciousness, convulsive seizures, coma, and even death can happen in extreme situations. Some diabetic patients experience hypoglycemia unawareness; a condition that resulted from recurrent episodes of hypoglycemia leading to loss of sensations and failure to experience the physiological warning signs of hypoglycemia, so measures to correct hypoglycemia are not taken leaving them at risk of having severe episodes. In addition, nocturnal hypoglycemia in these children may have an impact on the brain and cognitive functioning [14, 15]. Hyperglycemia is blood sugar level higher than 11.1 mmol/L (200 mg/dL), and 14 mmol/l or above is a level of symptoms may start. Poor regimen, non-compliance, as well as acute illness,

or any stressful condition can lead to frequent episodes of hyperglycemia. Hyperglycemia can lead to serious and devastating complications (e.g., nephropathy, neuropathy, and retinopathy,) in addition to diabetic ketoacidosis (DK), which may be complicated by cerebral edema, coma, and possibly death. 10-25% of affected children with DK experience chronic central nervous system morbidity [15-17]. It is thought that there is a continuum of brain damage in DK beyond massive cerebral edema [18]. Even in well-controlled children, there are intermittent oscillations in blood glucose levels. Therefore, it isn't unexpected that children with diabetes are at risk for neurocognitive impairments, which can be transient or chronic depending on the damaging insult [15].

## THE AIM

The aim of this research is to assess the patterns and severity of cognitive impairment in children with type 1 diabetes as well as its association with disease onset and poor glycemic control.

## MATERIALS AND METHODS

A case-control study was conducted on diabetic patients aged 7 to 14 years old, for 8 months period from December 1, 2021 to the end of July 2022. We studied 60 randomly selected patients with type 1 diabetes mellitus who had the disease for at least one month and matched them with the age and gender of 60 apparently healthy controls. Patients with any neurological, autoimmune, or other chronic diseases were excluded from the study. Informed consent was obtained from the parents for recruitment in the study. The local ethics committee at Mustansiriyah University approved the study with (IRB 7/2021 in November 21, 2021). The age of 7 years was chosen to make sure that the child at least passed his first grade of primary school so that he can read, write and know math, and asked about school performance that was required in the mini-mental state and Pediatric Symptoms Checklists. The control group was children not suffering from diabetes or any other significant chronic illness enrolled in the outpatient clinic in the central teaching hospital of pediatric visiting hospital for minor acute illnesses. All cases were subjected to detailed history (from the caregivers and the child) regarding the family income and number (large size family those who are more than 5) [19], age of onset and duration of diabetes, frequency of attacks of hypoglycemia and diabetics ketoacidosis, degree of glycemic control by HbA1c level, type of treatment whether conventional or multiple dose injections. Cognitive functions were assessed by using of a predesigned questionnaire form using the Modified Mini-Mental State (MMMS) examination [20] and Pediatric Symptoms Checklist (PSC) [21]. Modified Mini-Mental State Examination is a screening test for higher mental function and has been modified slightly for use in a children's outpatient clinic. The test, which takes 5 to 10 minutes to be performed, covers a range of cognitive functions including orientation, attention concentration, memory, language, and constructional skill. A pediatric symptoms checklist is a promising method for identifying children in need of psychiatric services through their pediatricians' consultation. The pediatric symptom checklist by [21] is a questionnaire that has been used in pediatric screening. The PSC is a 32- items questionnaire designed to be accomplished by parents of 4-18 years old children in pediatric outpatients' clinics. The PSC takes about 5 minutes to be done and reflects the parent's perceptions of their school-aged child's psychosocial performance. The PSC identifies dysfunctional children as likely to require further psychiatric assessment. PSC consists of 32 symptoms that caregiver's rate as "often, sometimes, or never" present in the child which is given a score of 0,1,2 respectively, then the mean score for all patients was compared to the mean score for the control group.

### STATISTICAL ANALYSIS

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were shown as mean and standard deviation and analyzed with a Student`s t-test. Categorical variables were presented as numbers and percentages and analyzed with the Chi-square test. The receiver operating characteristic curve (ROC- curve) was used to evaluate the efficiency of 3MS and symptom score in the detection of cognitive dysfunction in patients with type 1 DM. Pearson's correlation test was used to explore the possible correlation of MMMS and symptoms with other variables in diabetic patients. A p-value less than 0.05 were considered to specify a statistically significant difference. This study was approved by the local ethics committee at Mustansiriyah University (IRB7/2021 on November 21, 2021). Informed consent was obtained from every participant and his or her parents before being included in the study.

## RESULTS

The patient's mean age was 10.08±2.62 years. Females were more than males (65% of patients were female). In the control group, the mean age was 9.85±1.89

years with 75% of them being females. The income of more than half of the patient's family (61.67%) was fair. The family member of the majority of the patients was ≥5 members (large size family). The mean age of patients at the onset of the disease was 7.7±2.81 years; the disease duration was 3.17±2.79 years. In the majority of patients (73.33%) DKA occurred 0-2 times, while only a minority of patients (6.67%) experienced such complications 6-8 times throughout their illness. Hypoglycemia was reported to occur 0-2 times/month in 58.33% of the patients, while in 20% and 21.67%, hypoglycemia occurred 2-4 times and >4 times, respectively. There was a marked elevation in HbA1c with a mean of 10.49±2.43%. The vast majority of patients use a conventional treatment as shown in table I.

Diabetic patients demonstrated a lower MMMS score than controls (25.12±4.58 versus 30.08±2.95) with a highly significant difference. Furthermore, the mean pediatric symptoms checklist score (PSC) in patients was 39.08±8.18 which was much lower than that of controls (54.42±6.0) with a highly significant difference (table II).

Receiver operating characteristic curve was used for assessing the discriminative value of the MMMS as well as PSC scores in detection of cognitive dysfunction in children with type 1 DM. The area under the curve (AUC) for MMMS score was 0.816, 95% CI= 0.735-0.897, p<0.001. The test's sensitivity and specificity were 83% and 80%, respectively, at a cut-off value of 28.5. The AUC for PSC score was 0.937, 95% CI= 0.88-0.976, p <0.001. The test's sensitivity and specificity were 83% and 88%, respectively at a cut-off value of CALP= 47.5 (fig 1).

Pearson's correlation was used to find out the possible correlation of MMMS and Pediatric symptoms checklist score (PSC) with other continuous variables in diabetic patients. The MMMS score demonstrated a positive significant correlation with age (r= 0.286, p= 0.027), as shown in table III and fig 2.

Generally, the MMMS and PSC score had no association with gender and type of treatment. However, the MMMS score in patients with poor income was 23.61±4.47, which was lower than that of patients with fair income 26.05±4.46 with a statistically significant difference. Moreover, the MMMS score mean in patients experienced 6-8 times DKA was 22.5±2.64, which was significantly lower than that in patients with 3-5 times – 25.43±4.7 or those with 0-2 times – 29.5±4.04 with significant differences. Additionally, patients with >4 hypoglycemia/month had a mean of 32.92±5.93 for symptomatic score which was significantly lower than that of patients with 0-1 times/month – 40.5±7.49 or those with 2-4 times/month – 40.5±9.49 as shown in table IV.

**Table I.** Clinical and Demographic Characteristics of the patients

| Variables | Value |
|---|---|
| Age, years | |
| Mean ± SD | 10.08±2.62 |
| Range | 7-14 |
| Gender | |
| Male | 21(35%) |
| Female | 39(65%) |
| Income | |
| Poor | 23(38.33%) |
| Fair | 37(61.67%) |
| Family size, persons | |
| <5 | 11(18.33%) |
| ≥5 | 49(81.67%) |
| Age at onset, years | |
| Mean ± SD | 7.7±2.81 |
| Range | 1.0-12.5 |
| Disease duration, years | |
| Mean ± SD | 3.17±2.79 |
| Range | 0.25-10 |
| Diabetic ketoacidosis, No. | |
| 0-2 | 44(73.33%) |
| 3-5 | 12(20%) |
| 6-8 | 4(6.67%) |
| Hypoglycemia, No./month | |
| 0-1 | 35(58.33%) |
| 2-4 | 12(20%) |
| >4 | 13(21.67%) |
| HbA1c | |
| Mean ± SD | 10.49±2.43 |
| Range | 6.3-15.0 |
| Type of treatment | |
| Conventional | 56(93.33%) |
| MDI (multiple dialy injection) | 4(6.67%) |

**Table II.** The MMMS and PSC scores in diabetic patients and controls

| Variables | Patients (n=60) | Controls (n=60) | p-value |
|---|---|---|---|
| MMMS score | | | |
| Mean ± SD | 25.12±4.58 | 30.08±2.95 | <0.001 |
| Range | 15-35 | 23-35 | |
| PSC score | | | |
| Mean ± SD | 39.08±8.18 | 54.42±6.0 | <0.001 |
| Range | 22-55 | 42-63 | |

**Table III.** Pearson's correlation of MMMS and symptom score with other variables in patients with type 1 DM.

| Variables | MMMS-score | | Symptom score | |
|---|---|---|---|---|
| | Coefficient | p-value | Coefficient | p-value |
| Age | 0.286 | 0.027 | -0.152 | 0.247 |
| Age at onset | 0.244 | 0.086 | -0.126 | 0.339 |
| Disease duration | 0.087 | 0.508 | -0.006 | 0.966 |
| HbA1c | 0.039 | 0.769 | -0.062 | 0.638 |
| Family member | -0.054 | 0.683 | -0.009 | 0.944 |

**Table IV.** Association of MMMS and PSC scores with gender, type of treatment and income in diabetic patients

| Variables | MMMS-score | Symptom score |
|---|---|---|
| Gender | | |
| Male | 23.95±4.41 | 38.95±8.45 |
| Female | 25.74±4.61 | 39.15±8.15 |
| p-value | 0.150 | 0.928 |
| Type of treatment | | |
| Conventional | 25.16±4.73 | 39.41±8.66 |
| MDI | 24.5±1.73 | 34.5±8.66 |
| p-value | 0.783 | 0.250 |
| Income | | |
| Poor | 23.61±4.47 | 37.7±7.51 |
| Fair | 26.05±4.46 | 39.95±8.56 |
| p-value | 0.044 | 0.304 |
| Family size | | |
| <5 | 25.27±3.38 | 36.64±9.14 |
| ≥5 | 25.08±4.84 | 39.63±7.95 |
| p-value | 0.902 | 0.276 |
| Diabetic ketoacidosis, No. | | |
| 0-2 | 29.5±4.04[a] | 40.14±7.63 |
| 3-5 | 25.43±4.7[a] | 35.08±7.28 |
| 6-8 | 22.5±2.64[b] | 39.5±14.43 |
| p-value | 0.018 | 0.166 |
| Hypoglycemia, No./month | | |
| 0-1 | 25.97±4.51 | 40.5±7.49[a] |
| 2-4 | 24.5±4.91 | 40.5±9.49[a] |
| >4 | 23.38±4.23 | 32.92±5.93[b] |
| p-value | 0.195 | 0.007 |

Note: Different small letters indicate significant difference..

## DISCUSSION

In this study, the mean age of the patients was 10.08±2.62 years, which did not significantly differ from that of Eldamo A. et al., [22] in Egypt which was 11.46±3.21 years. In this study, the mean age at onset of diabetes was 7.7±2.81 years (range from 1-12.5 years) and disease duration was 3.17±2.79 years (range from 0.25-10 years). While in Eldamo A. et al., [22] the mean age of onset of diabetes-studied cases was 8.54±2.26 years (range of 4-13 years) and the duration of illness ranged from 1-8 years. Diabetic patients demonstrated a lower MMMS score with a highly significant difference than controls 25.12±4.58 versus 30.08±2.95. In agreement with Shuba N et al., [23] and Eldamo A. et al., [22] who screened the mental state of patients with type 1 diabetes through the modified mini-mental status examination, show that there was a highly significant difference between diabetic and control groups as regards to MMMS, being lower in diabetic patients. Furthermore, the mean pediatric symptoms checklist score in patients was much lower than that of controls with a highly significant difference: 39.08±8.18 versus 54.42±6.0. similar to results found by Reynolds KA et al., [24] and Eldamo A. et al., [22]: 38.96 ± 4.03 versus 50.26 ± 4.88; respectively. The area under the curve (AUC) for MMMS score was 0.816(81.6%), 95% CI= 0.735-0.897, p<0.001. The test's sensitivity and specificity were 83%, 80% respectively, at a cut-off value of 28.5 in the receiver operating characteristic (ROC) curve used to evaluate the discriminative value of the MMMS and PSC scores. The area under the curve for PSC score was 0.937 (93.7%), 95% CI= 0.88-0.976, p <0.001. The test's sensitivity and specificity were 83%, and 88% respectively at a cut-off value of CALP= 47.5, Nearly the same result s found by Eldamo A. A. et al., [22] shows that the best cut-off point for MMMS to detect cognitive dysfunction in diabetic patients was found ≤ 27 with a sensitivity of 58%, specificity of 76% and AUC of 74.4%. the best cut-off points for PSC to detect cognitive dysfunction in diabetic patients was found ≤ 42 with a sensitivity of 84%, specificity of 92%, and AUC of 96.1%. The MMMS and PSC score in patients with poor income were lower than that of patients with fair income with a significant difference in MMMs scores, this could be explained by poor access to institutional resources e.g., good schools, child care, and medical facilities. Frequent attacks of DKA were associated with more decline in cognitive function in these children in agreement with Ghetti S et al., [25] in the US who states that repeated DKA exposure was associated with lower IQ among diabetic children. Additionally, patients with >4 hypoglycemic attacks /month had a mean of 32.92±5.93 for a symptomatic score which was significantly lower than that of patients with 0-1 times/month or those with 2-4

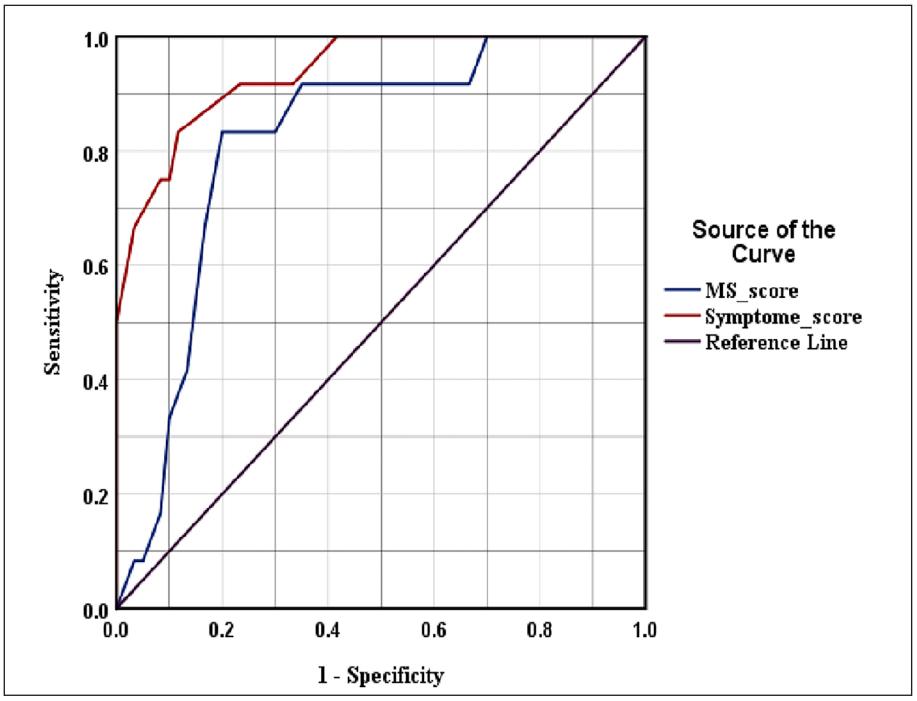


**Fig. 1.** Receiver operating characteristic curve of MMMS and symptom score to detect cognitive dysfunction in patients with type 1 DM

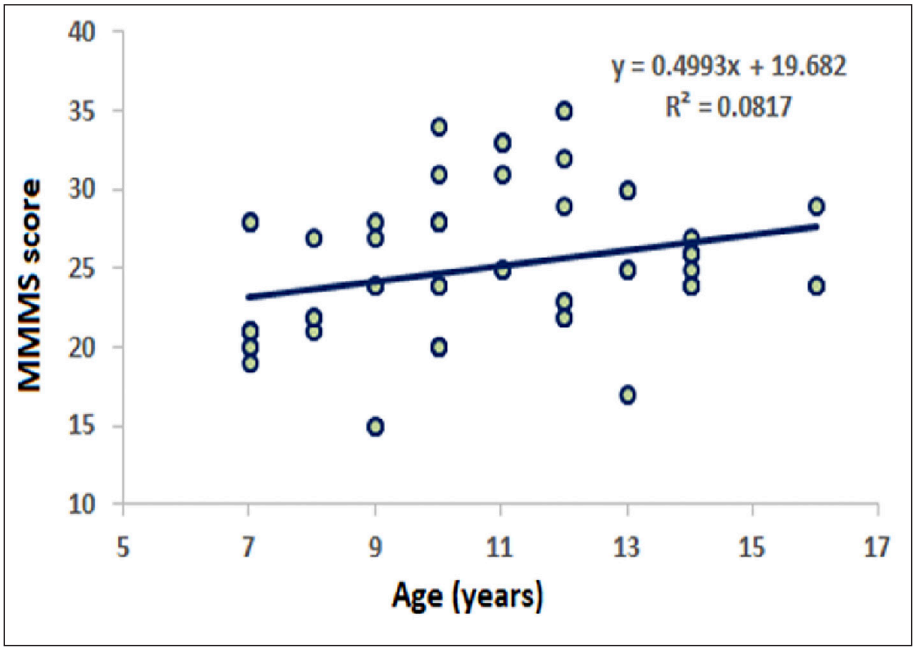


**Fig. 2.** Scatter plot and regression line between age and MMMS score in patients with type 1 DM

times/month results supported by Blasetti A et al., [26] who hypothesized that frequent severe hypoglycemia has a negative effect on cognitive functions of diabetic children. The MMMS score demonstrated a positive significant correlation with age but no correlation with gender, duration of the disease, level of HbA1c, and the number of family members, Shuba N Karan [23] states that diabetics patients showed significantly decreased cognition based on MMMS scores, and there was no significant correlation of age, sex, the duration of diabetes and HbA1C among the diabetics with cognitive function. Ohmann S et al., [5] in Australia found that DM type 1 is associated with cognitive dysfunction in adolescents independent of the degree of metabolic control and the disease duration. These deficits are probably related to early-onset of the disease. These variabilities could be explained by the small sample size and different socioeconomic states.

## CONCLUSIONS

There is cognitive impairment in diabetic children compared to non-diabetics, and poor glycemic control whether hyper or hypoglycemia could affect their cognition and mental health, to optimize the cognitive function of these children; more efforts should be made to normalize their blood glucose level.

## REFERENCES


1. Compas BE, Jaser SS, Reeslund K et al. Neurocognitive deficits in children with chronic health conditions. American Psychologist. 2017;72(4):326-338. doi: 10.1037/amp0000042.
2. Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. Environ Health Perspect. 2000; 108(3): 511-533.
3. McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. Lancet. 2012; 379(9833): 2291-2299.
4. Craig ME, Hattersley A, Donaghue KC. Definition,epidemiology and classification of diabetes in childrenand adolescents.Pediatric Diabetes. 2009; 10(12): 3-12.
5. Ohmann S, Popow C, Rami B et al. Cognitive functions and glycemic control in children and adolescents with type 1 diabetes. Psychol Med. 2010; 40(1): 95-103.
6. Brands AMA, Kessels RPC, De Haan EHF et al. Cerebral dysfunction in type 1 diabetes: Effects of insulin, vascular risk factors and blood-glucose levels. Eur J Pharmacol. 2004; 490(1-3): 159-168.
7. Cameron FJ, Northam EA, Ryan CM. The effect of type 1 diabetes on the developing brain. The Lancet Child & Adolescent Health. 2019; 3(6): 427-436.
8. Northam EA, Lin A. Hypoglycaemia in childhood onset type 1 diabetes-part villain, but not the only one. Pediatr Diabetes. 2010; 11(2): 134-141.
9. Price JC, Kelley DE, Ryan CM et al. Evidence of increased serotonin-1A receptor binding in type 2 diabetes: A positron emission tomography study. Brain Res. 2002; 927(1): 97-103.
10. Perantie DC, Wu J, Koller JM et al. Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. Diabetes Care. 2007; 30(9): 2331-2337.
11. Gaudieri PA, Chen R, Greer TF et al. Cognitive function in children with type 1 diabetes. Diabetes Care. 2008; 31(9): 1892-1897.
12. Perantie DC, Lim A, Wu J et al. Effects of prior hypoglycemia and hyperglycemia on cognition in children with type 1 diabetes mellitus. Pediatr Diabetes. 2008; 9(2): 87-95.
13. He J, Ryder AG, Li S et al. Glycemic extremes are related to cognitive dysfunction in children with type 1 diabetes: A meta-analysis. J Diabetes Investig. 2018; 9(6): 1342-1353.
14. Matyka K, Ford-Adams M, Dunger DB. Hypoglycaemia and counterregulation during childhood. Horm Res. 2002; 57(1): 85-90.
15. Desrocher M, Rovet J. Neurocognitive Correlates of Type 1 Diabetes Mellitus in Childhood. Child Neuropsychol. 2004; 10(1): 36-52.
16. Glaser N. Cerebral injury and cerebral edema in children with diabetic ketoacidosis : could cerebral ischemia and reperfusion injury be involved? Pediatr Diabetes. 2009; (6): 534-541.
17. Marcin JP, Glaser N, Barnett P et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. J Pediatr. 2002; 141(6): 793-797.
18. Cameron FJ, Scratch SE, Nadebaum C et al. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. Diabetes Care. 2014; 37(6): 1554-1562.
19. Dohan BR, Habib S, Abd Khazal A. Nutritional Status of Children and Adolescents with Type1 Diabetes Mellitus in Basra. The Medical Journal of Basrah University. 2021; 39(1): 54-60.
20. Ouvrier RA, Goldsmith RF, Ouvrier S et al. The value of the Mini-Mental State Examination in childhood: a preliminary study. J Child Neurol. 1993; 8(2): 145-148.
21. Jellink MS, Murphy M, Robinson J et al. Pediatric Symptom Checklist: Screening school-age children for psychosocial dysfunction. The Journal of Pediatrics. 1988; 112(2): 201-209.
22. Eldamom AA, Abd-Ellatif AA, Alnabawy AF et al. Cognitive functions in children with type I diabetes. Al-Azhar Journal of Pediatrics. 2019; 22(4): 560-581.
23. Shuba N. Assessment of the cognitive status in diabetes mellitus. J Clin Diagnostic Res. 2012; 6(10): 1658-1662.
24. Reynolds KA, Helgeson VS. Children with diabetes compared to peers: Depressed? Distressed? A meta-analytic review. Ann Behav Med. 2011; 42(1): 29-41.
25. Ghetti S, Kuppermann N, Rewers A et al. Cognitive function following diabetic ketoacidosis in children with new-onset or previously diagnosed type 1 diabetes. Diabetes Care. 2020; 43(11): 2768-2775.
26. Blasetti A, Chiuri RM, Tocco AM et al. The effect of recurrent severe hypoglycemia on cognitive performance in children with type 1 diabetes: A meta-analysis. J Child Neurol. 2011; 26(11): 1383-1391.


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ORIGINAL ARTICLE

# THE ROLE OF OXIDATIVE STRESS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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## ABSTRACT

**The aim:** To study the role of oxidative stress in patients with chronic kidney disease.

**Materials and methods:** By evaluating MDA and GSH in the serum, we tried to find out how oxidative stress affects CKD patients with end-stage renal dysfunction (ESRD). The study included 90 patients with ESRD disease whom were under hemodialysis treatment, and 30 healthy control people.

**Results:** Urea, creatinine, and MDA levels were noticeably greater in ESRD patients compared to controls, but GSH levels were noticeably lower. In conclusion, oxidative stress can cause more problems to these patients by its involvement in the appearance of metabolic and cardiovascular diseases.

**Conclusions:** Furthermore, GSH was reduced significantly in ESRD patients and associated negatively with the level of MDA. This indicates the strong involvement of antioxidants, especially GSH, in the development of oxidative stress in ESRD patients.

**KEY WORDS:** CKD, hemodialysis, ESRD, MDA, GSH

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## INTRODUCTION

Chronic renal disease (CKD) is a general phrase used to describe a variety of conditions that impair the function and structure of the kidneys. Disease severity, etiology, pathology, and rate of progression all play a role in disease manifestation [1]. Glomerular filtration rate (GFR) is the amount of fluid filtered by all of the active nephrons in one unit of time [2], is the broadest indicator of total renal function currently available. Current international criteria define CKD as loss of renal function demonstrated by a glomerular filtration rate below 60 mL/min/1.73 m2 or evidence of renal damage, or Both, persisting for at least three months, regardless of the underlying cause [3].

CKD is associated with anemia, metabolic acidosis (reduced acid excretion by the kidneys), and cardiovascular disease, which adds to the complexity of patient care [4]. In different parts of the world, the prevalence of all phases of CKD ranges between 7–12% CKD (all phases) is most common in adults over 65 years old, although the risk of progressing to end-stage renal dysfunction (ESRD) is higher in people under 65 years old [5]. Interestingly, despite the fact that women have a larger frequency of CKD than males, men are more likely to progress to ESRD [6]. Diabetes mellitus [7], as well as hypertension [8], are the most frequent underlying diseases linked with CKD, especially in high- and middle-income countries [4].

Reactive oxygen species (ROS) are relentlessly reactive metabolites and are so named because they contain an oxygen center [9]. ROS are found under normal conditions at a very low percentage inside cells for redox signaling, but they contribute to very severe oxidative damage to cellular compartments when their level is elevated [10]. One of the most important targets of ROS are the membrane lipids [11], in which ROS can cause an oxidative damage to these lipids in a process called lipid peroxidation [12]. The latter can be used as a proof of elevated oxidative stress [13], and one of final products of lipid peroxidation is widely used as indicator of oxidative stress, termed malondialdehyde (MDA) [14].

Before this oxidative damage occurs, cells contain the protective force of various lines called antioxidants [15]. Thus, oxidative stress can be developed when the antioxidants are unable to fight ROS either when ROS levels are elevated or when the antioxidants themselves are reduced [16]. The antioxidant is a property of many compounds that can be synthesized in the human cells

or obtained from the diet [11]. Glutathione (GSH) is one of the most important compounds with antioxidant properties, and it can be produced endogenously in the human body as well as, it can be obtained from exogenous sources [17]. The GSH removes peroxides from the cells, including lipid peroxides by donating an electron, and oxidized to glutathione disulfide (GSSG) [18]. In this regard, we have aimed to predict the oxidative status in the circulation of CKD patients at ESRD and hemodialysis treatment. This was performed by measuring the serum levels of MDA and GSH in these patient.

## THE AIM

To study the role of oxidative stress in patients with chronic kidney disease.

## MATERIALS AND METHODS

### PATIENTS

The patient was recorded at the Al-Kadhimiya Teaching Hospital-Dialysis Department Consultation Center (Baghdad, Iraq). They were briefed on the study's criteria and agreed to volunteer for the work. From May 2021 to August 2021, 90 ESRD patients undergoing hemodialysis were selected for the study, and 30 healthy volunteers were compared.

### METHODS

Venous blood was donated by ESRD patients and healthy controls. Blood from patients with ESRD was collected before dialysis surgery, the serum was kept at -20°C and then centrifuged at 4000 rpm for 10 minutes in a medical centrifuge, after which MDA and GSH PD-303 were measured using spectrophotometry (Apel, Japan). MDA levels were analyzed using the method of Benge and Aust [19], whereas GSH was determined using the method of Ellman [20]. Both urea and creatinine were measured in commercial kits from Linear Spain.

### STATISTICS

To compare means of independent samples using t-tests and ascertain the relationship between MDA and GSH based on the Pearson's correlation, data were processed computationally using an IBM tool named SPSS version 26.0. Finally, the sensitivity of MDA and GSH as diagnostic indications for ESRD was evaluated using receiver operating characteristic (ROC) curves, which were used to compute the area under the curve (AUC) for each variable.

## RESULTS

The volunteer participants' traits are listed in Table I for your convenience. Age differences between the ESRD patients (43.17±8.89 years) and the control group (44.90±9.11 years) were not statistically significant ($P>0.05$). The body mass index (BMI) of ESRD patients (22.95±1.60 kg/m$^2$) and controls (23.22±1.43 kg/m$^2$) did not differ statistically significantly ($P>0.05$).

The serum urea level of ERSD patients was found to be substantially ($P<0.05$) higher than that of serum controls (117.35±19.70 mg/dl vs. 22.02±3.55 mg/dl). Additionally, it was noted that ESRD patients' serum creatinine levels were significantly ($P<0.05$) higher (7.51±1.83 mg/dl) than serum controls' (0.73±0.09 mg/dl).

Compared with the control serum (0.67±0.13 µmol/L), MDA levels in the serum of ERSD patients were considerably ($P<0.05$) higher at (1.69±0.31 µmol/L). Nevertheless, the amount of GSH in the serum of ESRD patients was considerably ($P<0.05$) lower than that of controls (2081.30±288.79 µmol/L) (1194.03±193.84 µmol/L).

The results showed that there was a significant negative correlation between MDA and GSH in the serum of patients with ESRD, as shown in Table II.

The significance of this biomarker in the diagnosis of ESRD sickness has been proven by the MDA ROC curve. MDA has shown high sensitivity (AUC = 1.0, $P<0.0001$) in the diagnosis of ESRD patients when compared to healthy controls (Fig 1).

The GSH ROC curve demonstrated the value of this biomarker in the diagnosis of ESRD illness. When compared to healthy controls, GSH has demonstrated great sensitivity (AUC = 0.999, $P<0.0001$) in the diagnosis of ESRD patients (Fig 2).

## DISCUSSION

The results have indicated an elevated status of oxidative stress in ESRD patients. A pervious study performed by Abod et al. revealed a significant elevated levels of total oxidants accompanied by a decrease in the total antioxidant capacity in people with acute and chronic renal failure [21]. According to Siddharth et al., CKD patients' MDA levels considerably increased, especially in ESRD patients, while their total thiol levels decreased. The authors contend that oxidative stress plays a significant role in the pathophysiology of CKD. [22].

In the study of Xu et al. the workers have shown a significant increase in the levels of MDA with the degree of CKD, and the most change of MDA level was observed in ESRD patients. Additionally, they have revealed an association between elevated MDA levels and the appearance of inflammatory events in CKD patients, which linked to high production of proinflammatory cytokines [23].

**Table I.** Characteristics of volunteers.

| Parameter | ESRD | Control | P-value |
|---|---|---|---|
| N | 90 | 30 | - |
| Age (year) | 44.90±9.11 | 43.17±8.89 | 0.422 |
| BMI (kg.m2) | 23.22±1.43 | 22.95±1.60 | 0.419 |
| Urea (mg/dL) | 22.02±3.55 | 117.35±19.70 | 0.0001 |
| Creatinine (mg/dL) | 0.73±0.09 | 7.51±1.83 | 0.0001 |
| MDA (µmol/L) | 0.67±0.13 | 1.69±0.31 | 0.0001 |
| GSH (µmol/L) | 2081.30±288.79 | 1194.03±193.84 | 0.0001 |

**Table II.** Correlation in ESRD patients.

| Parameter | Urea | | Creatinine | | MDA | | GSH | |
|---|---|---|---|---|---|---|---|---|
| | r | p-value | r | p-value | r | p-value | r | p-value |
| Creatinine (mg/dL) | 0.206 | 0.115 | - | - | -0.007 | 0.960 | 0.243 | 0.061 |
| MDA (µmol/L) | 0.093 | 0.479 | -0.007 | 0.960 | - | - | -0.705 | 0.0001 |
| GSH (µmol/L) | 0.073 | 0.578 | 0.243 | 0.061 | -0.705 | 0.0001 | - | - |
| Age (year) | 0.161 | 0.220 | 0.055 | 0.676 | 0.077 | 0.559 | -0.129 | 0.327 |
| BMI (kg.m$^2$) | -0.195 | 0.136 | 0.167 | 0.202 | -0.045 | 0.735 | 0.033 | 0.800 |

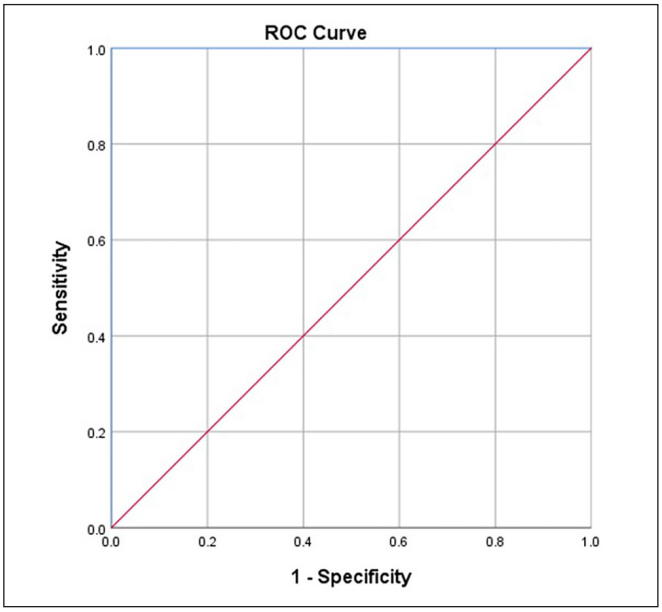


**Fig. 1.** The MDA ROC curve for ESRD disease diagnosis.

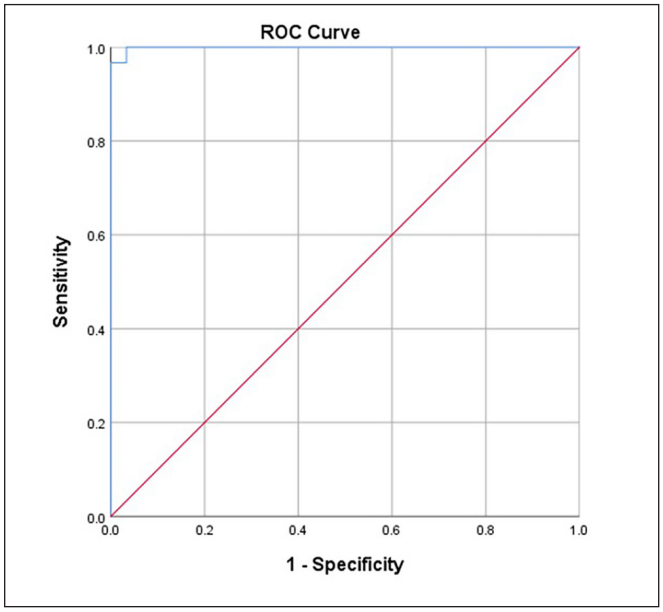


**Fig. 2.** The GSH ROC curve for ESRD disease diagnosis.

A pervious study performed by Agarwal, revealed a significant elevation of MDA and protein carbonyl levels in the plasma and urine of CKD patients. Also, he has found a significant reduction in the thiol group levels of CKD patients, as well as the thiol level was negatively correlated with the increased oxidative stress [24], which is agreed with our observations. Small et al. have proposed the involvement of antioxidant therapy in the management of CKD patients [25].

## CONCLUSIONS

Chronic kidney disease is a serious health condition of men and women that results in a setback in the physical, mental and economic health of the affected persons. The importance of understanding the pathophysiology and health consequences of the disease would help in the providing of the optimum health care for diseased people. ESRD patients have shown enhancement in the lipid peroxidation, which appeared in elevated MDA levels, indicating elevated ROS levels. Oxidative stress can cause more problems to these patients by its involvement in the appearance of metabolic and cardiovascular diseases. Furthermore, GSH was reduced significantly in ESRD patients and associated negatively with the level of MDA. This indicates the strong involvement of antioxidants, especially GSH, in the development of oxidative stress in ESRD patients.

## REFERENCES


1. Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;379(9811):165-180. doi: 10.1016/S0140-6736(11)60178-5.
2. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015;313(8):837-846. doi: 10.1001/jama.2015.0602.
3. Webster AC, Nagler EV, Morton RL et al. Chronic Kidney Disease. Lancet. 2017;389(10075):1238-1252. doi: 10.1016/S0140-6736(16)32064-5.
4. Romagnani P, Remuzzi G, Glassock R et al. Chronic kidney disease. Nat Rev Dis Primers. 2017;3:17088. doi: 10.1038/nrdp.2017.88.
5. Hill NR, Fatoba ST, Oke JL et al. Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. PLoS One. 2016;11(7):e0158765. doi: 10.1371/journal.pone.0158765.
6. Carrero JJ, Hecking M, Chesnaye NC et al. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. Nat Rev Nephrol. 2018;14(3):151-164. doi: 10.1038/nrneph.2017.181.
7. Shen Y, Cai R, Sun J et al. Diabetes mellitus as a risk factor for incident chronic kidney disease and end-stage renal disease in women compared with men: a systematic review and meta-analysis. Endocrine. 2017;55(1):66-76. doi: 10.1007/s12020-016-1014-6.
8. Hall ME, do Carmo JM, da Silva AA et al. Obesity, hypertension, and chronic kidney disease. Int J Nephrol Renovasc Dis. 2014;7:75-88. doi: 10.2147/IJNRD.S39739.
9. Taay YM, Mohammed MT. Evaluation of serum reactive oxygen species and glutathione peroxidase in iraqi obese/obese-hypertension females. Plant Archives, 2020;20(2):1165-1168.
10. Kadhim, SM, Abbood SM, Taay YM et al., Oxidative Stress in Multiple Sclerosis Disease. Diyala Journal of Medicine, 2021;21(2):33-40.
11. Mohammed MT, Kadhim SM, Jassimand AMN et al., Free radicals and human health. International Journal of Innovation Sciences and Research, 2015;4(6):218-223.
12. Halliwell B, Chirico S. Lipid peroxidation: its mechanism, measurement, and significance. Am J Clin Nutr. 1993;57(5):715S-725S. doi: 10.1093/ajcn/57.5.715S.
13. Kagan VE. Lipid peroxidation in biomembranes. CRC press. 2018, p.54.
14. Gaweł S, Wardas M, Niedworok E et al. Malondialdehyde (MDA) as a lipid peroxidation marker. Wiad Lek. 2004;57(9-10):453-455.
15. Mahdi MA, Mohammed MT, Jassim AN et al. Green synthesis of gold NPs by using dragon fruit: Toxicity and wound healing. in Journal of Physics: Conference Series. 2021; 1853:012039. doi: 10.1088/1742-6596/1853/1/012039.
16. Sies H, Berndt C, Jones DP. Oxidative Stress. Annu Rev Biochem. 2017;86:715-748. doi: 10.1146/annurev-biochem-061516-045037.
17. Lu SC. Glutathione synthesis. Biochim Biophys Acta. 2013;1830(5):3143-3153. doi: 10.1016/j.bbagen.2012.09.008.
18. Chen Y, Dong H, Thompson DC et al. Glutathione defense mechanism in liver injury: insights from animal models. Food Chem Toxicol. 2013;60:38-44. doi: 10.1016/j.fct.2013.07.008.
19. Benge J, Aust S. Estimation of serum Malondialdehyde level in hoffee PA. and Jones ME. Methods in Enzymology Hoffee Jones. Academic Press, New York, San Francisco, London, A Subsidinary of Harcoart Brace Jovanovich, Publisher. 1978;51: 302.
20. Pohanka M. Biosensors containing acetylcholinesterase and butyrylcholinesterase as recognition tools for detection of various compounds. Chemical Papers. 2015;69(1):4-16. doi: 10.2478/s11696-014-0542-x.
21. Abod KS, Mohammed MT, Taay YM. Evaluation of total oxidant status and antioxidant capacity in sera of acute-and chronic-renal failure patients. Journal of Physics. 2021. 1853(1): 012038. doi: 10.1088/1742-6596/1853/1/012038.
22. Siddharth M, Datta SK, Bansal S et al. Study on organochlorine pesticide levels in chronic kidney disease patients: association with estimated glomerular filtration rate and oxidative stress. J Biochem Mol Toxicol. 2012;26(6):241-247. doi: 10.1002/jbt.21416.
23. Xu G, Luo K, Liu H et al. The progress of inflammation and oxidative stress in patients with chronic kidney disease. Ren Fail. 2015;37(1):45-49. doi: 10.3109/0886022X.2014.964141.
24. Agarwal R. Chronic kidney disease is associated with oxidative stress independent of hypertension. Clin Nephrol. 2004;61(6):377-383. doi: 10.5414/cnp61377.
25. Small DM, Coombes JS, Bennett N et al. Oxidative stress, anti-oxidant therapies and chronic kidney disease. Nephrology (Carlton). 2012;17(4):311-321. doi: 10.1111/j.1440-1797.2012.01572.x.



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ORIGINAL ARTICLE

# ASSESSMENT OF QUALITY OF LIFE IN PATIENTS WITH GASTRIC CANCER IN UKRAINE

DOI: 10.36740/WLek202305111

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## ABSTRACT

**The aim:** To identify the main problems in the quality of life of patients with gastric cancer to optimize health care for them.

**Materials and methods:** The sociological study was performed by surveying 404 patients with gastric cancer usage questionnaires EORTC QLQ-C30 and QLQ-STO22. Calculations were performed according to the EORTC QLQ-C30 Scoring Manual and QLQ-STO22. The analysis of three main indicators was performed: functional scale, symptom scale and quality of life scale.

**Results:** The quality of life of gastric cancer patients amounted to 51.80±11.35 on a 100-point scale. According to the QLQ-C30 functional scale, the psycho-emotional sphere (59.62±12.91), social functioning (66.42±13.48) are the most impressive in patients. According to the results obtained in the QLQ-C30 symptoms scale, gastric cancer patients were most concerned about financial difficulties (57.18±12.45) and fatigue with a score of 50.12±10.86 on a 100-point scale. According to the QLQ-STO22 symptom scale in the study of patients, anxiety (59.07±12.46) and hair loss (56.97±11.78) amounted to the highest scores.

**Conclusions:** Given the low quality of life of gastric cancer patients, they need psychological support, which is aimed at adapting to the manifestations of the disease and should be a mandatory component in the development of models or strategies for providing medical care to cancer patients. Standardized psychological care should be organized at all stages of diagnosis, treatment and rehabilitation in all institutions that provide treatment to gastric cancer patients. It is also important to develop and implement a comprehensive program to support gastric cancer patients in interaction with society, family and work.

**KEY WORDS:** gastric cancer, quality of life, psychological support

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## INTRODUCTION

Gastric cancer (GC) is one of the most common forms of tumors for individuals of all ages in Ukraine. According to the latest published data from the Center of Public Health (CPH) of the Ministry of Health (MOH) of Ukraine, the GC ranks third in the structure of cancer among men and women [1]. Among all human tumors, GC accounts for 15%, and among tumors of the gastrointestinal tract, it accounts for 50%. Men get affected more often, almost twice more often. More than 85% of GC patients are in the age group of 40 and older [2].

Despite the fact that the death rate from GC has been declining for several decades, its incidence is still high worldwide. Efforts to improve survival in previous years include pre- and postoperative chemotherapy and chemoradiation therapy [3-5]. However, improved survival with multimodal treatment may also be associated with increased toxic side effects. Therefore, a full assessment of new treatments for GC should also include indicators of outcomes reported by patients, i.e. the quality of life.

## THE AIM

The aim of the study was to identify the main problems in the quality of life of patients with GC (C16) to optimize health care for them.

## MATERIALS AND METHODS

The sociological study was performed by surveying 404 patients according to a unified study protocol, which included the use of a comprehensive questionnaire consisting of a questionnaire to determine the quality of life in oncology, EORTC QLQ-C30, and a questionnaire to determine the quality of life of patients with GC, QLQ-STO22. Permission to use the data from "EORTC Quality of Life Group" questionnaires was obtained in November 2021.

EORTC QLQ-C30 is a questionnaire of the European Organization for Research and Treatment of Cancer, developed by the EORTC Quality of Life Study Group, which is currently one of the most widely used tools for determining the quality of life in oncology [6-8]. The

current version consists of 30 questions and includes 5 functional scales:

- physical functioning (PF2),
- role functioning (RF2),
- emotional functioning (EF),
- cognitive functioning (CF),
- social functioning (SF);

QLQ-C30 scale includes the following symptoms:

- fatigue (FA)
- nausea (NV)
- sleep disturbances (SL)
- appetite loss (AP)
- diarrhea (DI)
- dyspnea (DY)
- pain (PA)
- constipation (CO)
- financial difficulties (FI)

The required number of participants was calculated according to Glen's method, and was 398 people. Taking into account the possibility of elimination (10%), we sent 440 questionnaires proportionally to different regions of Ukraine (North, South, West, East, Central), from which we received 404 questionnaires. Primary data were collected from November 2021 to February 2022. All participants gave written consent to participate in the study.

The inclusion criteria were patients who were hospitalized with a histologically confirmed diagnosis «gastric cancer» and received inpatient treatment. Exclusion criteria were lack of written consent to participate in the study.

A randomized study was conducted with further control for distribution of patients by the gender and stage of the disease. Thus, 60.6 % of patients were men and 39.4 % – women. The distribution of patients by the stage of the disease is as follows: I stage – 8.0%, II stage – 15.9%, III stage – 22.3%, IV stage – 44.8%, the stage is not determined in 9.0% of patients. The distribution data are identical to the average data in Ukraine.

Secondary data [1, 2, 4, 9] was used in writing this article also.

Calculations were performed according to the EORTC QLQ-C30 Scoring Manual [8] and QLQ-STO22 [9]. The analysis of three main indicators was performed: functional scale (FS), symptom scale (SS) and quality of life scale (QoL). First of all, an average score (Raw Score – RS) was assessed for each indicator, which is presented as M±SD.

Since the structure of the questionnaire enables the questions to have a 4 or 7-point scale, the developers proposed a unified approach by using a 100-point scale for each of the parameters. Thus, the value of the functional scale (FS) per 100 points was calculated by the following formula:

$$\mathrm{FS} = \left(1 - \frac{RS-1}{range}\right) * 100$$

Where RS is average score of the scale, range is the range of the scale, which is determined by the difference between the possible maximum and minimum values of the scale.

Meanwhile, the symptom scale (SS) and quality of life (QoL) per 100 points were calculated according to the following formula:

SS = ((RS-1)/range)*100

Where RS is the average score of the scale, range is the scale range determined by the difference between the possible maximum and minimum scale values.

Interpretation of the obtained results was performed according to the traditional approach: a high level of functional scale (FS) indicated a high (healthy) level of functioning regarding this indicator. Similarly, a high quality of life scale (QoL) indicated a high quality of life, but a high level of symptom scale (SS) indicated a high level of existence of this problem or symptom.

For scales consisting of 2 or more questions, Cronbach's alpha was calculated as an indicator of scale consistency.

The statistical calculations were performed by using software RStudio v. 1.1.442 and R Commander v.2.4-4.

## RESULTS

According to the results, the quality of life of GLOBAL HEALTH STATUS / QoL in patients with GC amounted to 51.80±11.35 points on a 100-point scale. It should be noted that the answers of the respondents were of the same type, as indicated by sufficient consistency determined by the method of & Cronbach and is 0.78.

According to the questionnaire, within the QLQ-C30 functional scale, among other subscales, the worst indicators belong to the subscale of "Emotional functioning", which amounted to 59.62±12.91 points on a 100-point scale (Table I), and the average score is 2.21±0.87 (Fig.1).

The score on the "Social functioning" subscale is only 66.42±13.48 out of 100, thus habitual communication with people, communication in the family creates certain challenges, discomfort, and generally suffers due to the patient's physical condition or treatment.

"Role functioning" has a score of 68.86±13.74 on a 100-point scale, which indicates that there were some difficulties for the patient in performing their work, daily activities, there were restrictions on hobbies or leisure activities. In general, this indicator is often associated

**Table I.** The results of the survey with the QLQ-C30 functional scale in GC patients

| Scale items | Directory code | Score on a 100-point scale | & Cronbach |
|---|---|---|---|
| Emotional functioning | EF | 59.62 | 0.86 |
| Social functioning | SF | 66.42 | 0.74 |
| Role functioning | RF2 | 68.86 | 0.81 |
| Physical functioning | PF2 | 70.42 | 0.82 |
| Cognitive functioning | CF | 76.65 | 0.31 |

**Table II.** Results of the QLQ-C30 symptom scale questionnaire in GC patients

| Scale items | Directory code | Score on a 100-point scale | & Cronbach |
|---|---|---|---|
| Financial difficulties | FI | 57.18 | - |
| Fatigue | FA | 50.12 | 0.77 |
| Pain | PA | 44.10 | 0.64 |
| Sleep disturbances | SL | 40.69 | - |
| Appetite loss | AP | 37.62 | - |
| Diarrhea | DI | 35.64 | - |
| Constipation | CO | 34.99 | - |
| Dyspnea | DY | 31.76 | - |
| Nausea and vomiting | NV | 27.97 | 0.85 |

**Table III.** Scores the QLQ-STO22 symptom scale in GC patients

| Scale items | Directory code | Score on a 100-point scale | & Cronbach |
|---|---|---|---|
| Anxiety | ANX | 59.07 | 0.67 |
| Hair loss | HAIR | 56.97 | - |
| Body perception | BI | 39.78 | - |
| Dry mouth | DM | 37.14 | - |
| Chest and abdominal pain | PAIN | 36.14 | 0.84 |
| Reflux | RFX | 35.45 | 0.68 |
| Eating restrictions | EAT | 28.93 | 0.60 |
| Taste problems | TA | 23.68 | - |
| Dysphagia | DYS | 19.71 | 0.68 |

with patient support, particularly inside the family.

Compared to the previous items, "Physical functioning" suffers less, its score on the 100-point scale amounts to 70.42±14.27, and, according to the questionnaire, GC patients find it harder to perform strenuous physical work or carry a certain load.

"Cognitive functioning" has the highest indicators in the QLQ-C30 functional scale, its score on the 100-point scale amounted to 76.65±14.72. This indicates that most patients did not have difficulty remembering, concentrating, for example, while reading a newspaper or watching a TV show.

Overall, the Cronbach's alpha on the QLQ-C30 functional scale ranged from 0.74 to 0.86, indicating sufficient and high consistency in patient responses. Only in the subscale "Cognitive functions" it was equal to 0.31, which corresponds to the low consistency of patient responses.

The QLQ-C30 symptom scale survey of CG patients evaluated the following symptoms: fatigue (FA), nausea and vomiting (NV), pain (PA), sleep disturbances (SL), dyspnea (DY), appetite loss (AP), constipation (CO), diarrhea (DI), financial difficulties (FI).

As shown in Table II, CG patients were most concerned about financial difficulties, which amounted to 57.18±12.45 points on a 100-point scale, the average score was 2.72±0.87 (Fig. 2).

Patients are slightly less worried about fatigue, which was expressed in 50.12±10.86 points on a 100-point scale. This is one of the symptoms most often complained of by patients with malignant neoplasms. The presence of fatigue significantly affects the quality of life, as it is a kind of "mirror" of the psychological and physical condition of the patient.

Another symptom that significantly affects the quality of life of a cancer patient is pain. It is often among the

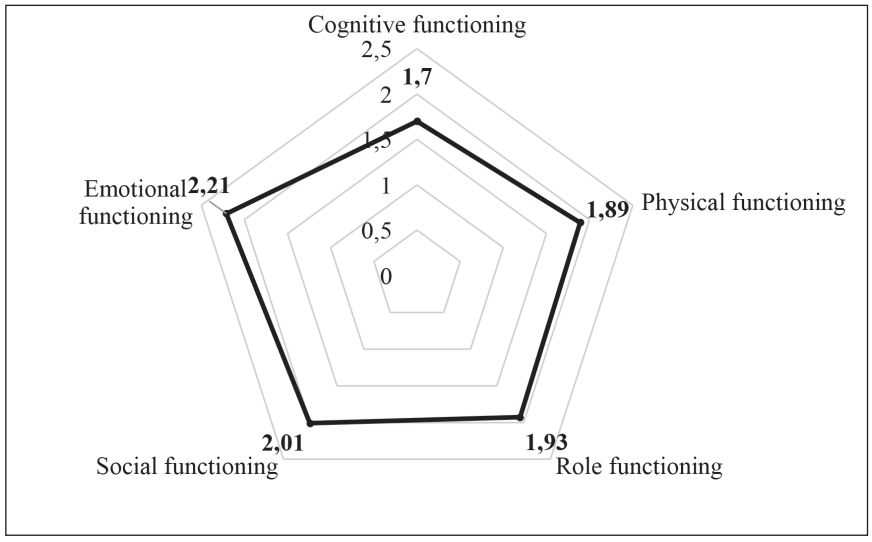


**Fig. 1.** The average score of the QLQ-C30 functional scale in GC patients (points)

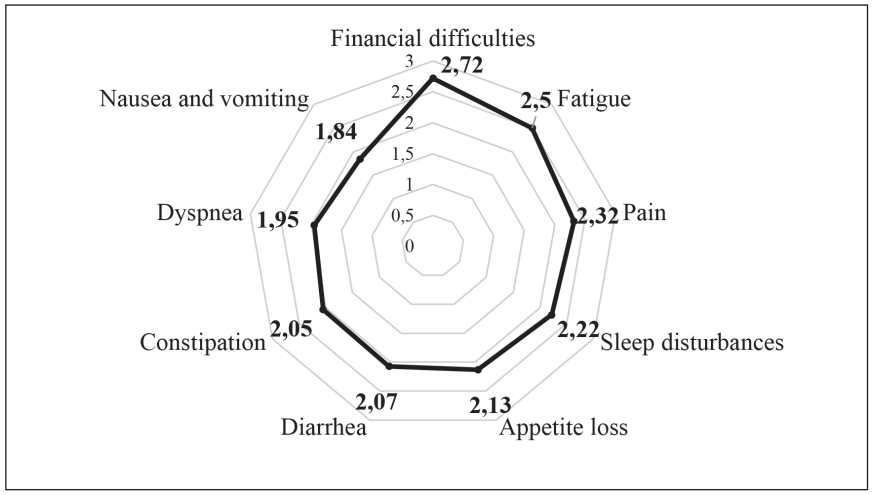


**Fig. 2.** The average score on the QLQ-C30 symptom scale in GC patients (points)

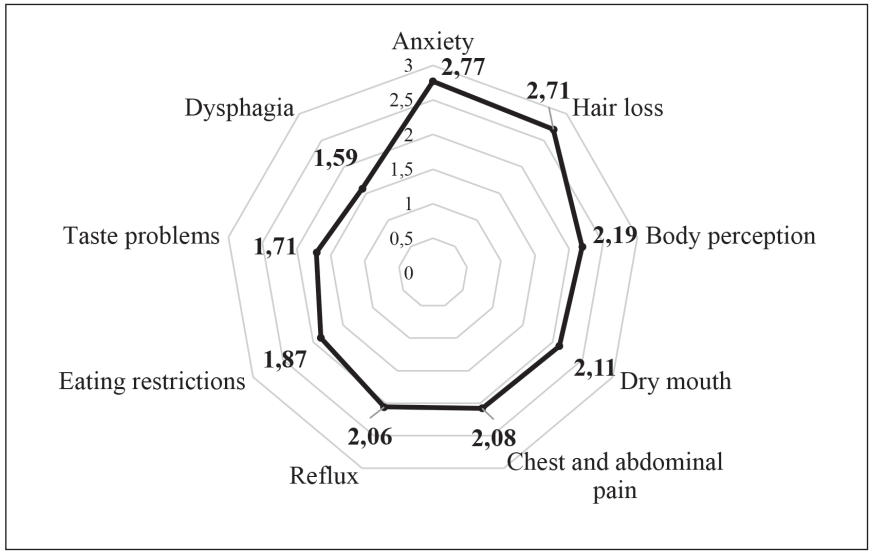


**Fig. 3.** Average score on the QLQ-STO22 symptom scale in GC patients (points)

"leading" symptoms that disturb, cause difficulties in the daily life of the patient, often together with fatigue, because it is exhausting, and it is also associated with the fear of losing independence and freedom of movement, restriction of movement. In this questionnaire, pain accounted for 44.1±10.17 points out of 100.

The "Sleep disturbances" subscale is slightly lower. It scored 40.69±9.82 points on a 100-point scale. This complaint is a component of the conditional complex "Fatigue-Pain-Sleep Disturbances", these are symptoms that often trigger each other and are a consequence of each other.

The lowest scores according to the QLQ-C30 symptom scale questionnaire belong to gastrointestinal problems. Gastric surgery, chemotherapy can cause a corresponding potential deterioration in the patient's quality of life. They have a huge impact on the anatomy and physiology of the patient, as they change the functions of digestion and often affect the patient's attitude to food. In the QLQ-C30 symptom scale questionnaire, "Appetite loss" amounted to 37.62±8.91 points. Slightly fewer patients were concerned about diarrhea, this item amounted to 35.64±7.83 points out of 100. "Constipation" indicator was almost consistent with the previous subscale item, as it amounted to 34.99±7.26 points on a 100-point scale. Also, patients were less worried about "Dyspnea". It scored 31.76±6.46 points on a 100-point scale. The lowest result in the QLQ-C30 symptom scale questionnaire, and in particular among gastrointestinal disorders was found in the item "Nausea and vomiting", which amounted to 27.97±5.84 points out of 100.

The Cronbach's alpha indicator of the QLQ-C30 symptom scale ranged from 0.77 to 0.85, indicating sufficient and high consistency of patient responses. The indicators of consistency on the subscale "Pain" were low, Cronbach's alpha was 0.63 (doubtful consistency), and the correlation was significant moderate ($R=0.47$; $p<0.001$).

The EORTC QLQ-STO22 questionnaire takes into account 22 additional indicators related to GC, including five scales: dysphagia (DYS), chest and abdominal pain (PAIN), reflux (RFX), eating restrictions (EAT), anxiety (ANX), as well as four separate items that reflect the symptoms of the disease, side effects of treatment and emotional problems: dry mouth (DM), body perception (BI), taste problems (TA), hair loss (HAIR) [7, 10, 11].

I n general, the patients' quality of life is affected by several factors, including the stage of the disease and the treatment associated with it [12]. Age, comorbidities and current (at the time of analysis) oncological medical treatments can have profound and negative effects on patients' responses. In the QLQ-STO22 symptom scale the highest indicator was that of "Anxiety", which amounted to 59.07±12.46 points on a 100-point scale (Table III), the average score was 2.77±1.00 (Fig. 3). This subscale includes questions about worrying about future health, worrying about being underweight, and the patient's thoughts about the disease.

Hair loss is one of the symptoms that GC patients often complain of, with a subscale amounting to 56.97±11.78 on a 100-point scale. The patient's assessment of their body also suffers, and a certain cohort of respondents stated that they felt less physically attractive due to the disease or its treatment. The item "Body perception" amounts to 39.78±9.47 points out of 100.

The lowest scores on the QLQ-STO22 symptom scale belong to dry mouth, chest and abdominal pain, reflux, eating restrictions, taste problems, and dysphagia. According to the questionnaire, the item "Dry mouth" equals 37.14±8.62 points on a 100-point scale, which is slightly higher than 36.14±8.33 points out of 100, which the subscale "Chest and abdominal pain" amounts to. Patients describe this symptom by asking questions about unpleasant sensations while eating, pain in the upper abdomen, bloating.

To a lesser extent, GC patients were concerned about reflux. This subscale amounts to 35.45±7.52 points on a 100-point scale. This item includes questions about the discomfort caused by bile and/or acid, belching, heartburn.

The item "Eating restrictions" amounts to 28.93±6.33 points on a 100-point scale. This subscale contains questions about the feeling of fullness of the stomach too soon after eating, discomfort to eat in the presence of other people, satisfaction from food.

The QLQ-STO22 symptom scale "Taste problems" item scores 23.68±5.73 on a 100-point scale. Patients were asked if they tasted food and drink differently than usual.

According to our data, dysphagia causes the least discomfort for GC patients with cancer. Its score on a 100-point scale is equal to 19.71±5.11. The questions on this subscale relate to difficulties in eating hard/or grated/or soft foods, as well as beverages, and general discomfort during eating.

According to the QLQ-STO22 questionnaire, only the "Chest and abdominal pain" scale was characterized by good values of internal consistency indicators – Cronbach's alpha was 0.84, which corresponds to high consistency. Other QLQ-STO22 questionnaire scales were characterized by Cronbach's alpha values at the level of questionable internal consistency in the range of 0.60–0.68.

## DISCUSSION

Quality of life is a wide concept that covers a person's physical and psychological health, level of independence, social aspects and relationship with the environment [13-15]. Quality of life is defined by the World Health Organization (WHO) as people's perception of their position in life in the cultural context and value system in which they live, as well as in relation to their goals, expectations, standards and concerns.

According to the results, the quality of life of GLOBAL HEALTH STATUS / QoL in GC patients amounted to 51.80 points on a 100-point scale, which is 8 points lower than the value described by Chinese authors Zhou Yangyang

and Xi Shuhua (60.1) [16] and 6 points above the value described by Iranian authors (45.7) [3].

According to our data, among other sub-scales, the worst indicators within the functional scale QLQ-C30 fell belong to the "Emotional functioning" subscale, which amounted to 59.62 points on a 100-point scale. Authors Zhou Yangyang, Xi Shuhua in their studies show a higher score of 79.4 points, and generally the item "Emotional functioning" was among the highest indicators of the QLQ-C30 functional scale, while "Cognitive functioning", which disturbed our respondents the least (76.65 points on a 100-point scale), received the lowest points in the aforementioned study and amounted to 71.0 points [16].

The results of our survey according to the QLQ-C30 symptom scale show the highest score among the complaints of financial difficulties (57.18), which is quite high compared to the studies by other authors (32.8) [16], but the score of 32.8 leads list of QLQ-C30 symptoms scale of other researchers and is second only to fatigue (33.9). In our survey, fatigue bothered GC patients up to 50.12 points on a 100-point scale and took second place after the "Financial difficulties" subscale. In general, fatigue is one of the most common symptoms in patients with malignancies. Fatigue is often associated with sleep problems, depression, pain. This indicator is significantly influenced by the current physical and psychological state.

According to our QLQ-C30 symptom scale studies, patients were least concerned about nausea and vomiting with a score of 27.97, while the Chinese authors give a score of 17.6 in their studies, but it is also the penultimate place in this scale and this symptom is less disturbing for GC patients [16].

According to our QLQ-STO22 symptom scale data, most patients complained of anxiety, which amounted to 59.07 points on a 100-point scale, consistent with Iranian authors (56.0) [3], and significantly higher than Chinese authors (26.6) [16]. Respondents with GC were also concerned about hair loss, this subscale accounted for 56.97 points out of 100. Iranian authors describe this point of the QLQ-STO22 symptom scale with significantly lower scores of 17.3 [3], while Chinese authors indicated 25.1 points on this subscale [16].

There is an interesting approach of comparing the results of various reconstructive surgeries from the quality of life viewpoint for the subscale "Reflux", Stefano Rausei, Alberto Mangano, Federica Galli and co-authors analyzed a subgroup of patients who underwent SG with Roux-en-Y or Billroth II reconstructions. Billroth procedures (I and II) are more commonly performed in Eastern countries due to the simplicity of surgical techniques compared to Roux-en-Y [12]. Theoretically, they tend to cause reflux of the duodenum and stomach [17], which causes many symptoms that adversely affect quality of life [18]. On the contrary, Roux-en-Y reconstruction, although a more risky and complicated procedure because two anastomoses need to be performed, is less likely to cause reflux symptoms. For this reason, this surgical reconstruction is used more often, especially in obese patients who are more prone to duodenal gastric reflux [10]. In a meta-analysis, Liang Zong and Ping Chen compared Billroth I, Billroth II, and Roux-en-Y from 15 studies involving 2,169 patients, finding that Roux-en-Y reconstruction was more effective in preventing duodenal reflux and esophagus-stomach with the corresponding best indicator of quality of life [19]. According to our data, "Reflux" accounts for 35.45 on a 100-point scale, which exceeds the data of Iranian and Chinese authors 19.4–20.3 [3,16].

According to our results, patients were least concerned about dysphagia. The scores on this point amounted to 19.71 out of 100, which exceeds 6.5–15.6 in studies by Iranian and Chinese authors [3, 16], but all authors were unanimous about the symptom of dysphagia, which in all studies had the lowest scores.

In general, the authors noted that the overall quality of life of GC patients returned to normal 3 years after surgery, but in some respects, especially symptoms associated with the upper gastrointestinal tract (e.g., nausea and vomiting, reflux, limitation of food) there is a gap in the results with healthy people, indicating that the effect of surgery on patients lasts for at least 3 years, so there must be targeted measures (including symptomatic treatment and psychotherapy) for treatment and care to improve postoperative GC patients' quality of life [16]. Tumor and treatment factors affect the quality of life after gastric cancer surgery. To improve the quality of life of patients, Stefano Rausei, Alberto Mangano, Federica Galli et al. believe that after gastrectomy for cancer, subtotal resection with Roux-en-Y reconstruction should be preferred when it is oncologically acceptable. The authors also noted that all possible factors should be taken into account for a proper analysis of the real consequences of gastric surgery for the well-being of patients [12].

## CONCLUSIONS

1. It is advisable to determine the quality of life of GC patients, one of the tools for this can be the questionnaires developed by European Organisation for Research and Treatment of Cancer (EORTC).
2. In Ukraine, as of the pre-war period (November 2021 – February 2022), the quality of life of GC patients amounted to 51.80±11.35 on a 100-point

scale. Psycho-emotional sphere (59.62±12.91), social functioning (66.42±13.48) are the most impressive in Ukrainian patients according to the QLQ-C30 functional scale. According to the results of the QLQ-C30 symptoms scale, GC patients were most concerned about financial difficulties with indicators of 57.18±12.45, and fatigue with results of 50.12±10.86. According to the QLQ-STO22 symptom scale in the study of Ukrainian patients, the highest rates were for anxiety (59.07±12.46) and hair loss (56.97±11.78).

3. Psychological support, which is aimed at adapting to the manifestations of the disease and prospects, should be a mandatory component in the development of models or strategies for the provision of medical care to cancer patients. Standardized psychological care should be organized at all stages of diagnosis, treatment and rehabilitation in all institutions that provide treatment to GC patients. It is also important to develop and implement a comprehensive program to support GC patients in interaction with society, family and work.

## REFERENCES


1. U 2019 rotsi novoutvorennia staly druhoiu naichastishoiu prychynoiu smerti ukraintsiv. Vysnovky z doslidzhennia hlobalnoho tiaharia khvorob. Sait Tsentru hromadskoho zdorov'ia MOZ Ukrainy. [In 2019, neoplasms became the second most common cause of death for Ukrainians. Conclusions from the study of the global burden of disease. Website of the Center for Public Health of the Ministry of Health of Ukraine]. https://phc.org.ua/news/u-2019-roci-novoutvorennya-stali-drugoyu-naychastishoyu-prichinoyu-smerti-ukrainciv-visnovki-z [date access 02.12.2022] (in Ukrainian).
2. Rak shlunku. Metodychni rekomendatsii dlia samopidhotovky do seminarskykh zaniat likariv-interniv za fakhom «Klinichna onkolohiia», «Zahalna praktyka–simeina medytsyny», «Khirurhiia». Uzhhorodskyi Natsionalnyi Universytet. Uzhhorod. [Gastric cancer. Methodical recommendations for self-preparation for seminars of interns in the specialty "Clinical Oncology", "General Practice-Family Medicine", "Surgery". Uzhhorod National University. Uzhhorod.] 2011, p.13. https://www.uzhnu.edu.ua/en/infocentre/get/2699 [date access 02.12.2022] (in Ukrainian).
3. Sadighi S, Montazeri A, Sedighi Z et al. Quality of life in patients with gastric cancer: translation and psychometric evaluation of the Iranian version of EORTC QLQ-STO22. BMC Cancer. 2009;9:305. doi: 10.1186/1471-2407-9-305.
4. All About Gastric Cancer. http://www.oncolink.com/types/article.cfm?c=5&s=14&ss=105&id=9463 [date access 02.12.2022]
5. Bertuccio P, Chatenoud L, Levi F et al. Recent patterns in gastric cancer: A global overview. Int J Cancer. 2009;125(3): 666–673. doi: 10.1002/ijc.24290.
6. Zikos E, Coens C, Quinten C et al. The Added Value of Analyzing Pooled Health-Related Quality of Life Data: A Review of the EORTC PROBE Initiative. J. Natl. Cancer Inst. 2015;108(5): djv391. doi: 10.1093/jnci/djv391.
7. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993; 85(5): 365–376. doi: 10.1093/jnci/85.5.365.
8. Fayers PM, Aaronson NK, Bjordal K et al., on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer. 2001, p.41.
9. Gastric cancer (update of QLQ-STO22). https://qol.eortc.org/questionnaire/gastric-cancer-update-of-qlq-sto22/ [date access 02.12.2022]
10. Vickery CW, Blazeby JM, Conroy T et al. Development of an EORTC disease-specific quality of life module for use in patients with gastric cancer. Eur J Cancer. 2001;37(8):966–971. doi: 10.1016/s0959-8049(00)00417-2.
11. Karanicolas PJ, Graham D, Gönen M et al. Quality of life after gastrectomy for adenocarcinoma. A prospective cohort study. Ann Surg. 2013;257(6):1039–1046. doi: 10.1097/SLA.0b013e31828c4a19.
12. Rausei S, Mangano A, Galli F et al. Quality of life after gastrectomy for cancer evaluated via the EORTC QLQ-C30 and QLQ-STO22 questionnaires: surgical considerations from the analysis of 103 patients. Int J Surg. 2013;11(1):104–109. doi: 10.1016/S1743-9191(13)60028-X.
13. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403–1409. doi: 10.1016/0277-9536(95)00112-k.
14. Kaptein A, Morita S, Sakamoto J. Quality of life in gastric cancer. World J Gastroenterol. 2005;11(21):3189–3196. doi: 10.3748/wjg.v11.i21.3189.
15. Gutor TG, Zaremba NI, Kovalska OR et al. Comparative analysis of the main social health determinants of life expectancy and infant mortality in Ukraine and Poland. Wiad Lek. 2021;74(3):750–755. doi: 10.36740/WLek202103235.
16. Zhou YY, Xi SH. Combined use of EORTC QLQ-C30 and QLQ-STO22 for assessment of quality of life in patients with gastric cancer after surgery for 3 years. World Chinese J Digestol. 2012; 20(19): 1782-1786. doi: 10.11569/wcjd.v20.i19.1782.
17. Kim BJ, O'Connell T. Gastroduodenostomy after gastric resection for cancer. Am Surg. 1999;65(10):905–907.
18. Svensson JO. Duodenogastric reflux after gastric surgery. Scand J Gastroenterol. 1983;18(6):729–734. doi: 10.3109/00365528309182087.
19. Zong L, Chen P. Billroth I vs. Billroth II vs. Roux-en-Y following distal gastrectomy: a meta-analysis based on 15 studies. Hepatogastroenterology. 2011;58(109):1413–1424. doi: 10.5754/hge10567.

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**Conflict of interest:**
*The Authors declare no conflict of interest.*

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ORIGINAL ARTICLE

# RESULTS OF INFLAMMATORY AND IMMUNOLOGICAL PARAMETERS OF THE ORAL CAVITY AFTER CYSTECTOMY WITH DIFFERENT METHODS OF CONNECTING THE EDGES OF THE OPERATED AREA

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## ABSTRACT

**The aim:** To analyze the results of inflammatory and immunological parameters of the oral cavity after cystectomy with different methods of connecting the edges of the operated area.

**Materials and methods:** The research was conducted in 87 patients who sought surgical treatment of odontogenic cysts of the jaws. Patients were divided into groups depending on the method of wound closure after surgery. We analyzed the results of laboratory tests (leukocytes, ESR, IL-1β, IL-6, TNF-α, IL-8, NO synthase, MMP-9).

**Results:** The analysis of the effectiveness of using different methods of approximation of the oral mucosa wound on inflammatory and immunological parameters showed that when using welding of the edges of the operated area using the EKVZ-300 "Patonmed" apparatus, we get positive results of laboratory indicators of inflammatory markers faster (leukocyte counts are normal on day 30, ESR, IL-1β – on the 14th day, TNF-α – on the 7th day, IL-6, IL-8, NO synthase, MMP-9 – on the 30th day), that is, healing in such patients is faster than in patients with wound closure with classic suture material or laser.

**Conclusions:** When comparing the methods of approximation of postoperative oral mucosa wounds by different methods, based on the results of these inflammatory and immunological parameters, the best results were obtained when using electric welding of tissues. Further research and use of the proposed method will facilitate and shorten the rehabilitation period of patients after surgery.

**KEY WORDS:** odontogenic cyst, cystectomy, electric welding of tissues, laboratory tests

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## INTRODUCTION

Odontogenic cysts of the jaws are one of the most common diagnoses requiring surgical treatment. Among them, radicular cysts are the most common. They are the result of an inflammatory process in the periapical tissues associated with necrotic and infected pulp [1]. Humoral and cellular immune responses play a central role in the pathogenesis of these lesions. The most important role in the growth of these lesions is played by the proinflammatory cytokines TNF-alpha, IL-1, and IL-6 [2]. The cytokine can be secreted by macrophages, monocytes, and other cells of the immune system and may be involved in skeletal homeostasis, including osteoclast formation, and bone resorption in the maxillofacial region [3]. For a more in-depth study of this issue, it is necessary to first give a generalized overview of the mechanism of growth of maxillofacial radicular cysts with an indication of the clinical aspect, as well as to clarify the role of cytokines in this pathophysiological process [4, 5].

Radicular cysts are the most common among jaw cysts, and, according to various authors [6, 7, 8], they account for 6 to 84 % of all periapical lesions. At the same time, tooth-containing cysts (follicular cysts) and keratocysts are diagnosed in 37 % and 6-32 % of patients, respectively. When studying the prevalence of radicular cysts by gender, a small difference was found between men and women. According to some authors, odontogenic cysts were more commonly detected in men (55.9-65.0 %) than in women (44.1-35.0 %) [9, 10]. Other authors report that odontogenic cysts are more common in women (52.37-65.0 %) and less common in men (35.0-47.62 %) [7].

Surgical operations performed at present and associated with cystectomy are based on two main points: tissue separation and subsequent connection [11, 12]. One of the conditions for a properly performed operation is the ability to achieve rapid wound healing, provide a good cosmetic effect, and prevent complications [13, 14, 15]. During many surgical interventions in the oral cavity, the failure of a single suture in the postoperative period can lead to significant complications that usually require repeated operations [16, 17, 18, 19].

## THE AIM

To analyze the results of inflammatory and immunological parameters of the oral cavity after cystectomy with different methods of connecting the edges of the operated area.

## MATERIALS AND METHODS

In accordance with the aim, laboratory tests were performed in patients after surgical treatment of odontogenic cysts of the jaws at the Educational-Treatment Center "University Clinic" (Chernivtsi, Ukraine).

The patients were divided into three groups: Group I (20 patients) – cystectomy with wound suturing using suture material «Vicryl»; Group II (28 patients) – cystectomy with wound edge consolidation using the laser scalpel LSP – "IRE-POLUS" and Group III (39 patients) – the edges of the postoperative defect were connected by using the electric welding apparatus EKVZ-300 "Patonmed".

After cystectomy, 20 patients (group A, 1 control) had their surgical wounds sutured with suture material «Vicryl». In 28 patients (group B, 2 control), after cystectomy, the wound edges were approximated using the LSP laser – "IRE-POLUS", with an irradiation wavelength of 0.97±1.56 μm, maximum irradiation power of 30/60 W; continuous, pulsed, pulsed-periodic mode of operation [20]. A laser with a wavelength of 1.06 μm, a power of 0.71-0.85 W, a continuous irradiation mode, a light guide diameter of 0.6 mm was used to join the wound edges in the area of contact by moving the source along the surface of the wound edge at a distance of 1.0-3.0 mm, with a light guide movement speed of no more than 1.0 mm/sec [21].

In 39 patients (group C, main), the edges of the postoperative wound, after cystectomy, were welded using the apparatus EKVZ-300 "Patonmed".

Patients in this group were treated with the wound edges using the apparatus EKVZ-300 "Patonmed" in the automatic welding mode N2 using the following parameters: voltage – 25 W, duration of exposure to high-frequency current on tissues no more than 2-6 s/per point, duration of voltage amplification – 150 ms, specific pressure force on tissues in the range of 0.3-0.7 N/cm², current frequency – 66 kHz, temperature in the exposure zone 55-65 °C. Patients of all research groups were given recommendations for wound care in the postoperative period and prescribed drug therapy: nimesulide – 100 mg, 1 sachet twice a day for three days after the intervention; rinsing the oral cavity with chlorhexidine 0.06 % after each meal; topical cold for 5 minutes three times a day for the first three days after the intervention.

## RESULTS

As a result of our studies, we found that in healthy subjects of the control group, the content of leukocytes in the oral fluid was 276.80±45.72 x $10^9$/L (Table I). On the first postoperative day, the content of leukocytes in the oral fluid increased in patients of all Patients of all research groups compared with the data in the control group: by 63.87 %, $p<0.05$ in group A, by 100 %, $p<0.01$ in group B, and by 81.94 % in group C. At the same time, the values of the obtained indicators did not differ in statistical significance in the intergroup comparison. On the 5th postoperative day, the quantitative content of leukocytes in the oral fluid in the patients of all research groups continued to increase and was significantly higher than in the control group in all Patients of all research groups, $p<0.01$. However, the minimum values were determined in patients of groups C and A – 523.90±61.80 x $10^9$/L and 554.20±60.15 x $10^9$/L, respectively, $p<0.01$, $p1>0.05$. The maximum value was studied in patients of group B – 763.90±62.18 x $10^9$/L, which was, on average, 29.43 % higher than in patients of groups A and C, $p1<0.05$, $p2<0.05$.

On day 7th, 14th and 30th day of postoperative follow-up, a moderate decrease in the number of leukocytes in the oral fluid was determined in patients of the research groups, which, however, remained significantly higher than in patients of control group B, $p<0.01$, $p<0.05$, than in patients of groups A and C, $p1>0.05$, $p2<0.05$, on average.

The investigation of ESR parameters in the research groups (Table II) revealed a tendency to increase the data of this parameter on the 1st-5th postoperative day, which reached maximum values on the 5th day of observation and was higher than in the control group: in 3.3 times in patients of group A; in 3.7 times in patients of group B and 3.0 times in patients of group C, $p<0.01$; p1, p2>0.05. It should be noted that on the 7th day of postoperative follow-up in patients of group C, the ESR was minimal (8.34±1.58 ml/h) and equal to that of the control group, p, p1, p2>0.05. At the same time, in

**Table I.** Dynamics of the number of leukocytes in the oral fluid in the patients of the patients of all research groups at different follow-up periods

| Research groups | 1st day | 5th day | 7th day | 14th day | 30th day |
|---|---|---|---|---|---|
| Control group | | | 276.80±45.72 x $10^9$/l | | |
| Group A | 453.60± ±56.20°° | 554.20± ±60.15° | 454.0± ±56.20°° | 353.50± ±51.18 | 273.50± ±49.82 |
| Group B | 553.60± ±58.42° | 763.90± ±62.18°,** | 603.70± ±57.83° | 503.20± ±50.00** | 400.70± ±49.97 |
| Group C | 503.60± ±57.28° | 523.90± ±61.80°,ΔΔ | 423.70± ±55.19°°,ΔΔ | 323.00± ±49.86ΔΔ | 272.50± ±48.22 |

Notes:
1.°p<0.01; °p<0.05 – significant difference in values relative to the average statistical norm.
2.**p1<0.05 – significant difference in values relative to group A.
3.ΔΔp2<0.05 – significant difference in values relative to group B.

**Table II.** Changes in ESR in patients of the research groups in different postoperative periods

| Research groups | 1st day | 5th day | 7th day | 14th day | 30th day |
|---|---|---|---|---|---|
| Average statistical norm | | | 5.5±1.10 mm/h | | |
| Group A | 13.28±1.46° | 18.33±1.72° | 10.56±1.62°° | 7.23±1.60 | 5.00±1.21 |
| Group B | 14.39±1.49° | 20.45±1.98° | 12.55±1.70° | 9.20±1.66 | 7.18±1.24 |
| Group C | 13,84±1.47° | 16.42±1.83° | 8.34±1.58 | 5.29±1.57 | 5,10±0.93Δ |

Notes:
1.°p<0.01; °p<0.05 – significant difference in values relative to the data in the control group.
2.Δp2<0.05 – significant difference in values relative to the data in group B.

**Table III.** Dynamics of IL-1β content in the oral fluid of patients after cystectomy at different follow-up periods

| Research groups | 1st day | 5th day | 7th day | 14th day | 30th day |
|---|---|---|---|---|---|
| Control group | | | 68.34±6.03 pg/ml | | |
| Group A | 98.65± ±6.68° | 118.76± ±9.13° | 88.46± ±6.13°° | 78.63± ±6.12 | 68.40± ±6.11 |
| Group B | 110.20± ±6.90° | 130.42± ±6.15° | 100.12± ±6.14°,** | 90.00± ±6.13°° | 75.15± ±6.13 |
| Group C | 104.42± ±6.69° | 114.62± ±6.14° | 84.32± ±6.12ΔΔ | 64.12± ±6.11ΔΔ | 64.50± ±6.12 |

Notes:
1.°p<0.01; °p<0.05 – significant difference in values relative to the control group.
2.**p1<0.05 – significant difference in values relative to the data of group A.
3.ΔΔp2<0.05 – significant difference in values relative to the data of group B.

patients of groups A and B, the value was in 1.9 times, p<0.05, and in 2.3 times, p<0.01 higher, respectively, compared to the control data. On the 7th-14th day of observation, the ESR value decreased compared with the control data, p>0.05, with the most pronounced positive dynamics in patients of group C.

The early action of interleukin IL-1β plays a key role in the development and regulation of innate and acquired immunity, being one of the first to be involved in the defense response to pathogenic factors, activating neutrophils, and stimulating the synthesis of acute phase proteins [12, 22].

It was established (Table III) that on the 1st post-operative day, the content of IL-1β in the oral fluid of patients of the research groups increased compared to the data in the control group: by 44.35 % in group A, by 61.25 % in group B, and by 52.79 % in group C, p<0.01, p1, p2>0.05.

On the 5th postoperative day, the maximum increase in values was noted relative to the data in the control group: by 73.78 % in group A, by 90.83 % in group B and by 67.72 % in group C, p<0.01, p1, p2>0.05. It should be noted that on the 7th, 14th, 30th postoperative days, the level of IL-1β in the oral fluid of the subjects decreased to the maximum and reached normal levels in the patients of group C.

The concentration of the proinflammatory cytokine IL-6, which plays a leading role in the induction of acute

phase proteins [24], increased in the oral fluid of the subjects on the 1st day after cystectomy compared with the control data: in 3.0 times in group A, in 3.3 times in group B, p1<0.05, and in 3.1 times, p1, p2>0.05, (Table IV).

On the 5th day of the postoperative period, in groups A and B, the level of IL-6 in the oral fluid increased and was higher than in the control group by 3.5 times and 3.8 times, p1<0.05, respectively, p<0.01. At the same time, in patients of group C, a decrease in the content of IL-6 in the oral fluid was studied relative to the data of the previous research period, but the obtained values remained in 2.7 times higher than in the control group, p<0.01. It should be noted that at this time of the investigation, the content of IL-6 in the oral fluid of patients in group C was, on average, in 1.3 times lower than in patients in groups A and B. On the 7th, 14th and 30th days of observation in patients of group C, IL-6 in the oral fluid did not differ statistically from the data in the control group, p>0.05, and was lower in patients of groups A and B.

**Table IV.** Dynamics of IL-6 content in the oral fluid of patients after cystectomy in different periods of observation

| Research groups | 1st day | 5th day | 7th day | 14th day | 30th day |
|---|---|---|---|---|---|
| Control group | | | 2.20±0.10 pg/ml | | |
| Group A | 6.65± ±0.19° | 7.76± ±0.21° | 6.00± ±0.15° | 3.48± ±0.12° | 2.95± ±0.10° |
| Group B | 7.29± ±0.21°,** | 8.40± ±0.23°,** | 6.49± ±0.16°,** | 4.00± ±0.13°,** | 3.15± ±0.11° |
| Group C | 6.90± ±0.20° | 6.00± ±0,17°.*,Δ | 4,82± ±0,13°.*,Δ | 2,80± ±0,10°.*,Δ | 2,10± ±0.09*,Δ |

Notes:
1.°p<0.01 – significant difference in values compared to the control group.
2.*p1<0.01; **p1<0.05 – significant difference in values relative to the data of group A.
3.Δp2<0.01 – significant difference in values relative to the data of group B.

**Table V.** Dynamics of TNF-α content in the oral fluid of patients after cystectomy at different follow-up periods

| Research groups | 1st day | 5th day | 7th day | 14th day | 30th day |
|---|---|---|---|---|---|
| Control group | | | 89.70±13.40 pg/ml | | |
| Group A | 109.90± ±14.20 | 180.00± ±15.43° | 166.55± ±14.82° | 100.36± ±14.10 | 93.26± ±23.10 |
| Group B | 99.80± ±12.65 | 160.63± ±14.80° | 140.80± ±14.20°° | 92.82± ±13.25 | 89.75± ±22.80 |
| Group C | 104.85± ±14.17 | 144.95± ±14.47°° | 90.22± ±14.00*,ΔΔ | 89.50± ±12.48 | 89.50± ±22.76 |

Notes:
1.°p<0.01; °p<0.05 – significant difference in values compared to the control group.
2.*p1<0.01 – significant difference in values compared to the data in group A.
3.ΔΔp2<0.05 – significant difference in values relative to the data in group B.

**Table VI.** Dynamics of IL-8 content in the oral fluid of patients after cystectomy in different periods of observation

| Research groups | 1st day | 5th day | 7th day | 14th day | 30th day |
|---|---|---|---|---|---|
| Control group | | | 5.77±0.67 pg/ml | | |
| Group A | 16.28± ±0.82° | 14.00± ±0.75° | 13.80± ±0.73° | 10.50± ±0.48° | 8.25± ±0.30° |
| Group B | 15.24± ±0.77° | 13.14± ±0.73° | 12.26± ±0.69° | 9.15± ±0.46°,** | 8.36± ±0.31° |
| Group C | 16.00± ±0.80° | 13.80± ±0.71° | 9.45± ±0.54°,* | 6.28± ±0.31*,Δ | 5.72± ±0.29*,Δ |

Notes:
1.°p<0.01 – significant difference in values compared to the control group.
2.*p1<0.01; **p1<0.05 – significant difference in values relative to the data of group A.
3.Δp2<0.01 – significant difference in values relative to the data of group B.

**Table VII.** Dynamics of NO synthase in the oral fluid of patients of the research groups at different observation periods

| Observation periods | Research groups | NO2, μmol/l | NO3, μmol/l | NO2 + NO3, μmol/l |
|---|---|---|---|---|
| 1 day | Control group | 13.08±2.18 | 22.50±3.25 | 35.58±3.81 |
| | Group A | 10.15±1.26 | 17.46±2.18 | 27.61±3.44 |
| | Group B | 9.24±1.15 | 16.35±2.00 | 25.59±3.15°° |
| | Group C | 9.70±1.18 | 16.91±2.15 | 26.61±3.33 |
| 5 day | Group A | 7.95±1.14°° | 8.73±1.36° | 16.68±2.50° |
| | Group B | 5.94±0.92° | 8.18±1.30° | 14.12±2.22° |
| | Group C | 6.95±0.98°° | 11.27±1.82° | 18.22±2.80° |
| 7 day | Group A | 9.05±1.10 | 9.84±1.50° | 18.89±2.60° |
| | Group B | 7.14±0.99°° | 9.29±1.48° | 16.43±2.47° |
| | Group C | 9.15±1.10 | 13.50±1.95°° | 22.65±3.05°° |
| 14 day | Group A | 10.20±1.24 | 14.89±2.00°° | 25.09±3.24°° |
| | Group B | 9.36±1.12 | 15.34±2.13 | 24.70±3.25°° |
| | Group C | 12.48±1.20 | 18.03±2.62 | 30.51±3.82 |
| 30 day | Group A | 12.00±1.21 | 18.92±2.66 | 30.92±3.87 |
| | Group B | 11.58±1.19 | 17.67±2.47 | 29.25±3.66 |
| | Group C | 13.62±1.22 | 21.36±2.92 | 34.98±4.14 |

Notes. °p<0.01; °p<0.05 – significant difference in values relative to the control data.

**Table VIII.** Dynamics of MMP-9 content in the oral fluid of patients of the research groups at different times of the postoperative period

| Research groups | Observation periods | | | | |
|---|---|---|---|---|---|
| | 1st day | 5th day | 7th day | 14th day | 30th day |
| Group A | 4.780± ±0.956° | 10.523± ±2.104° | 3.507± ±0.701° | 2.406± ±0.481° | 1.394± ±0.278°° |
| Group B | 6.200± ±1.240° | 11.634± ±2.326° | 5.817± ±1.163° | 4.706± ±0.941°,ΔΔ | 2.582± ±0.516°,ΔΔ |
| Group C | 3.990± ±0.798° | 9.745± ±1.949° | 2.784± ±0.556°,** | 1.673± ±0.334°°,* | 0.773± ±0.154* |
| Control group | 0.764±0.130 pg/ml | | | | |

Notes:
1.°p<0.01; °p<0.05 – significant difference in values relative to the control group.
2.ΔΔp1<0.05 – significant difference in values relative to the data of group A.
3.*p2<0.01; **p2<0.05 – significant difference in values compared to the data of group B.

In practically healthy subjects of the control group, the content of TNF-α in the oral fluid was at a low level (89.70±13.40 ng/ml), which probably provides only the physiological value of direct and feedback signals in the cytokine system, maintaining normal regulation of immunoreactivity (Table V). The increase in this indicator occurs under the influence of antigens of viruses or bacteria in response to the inflammatory process [22, 23].

On the 1st postoperative day after cystectomy, an increase in the level of TNF-α in the oral fluid was observed in patients of the research groups, on the 5th day of observation – a significant increase in this parameter in the research groups relative to the values in the control: by 100.66 % in group A, by 79.07 % in group B, p<0.01, p1>0.05; and by 61.59 % in group C, p<0.05, p1, p2>0.05.

On the 7th day, in patients of group C, the concentration of TNF-α in the oral fluid did not differ statistically from that in the control group, p>0.05, and was lower than in patients of groups A and B by 84.60 % and 56.06 %, respectively.

The content of IL-8, which is produced under the influence of bacterial endotoxins and cytokines, mainly TNF-α and IL-1 [24, 25], increased in the oral fluid of the subjects on the 1st postoperative day compared to the control data: in 2.8 times in patients of group A, in 2.6 times in patients of group B, and 2.7 times in patients of group C, p<0.01; p1, p2>0.05. On the 5th day of the research, a gradual decrease in the content of IL-8 was observed, on the 7th day of postoperative observation, the minimum values were studied in patients of group C – 9.45±0.54 ng/ml, p, p1, p2<0.01, which were 1.5 times and 1.3 times, p1>0.05, lower compared with those

in patients of groups A and B, respectively, p<0.01. On the 14th day of the postoperative research in patients of group C, the concentration of IL-8 in the oral fluid did not differ significantly from that in the control group, p>0.05 (Table VI).

On the 1st day of postoperative intervention in patients of the research groups, after cystectomy, the decrease in the content of NO synthase in the oral fluid was studied in relation to the data in the control group. At the same time, the maximum decrease in these parameters was determined in patients of groups B and C, on average, by the level of $NO_2$ – by 22.60 %, $NO_3$ – by 26.10 %, and $NO_2 + NO_3$ – by 26.64 %, p>0.05, p1>0.05. On the 5th postoperative day, a further decrease in the studied levels of indicators in the oral fluid was determined. On the 7th day of the postoperative period, positive dynamics of $NO_2$ content in the oral fluid of subjects of groups A and C was noted, relative to the data in the control group, p>0.05 (Table VII).

After 2 weeks of observation (14 days) in patients of group C, the data on the content of NO synthase in the oral fluid were normalized and equal to the values in the control group, p>0.05.

It should be added that during the study at all periods of observation, there was no significant difference in the values of NO synthase in the oral fluid in the intergroup comparison, p1, p2>0.05.

It was found that in the control group, the content of MMP-9 in the oral fluid (Table VIII) was 0.764±0.130 pg/ml. At the same time, in patients of the research groups on the 1st postoperative day, an increase in the values of the parameter was established relative to the data in the control group. On the 5th day of postoperative observation, the maximum increase in the level of MMP-9 in the oral fluid was studied.

At the same time, on the 7th-14th days of the investigation, the content of MMP-9 in the oral fluid decreased, but remained significantly higher than in the control group after two weeks of observation. At the end of the research (the 30th day), in patients of group C, who underwent electric welding of the edges of the postoperative wound, the content of MMP-9 in the oral fluid was equal to that of the control group, p>0.05, p2<0.01.

## DISCUSSION

One of the most common interventions in the clinic of surgical dentistry, which ranks second after tooth extraction and accounts for more than 40 %, is the removal of odontogenic cysts [26]. The share of radicular cysts among the total number of maxillofacial cysts accounts for 52 % [27]. Modern advances in medicine allow the use of fundamentally new methods of treatment of odontogenic cysts in order to improve the results of treatment and subsequent rehabilitation [28, 29]. The method we propose is based on the use of tissue electric welding technology to approximate the wound edges after cystectomy.

Analysis of the effectiveness of different methods of approximation of the oral mucosa wound on inflammatory and immunological parameters showed that on the first postoperative day the content of leukocytes in the oral fluid increased in patients of all research groups compared to the data in the control group, p<0.05; 0.01. At the same time, the values of the obtained indicators did not differ in statistical significance in the intergroup comparison. On the 5th postoperative day, the quantitative content of leukocytes in the oral fluid continued to increase and was significantly higher than in the control group in all research groups, p<0.01. However, the minimum values of the analyzed parameter were determined in the patients of groups C and A – 523.90±61.80 x $10^9$/L and 554.20±60.15 x $10^9$/L, respectively, p<0.01, p1>0.05. The maximum values of this parameter were studied in the patients of group B – 763.90±62.18 x $10^9$/L, which was, on average, by 29.43 % higher than in the patients of groups A and C, p1<0.05, p2<0.05. In 1 month after cystectomy in the patients of group A, where the edges of the postoperative wound were sutured with «Vicryl», and in patients of group C, when using the device ECVZ-300 «Patonmed», the quantitative content of leukocytes in the oral fluid was equal to that in the control group, p>0.05. At the same time, when approximating the edges of the oral mucosa with a laser, in patients of group B, the leukocyte content was by 36.26 % higher than in patients of the other groups, on average, p, p1, p2>0.05. Similar data were obtained by analyzing other indicators.

In a previous research [30] related to this problem, we studied the dynamics of clinical parameters when using different methods of approximating the edges of the oral mucosa. The results showed the effectiveness of the proposed method using electric welding of tissues.

## CONCLUSION

When comparing the methods of approximation of postoperative oral mucosa wounds by different methods, based on the results of these inflammatory and immunological parameters, the best results were obtained using electric welding of tissues. In the surgical treatment of odontogenic cysts by the proposed method, a decrease in inflammatory and immunological reactions in the oral fluid of the subjects was found, which was confirmed by a decrease in the levels of IL-1 β, p – p1>0.05, p2<0.05, TNF – L, p>0.05, p1 – p2<0.01, on the 7th day of observation; quantitative content of leukocytes, p – p1>0.05, p2<0.05, levels of IL – 8, p>0.05, p1 – p2<0.01, activity of NO – synthase, p – p2>0.05 on the 14th day of research; IL concentrations – 6, p>0.05, p1 – p2<0.01, MMP activity – 9, p – p2>0.05 on the 30th day after treatment and ESR parameters on the 7th day of observation, p – p2>0.05.

## REFERENCES


1. Bilodeau EA, Collins BM. Odontogenic Cysts and Neoplasms. Surg Pathol Clin. 2017;10(1):177-222. doi: 10.1016/j.path.2016.10.006
2. Neto ND, Porpino MTM., Antunes HD, Rodrigues RCV, Perez AR, Pires FR, et al. Pro-inflammatory and anti-inflammatory cytokine expression in post-treatment apical periodontitis. Journal of Applied Oral Science. 2018; 4:55. doi: 10.1590/1678-7757-2017-0455
3. Chen JH, Tseng CH, Wang WC, Chen CY, Chuang FH, Chen YK. Clinicopathological analysis of 232 radicular cysts of the jawbone in a population of southern Taiwanese patients. Kaohsiung J Med Sci. 2018;34(4):249-54. doi: 10.1016/j.kjms.2018.01.011
4. Mokryk O.YA., Havryl'tsiv S.T., Korniyenko M.M., Petrov B.P. Suchasni khirurhichni metody likuvannya odontohennykh kist shchelep [Modern surgical methods of treatment of odontogenic cysts of the jaws]. Ukrainian Journal of Medicine, Biology and Sports. 2021;6(6):8-19. doi: 10.26693/jmbs06.06.008 (in Ukrainian)
5. Pantus A, Rozhko M, Yarmoshuk I, Kohut V, Solodzhuk YU. Analiz khirurhichnykh metodyk ta pidkhodiv usunennya defektiv kistok lytsevoho skeletu [Analysis of surgical techniques and approaches to eliminate bone defects of the facial skeleton]. Journal «Art of Medicine». 2019; 1:100-104. (in Ukrainian)
6. Havryl'tsiv S.T. (2020) Vdoskonalennya diahnostychno-likuval'noho alhorytmu pry radykulyarnykh kistakh shchelep patsiyentiv iz dyferentsiyovanym osteoreheneratornym statusom [Improvement of the diagnostic and therapeutic algorithm in radicular cysts of the jaws of patients with differentiated osteoregenerative status] Extended abstract of candidate's thesis. Lviv. (In Ukrainian).
7. Havryl'tsiv S.T. Suchasni metody likuvannya kistkovykh defektiv shchelep, shcho utvorylys' pislya vydalennya radykulyarnykh kist [Modern methods of treatment of bone defects of the jaws formed after removal of radicular cysts]. Journal of Scientific Research. 2018; 3:5-12. doi: 10.11603/2415-8798.2018.3.9403
8. Malanchuk VO., Shvydchenko V.S., Halatenko N.A., Kulyesh D.V. (2018) Biodehraduyuchi kompozyty dlya usunennya peryradykulyarnykh defektiv kistky ta poperedzhennya zmishchennya zubiv [Biodegradable composites for the elimination of periradicular bone defects and prevention of tooth displacement]. Materialy Mizhnarodnoyi naukovo-praktychnoyi konferentsiyi "Suchasna stomatolohiya ta shchelepno-lytseva khirurhiya" – Materials of the International Scientific and Practical Conference «Modern Dentistry and Oral and Maxillofacial Surgery». (pp 101-104). Kyiv. (In Ukrainian)
9. Tanaka OM, Meira TM, Batista Rodrigues AC, Willems G, Baggio GL, Couto Souza PH. Marsupialization of a Large Radicular Cyst with Extensive Maxillary Tooth Displacement: Eight-Year Follow-Up. J Dent Child (Chic). 2019;86(1):64-8.
10. Tamiolakis P, Thermos G, Tosios KI, Sklavounou-Andrikopoulou A. Demographic and Clinical Characteristics of 5294 Jaw Cysts: A Retrospective Study of 38 Years. Head Neck Pathol. 2019;13(4):587-96. doi: 10.1007/s12105-019-01011-7
11. Dragovic M, Pejovic M, Stepic J, Colic S, Dozic B, Dragovic S, et al. Comparison of four different suture materials in respect to oral wound healing, microbial colonization, tissue reaction and clinical features-randomized clinical study. Clin Oral Investig. 2020;24(4):1527-41. doi: 10.1007/s00784-019-03034-4
12. Suthar P, Shah S, Waknis P, Limaye G, Saha A, Sathe P. Comparing intra-oral wound healing after alveoloplasty using silk sutures and n-butyl-2-cyanoacrylate. Journal of the Korean Association of Oral and Maxillofacial Surgeons. 2020;46(1):28–35. doi: 10.5125/jkaoms.2020.46.1.28
13. Bourdel N, Chauvet P, Roman H, Pereira B, Somcutian O, Dechelotte PJ, et al. Comparison between resection, bipolar coagulation and Plasmajet®: A preliminary animal study. Eur J Obstet Gynecol Reprod Biol. 2017; 211:127-33. doi: 10.1016/j.ejogrb.2017.02.004
14. Doroshenko M, Guerra A, Vu L. Airway For Laser Surgery [Internet]. Treasure Island (FL): StatPearls Publishing; 2021[cited 2022 Oct 18]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564406/
15. Nahaychuk VV, Shkil'nyak LI. Osoblyvosti diahnostyky, likuvannya i profilaktyky patolohichnykh rubtsiv shchelepno-lytsevoyi dilyanky [Features of diagnosis, treatment and prevention of pathological scars of the maxillofacial area]. Ukrainian dental almanac. 2017; 2:74-78. (In Ukrainian)
16. Pylypiv N.V., Korniyenko M.M. (2021). Osoblyvosti vyboru khirurhichnoho metodu likuvannya khronichnykh periapikal'nykh zapal'no-destruktyvnykh protsesiv [Features of the choice of surgical treatment of chronic periapical inflammatory and destructive processes]. Proceedings of the International Scientific and Practical Conference Medical and Pharmaceutical Sciences: Analysis of the Present and Forecast of the Future. (pp 22-25). Dnipro. (In Ukrainian)
17. Korniienko M.M. (2016) Udoskonalennia khirurhichnykh metodiv likuvannia khvorykh z khronichnymy periodontytamy ta odontohennymy kistamy shchelep [Improvement of surgical methods of treatment of patients with chronic periodontitis and odontogenic cysts of the jaws]. Extended abstract of candidate's thesis. Lviv. (In Ukrainian).
18. Hong B, Winkel A, Ertl P, Stumpp SN, Schwabe K, Stiesch M, et al. Bacterial colonisation of suture material after routine neurosurgical procedures: relevance for wound infection. Acta Neurochir (Wien). 2018;160(3):497-503. doi: 10.1007/s00701-017-3404-9
19. Li W, Xiao M, Chen Y, Yang J, Sun D, Suo J, et al. Serious postoperative complications induced by medical glue: three case reports. BMC Gastroenterology. 2019;19(1):224. doi: 10.1186/s12876-019-1142-6.
20. Gomathi P, Kavitha J, Rajasekar S, Srinivasan S, Lakshmisree S. Treatment of Chronic Inflammatory Gingival Enlargement Using Electrosurgery: A Case Report. Journal of Dental and Medical Sciences. 2020;19(3):17–20.
21. Fu W, Wo C. The use of laser in dentistry: a narrative review. J Biol Regul Homeost Agents. 2021;35(1 Suppl 1):11-8.
22. Malik A, Chawla S, Tauseef A, Sohail H, Ijaz F, Malik A, et al. Association of Oxidative Stress and Production of Inflammatory Mediators Matrix Metalloproteinase-9 and Interleukin 6: Systemic Events in Radicular Cysts. Cureus [Internet]. 2020[cited 2022 Nov 15];12(4): e7822. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7249770/pdf/cureus-001200000007822.pdf doi: 10.7759/cureus.7822

23. Alvares PR, de Arruda JAA, Silva LVO, da Silva LP, do Nascimento GJF, da Silveira MMF, et al. Immunohistochemical Analysis of Cyclooxygenase-2 and Tumor Necrosis Factor Alpha in Periapical Lesions. J Endod. 2018;44(12):1783-7. doi: 10.1016/j.joen.2018.09.002i
24. Brito LNS, de Lemos Almeida MMR, de Souza LB, Alves PM, Nonaka CFW, Godoy GP. Immunohistochemical Analysis of Galectins-1, -3, and -7 in Periapical Granulomas, Radicular Cysts, and Residual Radicular Cysts. J Endod. 2018;44(5):728-33. doi: 10.1016/j.joen.2018.01.008
25. Mangashetti LS, Khapli SM, Wani MR. IL-4 inhibits bone-resorbing activity of mature osteoclasts by affecting NF-kappa B and Ca2+signaling. Immunologia. 2017; 175:917-25. doi: 10.4049/jimmunol.175.2.917
26. Kilinc A, Gundogdu B, Saruhan N, Yalcin E, Ertas U, Urvasizoglu G. Odontogenic and nonodontogenic cysts: An analysis of 526 cases in Turkey. Niger J Clin Pract. 2017;20(7):879-83. doi: 10.4103/1119-3077.212448
27. Oliveros-Lopez L, Fernandez-Olavarria A, Torres-Lagares D, Serrera-Figallo MA, Castillo-Oyagüe R, Segura-Egea JJ, et al. Reduction rate by decompression as a treatment of odontogenic cysts. Med Oral Patol Oral Cir Bucal [Internet]. 2017[cited 2022 Sep 19];22(5): e643-50. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5694189/pdf/medoral-22-e643.pdf doi: 10.4317/medoral.21916
28. Kammer PV, Mello FW, Rivero ERC. Comparative analysis between developmental and inflammatory odontogenic cysts: retrospective study and literature review. Oral Maxillofac Surg. 2020;24(1):73-84. doi: 10.1007/s10006-019-00816-8
29. Kirsanova NM, Lomakin MV, Soloshchanskii II. General and specific cases of hemostasis in reconstructive surgery of oral cavity. Journal of Dentistry. 2018;22(4):212-6. doi: 10.18821/1728-2802-2018-22-4-212-216
30. Chepyshko S.I., Maksymiv O.O. Dynamika klinichnykh pokaznykiv pislya provedennya tsystektomiyi z vykorystannyam elektrozvaryuvannya krayiv operovanoyi dilyanky u patsiyentiv z odontohennymy kistamy shchelep. [Dynamics of clinical parameters after cystectomy using electric welding of the edges of the operated area in patients with odontogenic cysts of the jaws]. Journal «Modern dentistry». Kyiv,2022;1-2:52-56. (In Ukrainian).

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ORIGINAL ARTICLE

# RELATIONSHIP BETWEEN PROFESSIONAL MALADAPTATION OF DOCTORS – INTERNS WITH THE MEANINGFULNESS OF LIFE

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## ABSTRACT

**The aim:** To study relationship peculiarities between the manifestations of professional maladaptation of interns with their value and meaningful sphere of life for developing preventive measures to preserve their health and reduce the outflow of medical personnel from Ukraine.

**Materials and methods:** The study has involved 81 male and female interns. The following methods were used: diagnostic, psychological, analysis, relationships, comparison, systematization and mathematical statistics.

**Results:** Manifestations of professional maladaptation of interns were revealed. The peculiarities of the relationship between the manifestations of professional maladaptation of interns with their meaningful sphere of life are presented. Developed, tested and implemented effective measures for preventing professional burnout and maladaptation are presented.

**Conclusions:** The expediency of providing psychological knowledge in the program of education of interns, as well as the introduction of mandatory psychological support in the institutions of higher medical education are proved. These measures will contribute to future doctor's deeper psychological self-knowledge, self-development, self-regulation of their own behavior and emotions, keeping a healthy lifestyle and effective work to strengthen the state.

**KEY WORDS:** professional maladaptation, value- meaningful sphere of personality, professional motivation

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## INTRODUCTION

The phenomenon of intern's professional maladaptation is studied not enough. In the national psychological encyclopedia, professional maladaptation is considered as a persistent violation of the process of adaptation of the individual to the professional conditions of activity, which arises due to the impossibility to achieve the goal of activity [1]. The researcher T. Molodtsova considers that professional maladaptation is a violation of the adaptation mechanisms of the employee due to internal or external disharmony of personality and organization, which is expressed through the changes in behaviour, conflict, increased anxiety, a number of diseases and distortions in self-development [2].

The domestic scientist G. Pylyagina considers maladaptation as suboptimal or pathological adaptation, which causes significant disturbances in the vital functions of the individual [3]. The authors of the article agree with the opinion of V. Shtyfurak and O. Shportun that maladaptation is a violation of the adaptive processes of personality [4].

V. Khalanska and M. Sytnikova mark that professional maladaptation is generally manifested in such cases as: lack of work, mismatch between the level of training and activities performed, the harmful effects of professional activities, chronic dissatisfaction with work, inadequate working conditions [5]. V. Kostina, N. Konyukhov supplement the main signs of professional maladaptation, in particular they include: fatigue, exhaustion, insomnia, psychosomatic disorders, simultaneous performance of various work actions, low appetite, abuse of various stimulants or sedatives, lack of motivation for professional activity, manifestations of irritability, anxiety, feeling of guilty, cynicism, pessimism, apathy and, in extreme cases – depression [6]. According to the results of his own research, V. Vyun states that the triggers for the development of professional maladaptation with interns are: high rates of occupational stress, prolonged mental tension, exhaustion of adaptive reserves, frustration of significant basic personal needs, and also high manifestation of anxiety and depression [7].

On the basis of scientific works analysis on social psychology, such researchers as T. Vilchynska, V. Kostina,

V. Krysko point out the basic types of personality maladaptation: stable situational (ineffective) adaptation, where a person seeks to act, but does not find effective ways and means to solve existing real problems in social conditions; temporary (unstable) adaptation (a kind of maladaptation), which that are overcome only with the help of special adaptive measures; general stable adaptation (a kind of maladaptation), which is characterized by a state of frustration and manifestation of pathological defense mechanisms [6-9].

G. Akopov, O. Bodalov, B. Bratus, D. Leontiev, V. Chudnovsky, and others studied the meaningful sphere of life personality. Such scientists as K. Zhatkin and D. Roshchin believe that meaning-of-life orientations of an individual are a certain projection of the meaning-of-life concept of a man for the real social situation of its development, i. e. in the conditions of "here and now" [10, 11]. D. Leontiev points out that they are complex socio-psychological formations which are generated by real relations "personality-being" and characterize the features of the relevant personality's attitude to the life of the individual, indicate the direction and boundaries of self-realization of the individual through its structural organization of life goals [12].

The scientist K. Abulkhanova-Slavska has focused on the significance of the individual aspect of this phenomenon. She points out that the low expression of individuality and high conformity of a person can lead to the substitution of his own "meaning of life" by "vital meanings", as a result of this the frustration occurs and the meaning of life is lost. We can say that the structure of the personality changes, the deformation of activity is manifested, the will and initiative disappear and in general, the individuality is leveled [13].

Thus, it can be argued that manifestations of professional intern's maladaptation directly depend on the factors of professional activity and individual personality traits. In general, professional maladaptation is a subjective reaction of the individual's body to the violation of its interaction with the professional environment and as a result a number of negative changes appear. The level of formation of meaning-life orientations of interns acts as a measure of their attitude to life and reveals the nature of personality and is able to influence the personality's adaptation in society.

Having defined the basic concepts of the research thematics, we consider it to be necessary to reveal the peculiarities of the relationship between the manifestation of professional maladaptation of interns with their holistic and meaningful sphere. The analysis of scientific researches and publications demonstrates the relevance of the problems of professional maladaptation of the intern personality. In general, the field of his professional activity has both constructive and destructive influence. The intensive involvement of an intern in the activity objectively leads to a number of transformations and puts him in front of a real choice: to follow the specific requirements of the profession and adapt or resign, transforming the life situation according to his own wishes.

The doctor undergoes significant changes under the influence of a number of professional factors, especially at the stage of initial adaptation to the conditions and specifics of the activity. This is generally due to the schedule of work and rest, irregular working hours, nature, content and multifunctionality of tasks, change in the social environment, peculiarities of interpersonal interaction with colleagues, patients, and so on. It is the specifics of the work that can influence the emergence of professional maladaptation of the individual, because radical changes in the social environment of the young specialist lead to the rupture of habitual relationships, and also to the emergence and establishment of new ones.

During the internship the influence of educational and professional activities is marked, which leads to the appearance signs of professional maladaptation: being overloaded with tasks, fatigue and exhaustion, irritability, impulsivity, cynicism, apathy, sleep disorders, interpersonal interaction, the emergence of a number of somatic diseases, negative attitude to work and decrease of motivation, etc. Occupational maladaptation can be also the result of prolonged exposure of stress and extreme factors.

That is why the study of the manifestations of young doctor's professional maladaptation will allow to establish the level of their adaptability and satisfaction with their own self-realization in the new professional environment. Preliminary problems studies indicate the interns real risks in their professional development, lack of motivation for chosen profession or specialization, and certain learning disappointment associated with health care reform. The relevance of the article is identify the manifestations of professional maladaptation and develop effective measures for its prevention and keeping health with trained professionals.

## THE AIM

The purpose of the article is to study relationship peculiarities between the manifestation of professional maladaptation with interns with their value meaningful sphere in order to understand the range of problematic issues in the process of professional development and creation of a number of preventive measures to reduce the outflow of young specialists from profession.

## MATERIALS AND METHODS

The authors conducted an experimental reseach to study the manifestations of professional maladaptation of interns and establish the relationship with the meaningfullness of life. The sample consisted of 81 males and females (n = 81), with an average work experience of 1.10 years. Among the examinees, 95.19% (n = 77) were females and 4.90% (n = 4) were males. Psychological diagnostic testing of interns took place in the morning and was done with the blank method in groups of 8-15 people.

The study included three stages. At the first stage of the research the theoretical analysis of the scientific literature deals with professional maladaptation of the personality is carried out. The second stage forsaw an empirical study of the manifestations of professional maladaptation and meaningfulness of life through the use of psychological diagnostic tools. At the third stage, the generalization and analysis of the experiment results and summing up aconducted.

The study uses a set of complementary scientific methods: analysis, interdependence, and interconditionelity comparison, systematization, psychological diagnostic methods and methods of mathematical statistics.

We used psychological diagnostic techniques as the main tool. They were used to identify the negative effects of professional aspects on the intern personality, to establish cause-and-effect relationships and further integration of the research results into a common scientific vision concerning a number of personality problems related to his professional activity as a doctor.

We carried out our study of manifestations of professional maladaptation with the help of psychological diagnostic methods of M. Dmitrova "Assessment of professional maladaptation" [14]. The total number of points was accomplished by means of comparison with the decoder. The assessment was based on five main features and a generalisation of occupational maladaptation indices. The obtained results of the research have been analyzed in two directions: according to the assessment of individual features as sources of professional maladaptation and according to the level of manifestation of the maladaptation indicator.

D. Leontiev's psychological diagnostic technique "Meaning-life orientations" (SJO) [15] is also applied, which is aimed at determining the value- meaningful sphere of personality and includes the following scales: life goals, emotional saturation of life, effectiveness, locus of "I" control, locus of life control and the general meaning of life. This technique consists of twenty undivided pairs of opposite statements that reflect a person's notion of the factors of life consciousness. The authors of the article aspired to find out the real intern vision of meaning of his own life. The interpretation of the results was made by tranferring the total score into standard meaning according to the key methods and after summing them up on scales, the results were interpreted. In our opinion the method used is quite meaningful and informative.

Descriptive statistics methods, correlation and comparative analyses (Spearman's rank correlation coefficient) were used to process the research results. Mathematical data processing and graphical presentation of the research results were performed with the help of Microsoft Office MS Excel and the standardized software package IBMSPSS Statistics 23.0.

## RESULTS

In our empirical study, professional maladaptation is interpreted as a violation of the adaptive processes of intern in the professional environment. The results of empirical study using the method of "Assessment of professional maladaptation" of M. Dmytrova have shown the presence with 50.62% (n = 41) of those under investsgation a moderate manifestation of professional maladaptation (from 32 to 64 points), with 34.57% (n = 28) of young doctors a low level (from 0 to 32 points), and with 14.81% (n = 12) of people – high manifestation (from 65 to 95 points).

It was stated that the manifestations of professional maladaptation of those under investigation are most often manifested with deterioration of health, sleep and rest disorders, fatigue, changes in the emotional sphere, causing certain somatovegetative disorders. The established symptoms directly affect the quality of accomplishment of professional tasks, the effectiveness of internship training, as well as can affect the health of a young doctor. That is, a number of professional factors contribute to the emergence of professional maladaptation.

To establish the nature of the relationship between the professional maladaptation of the young doctor and his value – meaningful sphere, the correlative analysis was performed by Spearman's rank correlation coefficient. The results of correlative analysis allow us to state the presence of statistically significant reverse relationships between indicators of occupational maladaptation and the scales of meaningfulness of life. Let's present the most significant of them (Table I).

It is stated that the sign of "decrease in total activity" has significant ($p < 0.001$) inverse correlation links with the life process (-0.595), general indicator of life meaningfulness (-0.579), life effectiveness (-0.568), locus of life control (-0.523), locus of "I" control (-0.452). This indi-

**Table I.** Spearman Rank Correlation between indicators of professional maladaptation and meaningful sphere of interns

| Indicators of methods | Overall indicator MLO | Goals in life | Pprocess of life | Productivity of life | Locus of I control | Locus of Life control |
|---|---|---|---|---|---|---|
| Deterioration of health | -0,573*** | -0,424*** | -0,544*** | -0,543*** | -0,403*** | -0,534*** |
| Emotional shifts | -0,423*** | -0,283** | -0,430*** | -0,457*** | -0,260* | -0,358*** |
| Decrease in total activity | -0,579*** | -0,458*** | -0,595*** | -0,568*** | -0,452*** | -0,523*** |
| Fatigue | -0,483*** | -0,364*** | -0,442*** | -0,475*** | -0,330*** | -0,451*** |
| Peculiarities of social interaction | -0,418*** | -0,232* | -0,424*** | -0,386*** | -0,284** | -0,309** |
| Decreased motivation to act | -0,557*** | -0,490*** | -0,536*** | -0,459*** | -0,439*** | -0,480*** |
| Professional maladaptation | -0,573*** | -0,424*** | -0,544*** | -0,543*** | -0,403*** | -0,534*** |

Notes:* $p \leq 0,05$,** $p \leq 0,01$, *** $p \leq 0,001$

cates that insufficiently active, tired, exhausted interns, who prefer relationships in the professional sphere – are more likely to be dissatisfied with life experience and disappointed in life.

Reverse correlative relationships ($p < 0,001$) have been found between the sign of "decreased motivation to act" and general indicator of meaningfulness of life (-0.557), life process (-0.536), goals in life (-0.490), locus of life control (-0.480), life effectiveness (-0.459), locus of "I" control (-0.439). We can say that with insufficient professional motivation, the meaning and interest in the future life and the desire for self-realization are lost, the dependence on important people and disbelief in their own strength are observed.

It is established that the sign of "deterioration of health" is connected ($p < 0,001$) with general indicator of life meaningfulness (-0.573), life process (-0.544), life effectiveness (-0.543), locus of life control (-0.534), life goals (-0.424), locus of "I" control (-0.403). This indicates that the constant load, fatigue, overexertion affect the appearance of frustration in their own future, dissatisfaction with their own life, cause a loss of its emotional colour and sense.

Reverse correlative relations ($p < 0,001$) have been found between fatigue and the general indicator of life meaningfulness (-0.483), life effectiveness (-0.475), the locus of life control (-0.451), life process (-0.442). The results show that tired interns have reduced rates of meaningfulness of their own life.

It has been determined that the sign "professional maladaptation" has significant ($p<0.001$) reverse correlative relations with the general indicator of life meaningfulness (-0.573), life process (-0.544), life effectiveness (-0.543), locus of life control (-0.534), life goals (-0.424). That is, in the manifestations of professional maladaptation there is dissatisfaction with their own life passed, meaninglessness of the future and loss of existence.

Inverse significant correlations ($p<0.001$) have been noted between emotional shifts and general indicator of life meaningfulness (-0.423), life process (-0.430) and life effectiveness (-0.457). It can be argued that negative emotional manifestations of future doctors affect the decrease in emotional saturation and their being field with their own sense of life, and cause dissatisfaction with it.

It has been also established that the feature of "particularity of social interaction" is related ($p < 0,001$) to the life process (-0.424), general indicator of life meaningfulness (-0.418) and life effectiveness (-0.386). This indicates that young doctors who are dissatisfied with their own lives have problems in interpersonal relationships, incline to conflict and solitude.

Thus, professional maladaptation has a close relationship with the value-meaningful sphere of the intern personality. Having analysed all these, it can be marked that with a decrease in the adaptation of the individual to the professional intern activity, the meaningfulness of their own life and its sense fullness decrease.

## DISCUSSION

The obtained results of an empirical study of professional maladaptation of interns clearly demonstrate the level of manifestation of maladaptation indicators of them, that directly affect the meaningfulness of their own life. The authors of the article agree with the opinion of the researcher O. Meshko, who indicates a

special role in the formation of a harmonious system of meaningful life constructs of the personality psyche, namely professional meanings, which occupy a high rank in the hierarchy of meaningful life orientations [16]. We believe that V. Vyun's observations also prove the need to prevent professional maladaptation of interns and expedience of using comprehensive psycho-corrective and psychotherapeutic effects during the professional training [17].

In our opinion, the presence of the formed manifestation of high rates of professional maladaptation with respondents has several reasons. Firstly, the lack of professional and psychological selection for the institution of higher education, which increases the likelihood of entering the profession of people with low level of fitness. Secondly, as a disadvantage, there is a lack of constant psychological support of interns in educational institutions, which, if available, would promote the provision of psychological assistance to those who need it in time. Thirdly, it indicates the necessity to develop and implement in the educational process the programs on psychological thematic (the psychology of doctor's personality, the peculiarities of doctor's communication, etc.) that would help young professionals to successfully adapt to the chosen profession, realize their own psychological problems, learn their own individual characteristics and work on their self-development and self-improvement. As we can see, these factors play an important role in preserving the potential of young workers.

## CONCLUSIONS

Thus, the results of an empirical study found that 65.43% (N=53) of young doctors have moderate or high manifestations of occupational maladaptation, which are characterized by fatigue, changes in the emotional sphere, deterioration of health and somatovegetative disorders. The manifestations of occupational maladaptation affect both the deterioration of health and lead to frustration in the profession and reduced the efficiency in activity.

Based on the analysis of the study results, it is found that there is a close relationship between the professional maladaptation and value-meaningful sphere of the young doctor's personality. It has been found that interns are dissatisfied with their own real life, do not set goals for the future and show fatalism in their judgments.

Having analysed the problems of professional maladaptation with future doctors, we consider it appropriate to develop a number of measures to prevent negative psycho-emotional states in order to preserve their health and reduce the outflow of trained personnel from the profession. The scientists' work results and our own experimental research lead us to the thought about the feasibility of improving psychological education among interns and introduction of compulsory psychological support during the process of higher education, which will expand their education, self-development, self-knowledge, prevention of destructive demonstration of self-regulation of their own behaviour and emotions, maintaining health and motivation for the future, as well as their effective performance of professional duties.

## REFERENCES


1. Konyukhov NI. Prikladnyye aspekty sovremennoy psikhologii: terminy, kontseptsii, metody. [Applied aspects of modern psychology: terms, concepts, methods] 1992. https://vocabulary.ru/termin/professionalnaja-dezadaptacija.html [date access 15.10.2022] (in Russian).
2. Molodtsova TD. Osnovnyye vidy i tipy podrostkovoy dezadaptatsii. Nauchno-metodicheskiy elektronnyy zhurnal «Kontsept». [The main types and types of adolescent maladaptation. Scientific and methodological electronic journal "Concept"]. 2013;5:51-55. (in Russian).
3. Pylyahina HYA, Khaustova OO, Maruta NO et al. Medychna psykholohiya: v 2-kh t. T. 2. Spetsial'na medychna psykholohiya. Pylyahynoyi. Vinnytsya: Nova Knyha. 2020, p.496. (In Ukrainian).
4. Shtyfurak VS, Shportun OM. Fenomenolohiya, praktyka ta korektsiya psykholohichnoho zdorov''ya osobystosti: monohrafiya. Vinnytsya. 2019, p.331. (in Ukrainian).
5. Khalanskaya VA, Sitnikova MA. Soderzhaniye i metodika psikhosotsial'noy raboty v sisteme sotsial'noy raboty: uchebno-metodicheskoye posobiye. [The content and methodology of psychosocial work in the system of social work: teaching aid.] Belgorod : Izd-vo BelGU. 2009, p.222. (in Russian)
6. Kostina VV. Teoretychni i metodychni zasady profesiynoyi pidhotovky maybutnikh sotsial'nykh pedahohiv i sotsial'nykh pratsivnykiv do profilaktyky dezadaptatsiyi uchniv. Kharkivs'kyy natsional'nyy pedahohichnyy universytet imeni H.S. Skovorody. Kharkiv. 2018, p.390. (In Ukrainian).
7. V'yun V. Klinichna tipologiya i mekhanizmi psihogenezu staniv psihologichnoï dezadaptaciï likariv-interniv. [Clinical typology and mechanisms of psychogenesis in the psychological disadaptation of doctors and interns] Psihiatriya, narkologiya ta medichna psihologiya. 2019;3(84):55-60. doi: 10.35339/msz.2019.84.03.09. (in Ukrainian).
8. Vil'chinskaya TP. Psikhologicheskiye problemy dezadaptatsii detey mladshego shkol'nogo vozrasta. [Psychological problems of maladjustment of children of junior school age]. Moskva: Moskovskiy otkrytyy sotsial'nyy universitet. 2000, p.27. (in Russian).
9. Krys'ko VG. Sotsial'naya psikhologiya: ucheb. dlya vuzov. 2-ye izd. [Social psychology: textbook. for universities]. Sankt-Peterburg : Piter. 2006, p. 432. (in Russian).

10. Zhatkina KA. Proyavleniye smyslozhiznennykh oriyentatsiy v yunosheskom vozraste. [Manifestation of meaningful orientations in youth]. Molodozh'i nauka : Sbornik materialov VI Vserossiyskoy nauchno-tekhnicheskoy konferentsii studentov, aspirantov i molodykh uchonykh. Krasnoyarsk : Sibirskiy federal'nyy un-t. 2011, p.95-98. (in Russian).
11. Roshchin DG. Ponyatiye «smysl zhizni», «smyslozhiznennaya oriyentatsiya» i «smyslozhiznennaya kontseptsiya»: distsiplinarnyye i teoretiko-etimologicheskiye ramki kontseptualizatsii. Vestnik Khar'kovskogo natsional'nogo universiteta imeni V.N. Karazina. 2010;891:108-113. (in Ukrainian).
12. Leont'yev DA. Psikhologiya smysla: priroda, stroyeniye i dinamika smyslovoy real'nosti. [Psychology of meaning: nature, structure and dynamics of meaning reality]. 4-ye izd., isprav. i dop. Moskva : Smysl. 2019, p.584. (in Russian).
13. Abul'khanova-Slavskaya KA. Strategiya zhizni. [Life strategy]. Moskva : Mysl'. 1991, p.463. (in Russian).
14. Nikiforov GS, Dmitriyeva MA, Snetkov VM. Praktikum po psikhologii professional'noy deyatel'nosti i menedzhmenta: uchebnoye posobiye. Sankt-Peterburg. 2003, p.448. (in Russian).
15. Leont'yev DA. Test smyslozhiznennykh oriyentatsiy (SZHO) 2-ye izd. [Meaningful Orientation Test (LSS)]. Moskva : Smysl. 2000, p.18. (in Russian).
16. Meshko OI. Tvorcha samorealizatsiya osobystosti vchytelya i de-yaki aspekty rozvytku yoho profesiyno-pedahohichnoyi pozytsiyi. [Creative self-realization of the teacher's personality and some aspects of the development of his professional and pedagogical position]. Problemy zahal'noyi ta pedahohichnoyi psykholohiyi. 2011;13(4):240-247. (in Ukrainian).
17. V'yun V. Sistema mediko-psihologichnoï pidtrimki likarya u period adaptacïï do profesijnoï diyal'nosti. [A system of medical and philosophical support for a doctor during the period of adaptation to professional activity]. NEJRONEWS. 2018;4-5(97):52-54. (in Ukrainian).

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ORIGINAL ARTICLE

# EVALUATION OF VEST-OVER-PANT TECHNIQUE IN THE TREATMENT OF POST-HYPOSPADIAS URETHROCUTANEOUS FISTULA

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## ABSTRACT

**The aim**: In this study, we present and evaluate the vest-over-pants technique as a simple way to correct urethrocutaneous fistulas after hypospadias.

**Materials and methods:** Between October 2018 and June 2020, twenty male patients aged 5 to 20 years came to us with post hypospadias repair fistula, these patients underwent vest-over-pant repair of their fistula. The size of fistula was ranging between 2.5-5 mm. The distribution of fistula was coronal (3 patients), distal penile (9 patients), midshaft (2 patients) and proximal penile (6 patients). In 14 patients there were single fistula and 6 patients had more than one fistula. Eleven of patients were exposed to a previous failed fistula repair procedure.

**Results:** Six months after the operation, the fistula recurred only in 2 patients, and our operation was successful in 90% of cases without complications.

**Conclusions**: The vest-over-pants technique is a simple and effective way to treat penile fistulas after hypospadias in properly selected patients. It is a technically simple procedure with a short learning curve and no major postoperative complications.

**KEY WORDS:** urethrocutaneous fistula, hypospadias urethrocutaneous fistula, surgical technique

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## INTRODUCTION

One of the most common complications after hypospadias repair is urethrocutaneous fistula formation. Back in 1973, both Horton and Devine estimated the incidence of urethrocutaneous fistula formation to be range between 15% and 45%. However, nowadays the incidence of fistula formation has decrease gradually. In general the incidence of fistula is varying with severity of hypospadias, surgical technique and experience of operating Surgeon [1, 2]. There are many factory that might lead to post hypospadias repair fistula formation, and these including ischemia, local infection, poor tissue handling, inadequate procedure and distal obstruction or stenosis [3, 4]. Post-hypospadias urethrocutaneous fistula could be classified according to many aspects, including: according to site, according to size, according to its track path and according to number [3]. A fistula can occur immediately after removal of urinary catheter or many years after the repair [5]. Successful fistula repairing, in large part, depends upon meticulous attention to surgical details, also on the using of interposing tissue, however there is no perfect standard surgical repair of urethrocutaneous fistula and this is due to influence of many factors like size, site, number of fistula, and status of surrounding tissues [6].

## THE AIM

The purpose of this study is to evaluate of the vest over pant procedure, that had been utilized to treat post-hypospadias urethrocutaneous fistula and assessment its effectiveness in term of prevention of recurrence of fistula formation.

## MATERIALS AND METHODS

Between the period from October 2018 to June 2020, a total number of 20 patients who were presented to us with history of post-hypospadias repair of urethrocutaneous fistula were subjected to surgical closure of fistula by using of vest-over-pant technique. Patient's age was from 5 to 20 years; 12 of them had been operated using the Snodgrass technique, and 8 patients had been operated using multistage repair

with using of buccal mucosal graft (5 patients) and skin graft (3 patients). Site of fistula were coronal (3 patients), distal penile (9 patients), midshaft (2 patients) and proximal penile (6 patients). Size of fistula was ranging between 2.5 to 5 mm; in 14 patients there were single fistula and 6 patients had more than one fistula. Eleven of patients were exposed to a previous failed fistula repair procedure. We scheduled the surgical repair of urethrocutaneous fistula only after 6 months from last intervention, as any local inflammation and indurations completely resolved at time of our intervention. The mean term of follow up period was the 6 months after operation. All of our patients were subjected to detailed anamnesis, including initial operative repair, time of developing the fistula after hypospadias repair, number of previous surgical procedures if the fistula was recurrent and, if possible, the surgical technique which was used (it was taken from discharging card of patients when present). The presence of single or multiple fistula in ventral part of penis with dripping of urine during micturition was the main complain of our patients, and other patients (especially with the large fistula) were complain from thin stream of urine from fistula during micturition. Examination was done to assess the size, site and number of fistula, presence of distal obstruction and status of surrounding tissue. All patients underwent a standard preoperative examination. Ultrasound of genitourinary system was done to exclude any associated anomalies. For those patients who had different calibration, cystourethroscope and urethrogram had been done. Informed consent was taking from all patients and/or their parents.

## SURGICAL PROCEDURES

All operations were done under general anesthesia; following the standard procedures for prepping and draping, a traction suture of 3/0 silk inserted to the glans, follow by urethral calibration by using urethral dilators to rule out any distal stenosis. A methylene blue dye were injected under pressure from terminal orifice of urethra with tourniquet at the base of penis, and this maneuver helps in identifying of any additional fistula and also helps us to trace the tract of fistula. Then we inserted a silicon catheter in the urethra, and the size of catheter were depended on the caliber of the urethra. Marking were done by using methylene blue, and primary we marked the margins of fistula and then the two lateral skin flaps are marked which are located on both sides of fistula. After finishing of marking, the local infiltration of the area were done with diluted epinephrine and lidocaine 2% (1/200,000) which assist in bloodless field. The operation begins after waiting of 10 minutes, and when there is more than one fistula, the intervening tissue were removed to create single big fistula. Then, by using fine tipped pointed scissor a circumferential incision is done around the fistula down to the dartos fascia of penis , fistula edge were undermined and the fistula tract completely dissected from surrounded tissue down to the healthy thin urethral tissue. The fistula is closed primarily as a first layer by turning the incised margins upside down using Continuous Subdermal 5/0 or 6/0 polyglactine sutures. The two laterally based skin flaps were elevating and mobilized, and one of these flaps is then de-epithelized. This de-epithelized flap advanced to cover the fistula and suture and undeneably the opposite skin flap as second layer of closure to the fistula, and this flap were fixed by using of interrupted 6/0 polyglactine (vicryl) suture. Then, the second skin flap i.e. the contralateral skin flap were advanced and the repair in vest-over-pant fashion as third layer, closure done without overlapping suture line, this layer closed to the adjacent penile skin using 4/0 polyglactine (vicryl) interrupted sutures without tension. Simple dressing which consist of antibiotic impregnated gauze were wrapping around the incision and it secured to its position by using the second layer of dry gauze which were fixed to the abdominal wall using medical adhesive plaster. All patients were kept one night in the hospital and in next day they were discharges. After dressing removal inspection of the wound was done for presents of any hematoma or flap necrosis. All patients were kept on injectable third generation cephalosporin for 5 days postoperatively and then on oral antibiotic till the time of catheter removal which usually done 14 days postoperatively. All of our patients were followed up and visited regularly weekly for the first month, then biweekly for the second month, and then once a month for up to 6 months after surgery. Patients or their parents were instructed to keep dilatation of urethra using urethral dilator with xylocaine gel for lubrication during the period of flow-up. During follow-up history about urine stream or any abnormal unine flow from opening other than meatus is taken. Clinical examination during the follow-up period is focusing about any recurrence of fistula or formation of new fistula and also about any penile deformity or scars (figure 1).

# RESULTS

This study involved 20 patients who were present with post-hypospadias repair urethrocutaneous

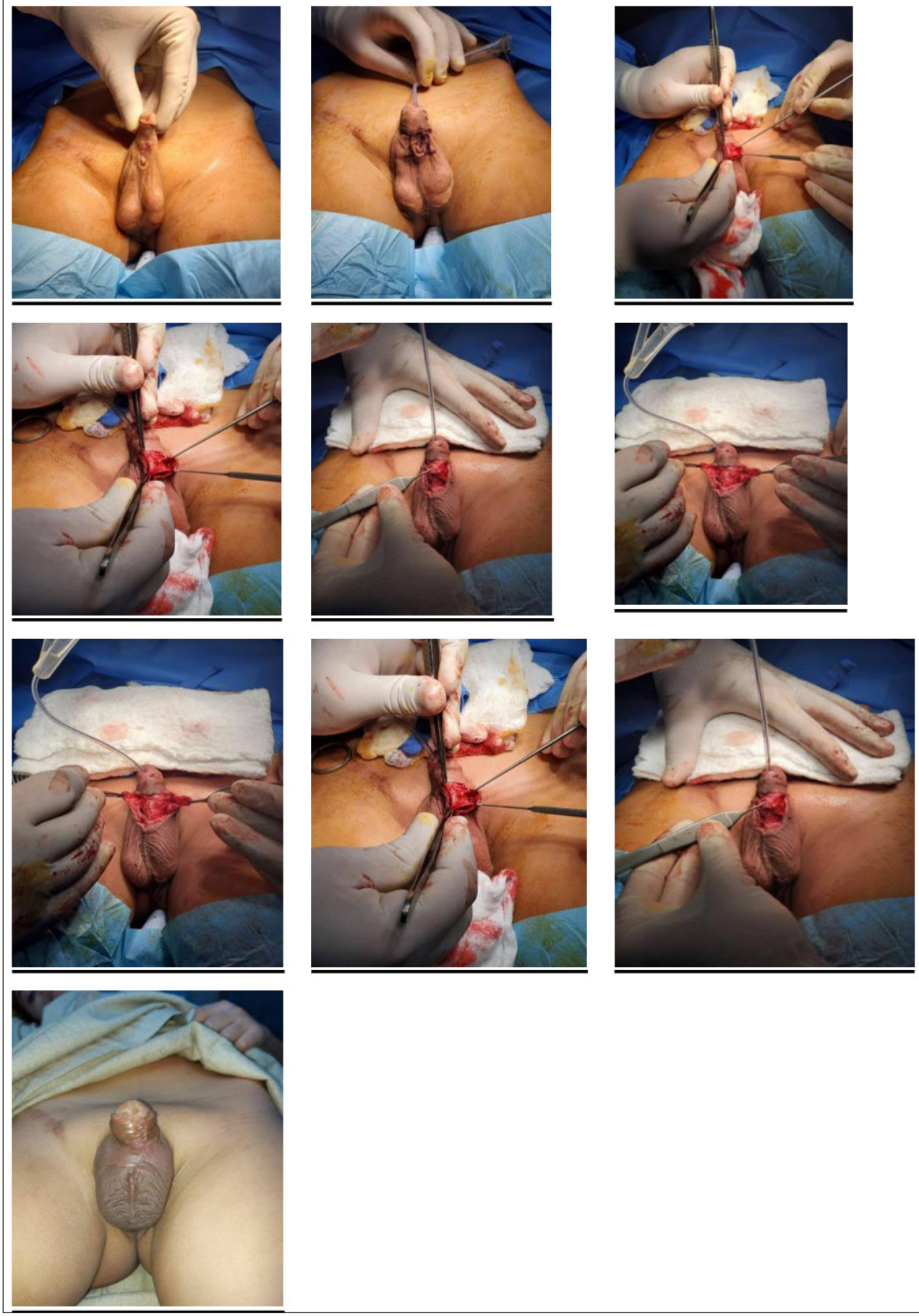

**Fig. 1.** Algorithm of surgery procedure

fistula. The size of fistula was ranging between 2.5-5 mm and most common site of fistula was the distal penile. Six of our patient had more than one fistula while 11 of them had previously failed fistula repair procedure. Eighteen patients (90%) had a successful fistula repair with normal urine stream and those patients showed no fistula recurrence during the follow-up period, which was 6 months postoperatively. Only two of our patients show developing the recurrence of fistula which was seen at 14th postoperative day at the time of catheter removal, and those two patients had no clear cause of fistula formation like postoperative infection, flap ischemia or distal obstruction. In all of treated patients, hadn`t been recorded the postoperative complication like wound dehiscence, wound infection, flap necrosis, hematoma or torsion of penis.

## DISCUSSION

Although some tiny urethrocutaneous fistula may spontaneously disappear, most of fistulas need for later surgical repairing. There are many surgical repairs that have being described for treatment of post hypospadias repair of urethrocutaneous fistula; however, it remains a frustrating problem to the patient and surgeon. These types of operations have a high risk of fistula recurrence, which will require re-fistula repair, which will further complicate subsequent fistula repair due to increased fibrosis and scarring of surrounding tissues. [7-9]. Although the simple closure of the urelurachaneon fistula provides less labor-intensive surgery and less technical effort, it is still associated with a high recurrence rate even in small fistulas, which is associated with overlapping suture lines [10]. Holland et al. [9] reported that the risk of recurrent urethral fistula significantly increased after simple closure. Published data showed that the mean success rate for simple fistula closure after hypospadias repair was 77%. The probability of success decreased from the second and third attempts when using a simple closure and can be as high as 50% [4]. Redman reported that the success rate for a fistula repair using simple closure was 80% of 51 fistulas, and this rate was decreased to half of those patient who had recurrence at the second closure [11]. In another study by Guan [12], in which they compared modified repair with foreskin glove removal with simple closure, they showed a significantly lower long-term recurrence rate compared to simple closure. To avoid overlapping of the suture line that occurs with a simple closure of a fistula, multi-layer plasty with highly vascularized tissue is offered, various vascularized flaps of various designs are offered, including penile and scrotal dartos fascia, Buk's fascia, the vaginal membrane and de-epithelialized skin. The last option was adapted in our study [7]. In the present study, a de-epithelialized skin flap was used for multi-layer closure of a urethrocutaneous fistula using the pant-over-vest technique. This method shows a 90% success rate with watertight closure of the fistula and no recurrence during the 6 month postoperative follow-up period. It has been shown that the vest-over-pants technique is a simple and effective method that can be used to close urethrocutaneous fistulas of various sizes and locations. We do not face the problem of closing the fistula without tension without deforming the shaft of the penis or the waist, such as constriction after surgery. This procedure provides a well-vascularised thick pliable tissue that provides a waterproof layer to close the fistula, and due to the design of their procedure, no overlap of the suture line is encountered, which may play a role in its high success rate. The use of a deepithelialized skin flap as a second layer to close the fistula would obviate the need for a hyoid flap, which requires a relatively excessive incision to collect the flap, which is of course difficult, especially in those parents who have previously failed surgery. In addition, harvesting of the dartos fascia may be associated with impaired vascularization of the overlying skin, which can lead to ischemia and necrosis. Our procedure did not require an extensive dissection and then reduced both the procedure time and the technical requirements of the operation. However, this procedure requires pliable healthy surrounding tissue that provides adequate mobility and compliance to cover the fistula, our procedure is limited to glandular and coronary fistulas. Since there is not enough local tissue in these areas to close the fistula without tension and subsequent complications, this was noted in our study, where those 2 cases of fistula recurrence were noted in the coronal area. The latter was reported in another study in Elbakri [8] where he reported of 371 recurrences of fistulas seen in the coronary sulcus, and Latifuglu showed that 52% of recurrent fistulas were observed in the area of the coronal sulcus. Another problem is associated with the use of the vest-over-pants technique for urethrocutaneous fistulas near the scrotum, since there is a risk of inclusion of hair -bearing tissue inside the repaired area. The vest-over-pants technique was used by Gite [14] for the treatment of 20 patients with postoperative hypospadias fistula. The size of the fistula was less than 5 mm in 15 patients and more than 5 mm in 5 patients. The fistula site was distributed as follows: coronal 10%, distal

penis 35%, medial penis 35%, and proximal penis 20%. Their results showed that the use of the vest-over-pants technique had a 100% success rate in the treatment of postoperative hypospadias in the form of urethral fistula repair, and this was consistent with our results. Another study by CiModor [15] compared simple fistula closure with repair of pants-over-vest, their result showed that the success rate on the first attempt of simple fistula closure was 74% and 94% for pants-over-vest repair, at the second attempt to close it was 80% with a simple closure of the fistula and 100% for pants-over-vest repair.

## CONCLUSIONS

The pants-over-vest technique provides a simple and effective way to eliminate a urethral fistula after hypospadias surgery with a high success rate and without deforming the penile skin shaft or constricting the waist after surgery.

## REFERENCES


1. Hadide AT, Azmy AF. Hypospadias surgery an illustrated guide. 2004. https://link.springer.com/book/10.1007/978-3-662-07841-9. [date access 02.01.2023]
2. Dodson JL, Baird AD, Baker LA et al. Outcomes of delayed hypospadias repair: implications for decision making. J Urol. 2007; 178(1):278-81, doi: 10.1016/j.juro.2007.03.055.
3. Sheheta S, Hashish M. Management of posthypospadias urethral fistula. Current concept of urethroplasty. 2011; 51: 48-60. doi: 10.5772/22653.
4. Strivastava RK, Tantale MS, Panes N et al. Management of urethrocutaneous fistula after hypospadias Surgery-An experience of thirty-five cases. Indian J Plast Surg. 2011; 44(1): 98–103, doi: 10.4103/0970-0358.81456.
5. Thomas DFM, Duffy PG, Rickwood AMK. Essentials of pediatric urology. 2nd ed., Informa healthcare. 2008, p. 229.
6. Soni A, Sheoron S. Repair of large urethrocutaneous fistula with dartos bases flap a study of 23 Cases. Indian J. Plastic Surgery. 2007; 40: 887-895.
7. Cimador M, Castagnetti M, De Grazia E. Urethrocutaneous fistula repair after hypospadias surgery. BJU Int. 2003; 92(6):621-3. doi: 10.1046/j.1464-410x.2003.04437.x.
8. Elbakry A. Management of urethrocutaneous fistula after hypospadias repair: 10 years' experience. BJU Int. 2001;88(6):590-5. doi: 10.1046/j.1464-4096.2001.02390.x.
9. Hollond AJ, Abubacker M, Smith GH, Coss DT. Management of urethrocutaneous fistula following hypospadias repair. Pediatr Surg Int. 2008; 24(9):1047-51. doi: 10.1007/s00383-008-2202-0.
10. Yassin T, Husein K, Husein A, El Minawi H. Assessment and Management of urethrocutaneous fistula developing after hypospadias repair. Annals of Pediatric Surgery. 2011; 7: 88-93. doi: 10.1097/01.XPS.0000397066.98404.82.
11. Redman JF. Result of unriveted Simple Closure of 51 urethrocutaneous fistula in boys. Urology. 1993; 41(4): 369-71. doi: 10.1016/0090-4295(93)90599-6.
12. Guen ZI, Wang SQ, Liu JL et al. Modified prepuce degloving repair for urethrocutaneous fistula following hypospadias surgery. Zhoughua Nan Ke Xue. 2013;19(12):1091-4.
13. Oglu LO, Yavuzer R, Unal S et al. Surgical treatment of urethral fistula following hypospadias repair. Ann Plast Surg. 2000; 44(4):381-6. doi: 10.1097/00000637-200044040-00005.
14. Gite VA, Patil SR, Bote SM et al. Durham Smith Vest Over – pants technique simple procedure for a complete problem (Post hypospadias repair fistula). Urol Int. 2017; 99(1):29-35. doi: 10.1159/000455159.
15. Cimador M, Castagnetti M, De Gvazia E. urethrocutaneous fistula repair after hypospadias surgery. BJU Int. 2003; 92(6):621-3. doi: 10.1046/j.1464-410x.2003.04437.x.



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ORIGINAL ARTICLE

# MENSTRUAL DISORDER IN ADOLESCENTS DURING WAR

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## ABSTRACT

**The aim:** To investigate the peculiarities of menstrual cycle disorders in teenagers against the background of excessive stress in order to develop a scientifically based set of measures for their correction.

**Materials and methods:** 120 girls aged 9-18 who were in the war zone or became forced migrants were examined. Examination methods included anamnesis collection, assessment of psycho-emotional state, anthropometry, laboratory and instrumental studies.

**Results:** It was found that the frequency of menstrual cycle disorders in the subjects was 65.8% (n = 79). Among menstrual cycle disorders: dysmenorrhea – 45.6% (n = 36), excessive menstruation – 27.8% (n = 22), secondary amenorrhea – 26.6% (n = 21). 71.7% (n = 86) of the examinees noted a change in eating behavior over the past few months. Almost half of these children had dyshormonal disorders or met the criteria of metabolic syndrome – 45.3% (n = 39).

**Conclusion:** Timely detection and adequate correction of psycho-emotional and metabolic disorders in adolescent girls in stressful conditions contributes to the prevention of disorders of menstrual and reproductive function.

**KEY WORDS:** chronic stress, abnormal uterine bleeding, metabolic syndrome, adolescent reproductive health, polycystic ovary syndrome, menstrual cycle disorders, menarche, adolescent obesity

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## INTRODUCTION

The United Nations (UN) reported that from the beginning of the Russian aggression against Ukraine until January 3, 2023, there have been 6,919 deaths and 17,994 injured. Disturbingly, a significant portion of these casualties were children, with an estimated 1,000 being under the age of 18 [1]. This is an average of more than five children per day. Only confirmed and identified cases are concerned. According to estimates, about 13 million Ukrainians left their homes, fleeing the war to other regions of Ukraine or abroad. And according to the latest research by the International Organization for Migration, as of July, more than 6.6 million people in Ukraine are internally displaced. Massive rocket attacks on critical infrastructure facilities in Ukraine, which left entire cities without electricity and heat, forced a large part of the population to leave their homes and move to other regions. This figure was 15% of the total population of Ukraine and continues to grow [2]. According to UN data, 6.65 million Ukrainians left for Europe as of mid-August. Almost 4 million of them are mainly women and children. Poland, Germany, and the Czech Republic sheltered the most Ukrainian refugees among European countries. The latter received 388,000 Ukrainian citizens [2].

War destroys a person's mental and physical health due to disruption of sleep and adequate rest, changes in eating behavior and physical activity. This is due to the fact that during the war, the human body is in a state of constant readiness to «defend or run.» Stress is a protective reaction to external stimuli and enables us to adapt to changes due to the active secretion of hormones of the adrenal glands: adrenaline and cortisol. Women are more sensitive to stress. This is due to the stimulating effect of estrogen on the hypothalamic-pituitary-adrenal system, which makes it more susceptible to stress factors than in men [3].

Teenagers are especially sensitive to stress. This is due to the fact that in the period of puberty undergoes individual important changes , its course depends on social and household, climatic and other conditions. Adolescence is one of the most important periods in a girl's development, its course programs the future psychosomatic state and reproductive function. Given the incomplete development of the reproductive system, gynecological diseases in teenage girls have a different

course than in adults, in addition, there are a number of pathological conditions that are not characteristic of adult women. Gynecological diseases of puberty are a risk factor for obstetric and perinatal complications leading to female infertility [4].

During puberty, the body is more susceptible to the effects of the environment, sensitive to acute and chronic stress factors, and has limited adaptive resources . The unstable balance of the hypothalamic-pituitary system is easily disturbed under the influence of adverse factors. The follicular apparatus of the ovaries and the receptor apparatus of the uterus can be affected, both as a result of injuries and intoxications, as well as a violation of hormonal regulation [4, 5].

During the war, most Ukrainian children and adolescents were separated from their families, mistreated, sexually assaulted, or forcibly deported [5, 6, 7]. According to the UN, at least 7.5 million children suffer both physical and mental trauma during military conflicts. The acute stress, loss of housing, malnutrition and infectious diseases accompanying children during military conflicts increase the likelihood of chronic non-communicable diseases in adulthood, including diabetes, cardiovascular disease, chronic lung disease and reproductive disorders [1, 8].

High levels of cortisol caused by stress affect all levels of the hypothalamic-pituitary-ovarian system, leading to an imbalance of estrogen, progesterone, and testosterone. Acting on the hypothalamus, cortisol reduces the secretion of releasing hormones, directly suppresses the synthesis of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and in the ovaries, the stress hormone reduces their sensitivity to the already insufficient amount of FSH and LH. Therefore, even short-term stress can contribute to the development of transient hyperandrogenism, anovulation, violation of the menstrual cycle, fluctuations in body weight, and the formation of polycystic changes in the ovaries [6, 7, 8, 9].

During military conflicts, factors such as chronic stress and sleep disturbances lead to hyperstimulation of the adrenal cortex and increased levels of circulating cortisol in the blood. Violation of the circadian level of cortisol stimulates the deposition of fat in the upper body. Abnormal daily rhythms of cortisol combined with disordered eating behavior, which is also characteristic of wartime, increase the risk of hypertrophy of visceral adipocytes. Therefore, the development of visceral obesity can be considered an inadequate response to stress [7]. It is known that adipose tissue is also involved in the regulation of the menstrual cycle, as it synthesizes female sex hormones. Chronic stress and the influence of adverse environmental factors against the background of metabolic syndrome (MS) and obesity disrupt adaptation mechanisms, the work of the hypothalamic-pituitary-ovarian system, which leads to hormonal and reproductive disorders [8]. These disorders are especially evident during puberty, which is the main crisis period in the functioning of a woman's reproductive system. Dysfunction of the hypothalamic-pituitary-ovarian system against the background of MS affects the normal maturation of the follicle, disrupts the adequate secretion of FSH and LH, changes the sensitivity of progesterone receptors and leads to progesterone deficiency. As a result, such features of the endocrine profile in adolescent girls are manifested by menstrual cycle disorders and chronic anovulation [8]. Oligomenorrhoea or amenorrhoea can be used as potential components of the metabolic syndrome in adolescent girls, which develops against the background of chronic stress.

Prolonged stress can lead to a state of chronic hypercorticism, which contributes to the development of insulin resistance, the progression of obesity and the formation of type 2 diabetes. In addition, obesity creates a special hormonal environment in a woman's body, in the form of hyperinsulinemia, hyperandrogenemia, hyperestrogenemia, increased leptin levels, which negatively affects female fertility. As a result, there is a violation of the menstrual cycle, irregular ovulation, a long absence of conception and, even when using assisted reproductive technologies, a low percentage of their effectiveness [9 – 11].

Another indicator involved in the regulation of stress processes is prolactin (PRL). Hyperprolactinemia promotes the synthesis of adrenocorticotropic hormone (ACTH) and directly increases the levels of adrenal androgens, cortisol and aldosterone, stimulates the synthesis of catecholamines in the adrenal glands. In addition, receptors for PRL are also on adipocytes, and therefore it has a direct effect on biologically active substances in adipose tissue. First of all, this dynamic interaction of ACTH and PRL is aimed at forming the body's adaptive response to stress through the coordinated secretion of cortisol and dehydroepiandrosterone-sulfate (DHEA-c) in the adrenal glands. However, with chronic stress, the ratio of cortisol and DHEA-c is disturbed in the direction of increasing the latter, which leads to hyperandrogenic states and reproductive disorders [9, 10].

It is important to note that obesity and metabolic disorders in adolescents are reversible. Therefore, early detection, timely and effective correction of metabolic disorders and menstrual function is an important component of the prevention of MS and its complications [2, 3, 11].

Primary dysmenorrhea, aggravated by the appearance of pain during menstruation without severe pelvic pathology at the beginning of menstruation, also increases before the age of 20 years. Primary dysmenorrhea is associated with uterine contraction and vasoconstriction, a significant elevation in endometrial prostaglandin F2α level in the late secretory phase, an increase in myometrial tone, and a significant growth in uterine contraction. However, other factors related to the sensation and stimulation of pain may also be involved. Menstrual cramps have a negative impact on girls' quality of life and can interfere with their daily lives, leading, for example, to missing school, depression, which is exacerbated by the stress of fighting. [9, 12, 13].

Thus, studying the distribution and nature of reproductive health disorders against the background of long-term stress is an urgent issue for reproducing a complete picture of the pathogenesis of the development of reproductive disorders, which will allow the development of effective prevention and treatment strategies.

## THE AIM

To investigate the peculiarities of menstrual cycle disorders in teenagers against the background of excessive stress in order to develop a scientifically based set of measures for their correction.

## MATERIALS AND METHODS

120 girls aged 9-18 who were in the war zone or became forced migrants were examined. Examination methods included anamnesis collection, assessment of psycho-emotional state, anthropometry, laboratory and instrumental studies. A survey was conducted on socio-demographic context and menstrual cycle characteristics, as well as weight and height measures. Body mass index (BMI) was classified according to the criteria of the International Working Group on Obesity. This study adhered to the ethical principles of research involving human subjects. Information about the aims and procedures of the study was provided to each participant, and written informed consent was obtained from the participants' legal guardians or from themselves if they were 18 years of age or older. Confidentiality, anonymity and non-transferability of data were ensured. Students were asked to complete an anonymous questionnaire that included questions about health and well-being, lifestyle, and sociodemographic characteristics. Information about the menstrual cycle using the Menstrual Disorder of Teenagers (MDOT) questionnaire. The menstrual cycle was characterized by the following characteristics: regularity of the menstrual cycle (regular or irregular), duration of the menstrual cycle (≤6 or >6 days), dysmenorrhea (yes or no), impact of dysmenorrhea on school absences (yes or no), and use of pain medication for dysmenorrhea (yes or no). Girls were also asked whether they previously recorded the first day of their period (yes or no) as a proxy for self-monitoring of their cycle.

Anthropometric measurements were performed using standardized procedures. A trained researcher measured the height and weight of each participant in light clothing and without shoes. Weight (kg) was measured using electronic portable scales with an accuracy of 0.1 kg.

The menstrual cycle was assessed according to the FIGO 2018 classification (Table I). Pathological menarche was defined as the early (up to 10 years) or late (after 15 years) onset of menstrual function and/or the onset of menarche later than 3 years after thelarche.

According to the recommendations of IDF (2007) [13], the criteria for identifying the components of MS were: obesity – body mass index (BMI); arterial hypertension – arterial pressure (BP); hyper dyslipidemia – serum levels of triglycerides, total cholesterol (cholesterol), low-density lipoprotein (LDL) and high-density lipoprotein (HDL); insulin resistance (IR) – HOMA index; hyperglycemia – fasting blood glucose. Threshold values of the lipid profile were: triglycerides – 1.7 mmol/l, HDL – 1.03 mmol/l, cholesterol – 4.25 mmol/l, LDL – 2.75 mmol/l. Fasting hyperglycemia was considered at blood glucose levels > 5.6 mmol/l. IR was diagnosed at the HOMA index level > 2.5.

Polycystic ovary syndrome (PCOS) was diagnosed according to the Rotterdam criteria (2003): oligo – or anovulation (≤ 6 menstrual periods per year); clinical or laboratory hyperandrogenism (hirsutism/acne) and/or hyperandrogenemia (increased levels of free testosterone in the blood); polycystic ovaries during transvaginal ultrasound (≥ 20 follicles 2–9 mm in size in each ovary).

Statistical processing and analysis of the obtained data was performed using «Microsoft Excel» programs using the methods of mathematical statistics and the software package Statistica 8.0. Charts and diagrams were built using «Microsoft Excel». Mathematical processing of indicators was performed using the methods of variation statistics for comparing inhaled sets by averages using the t-Student test.

## RESULTS

The average age of the girls was 15.5±1.6 years, 57.7% of them were between 15 and 18 years old. Most of the girls were from families where the mother and father

**Table I.** Characteristics of the normal menstrual cycle (FIGO 2018)

| Parameter | Normal | Abnormal |
|---|---|---|
| Frequency | Absent (no bleeding) = amenorrhea | |
| | Infrequent (> 38 days) | |
| | Normal (≥ 24 to ≤ 38 days) | |
| | Frequent (< 24 days) | |
| Duration | Normal ( ≤ 8 days) | |
| | Prolonged (> 8 days) | |
| Regularity | Normal or "Regular" (shortest to longest cycle variation: ≤ 7–9 days)* | |
| | Irregular (shortest to longest cycle variation: ≥ 8–10 days)* | |
| Flow Volume (patient determined) | Light | |
| | Normal | |
| | Heavy | |
| Intermenstrual Bleeding (IMB) Bleeding between cyclically regular onset of menses | None | |
| | Random | |
| | Cyclic (Predictable) | Early cycle |
| | | Mid cycle |
| | | Late cycle |
| Unsheduled Bleeding on Progestin ± Estrogen Gonadal Steroids (birth control pills, rings, patches or injections) | Not Applicable (not on gonadal steroid medication) | |
| | None (on gonal steroid medication) | |
| | Present | |

**Table II.** Frequency of menstrual disorders among adolescents n (%)

| | The number of examinees n = 120 | |
|---|---|---|
| | abs | % |
| Frequency of menstrual disorders | 79 | 65.8 |
| Secondary amenorrhea | 21 | 26.6 |
| Excessive menstruation during puberty | 22 | 27.8 |
| Pathological menarche | 63 | 52.5 |
| Dysmenorrhea | 36 | 45,6 |
| Metabolic syndrome | 74 | 61.7 |

had ≤ 9 years of education (61.8 and 60.0%, respectively), and the parents were married (62.9%). The average age at menarche of the examined patients was 12.4 years, and the average BMI was 22.0 kg/m$^2$.

It was established that the frequency of menstrual cycle disorders in the examined group was 65.8% (n = 79). Among the disorders of the menstrual cycle, the following were most often noted: dysmenorrhea – 45.6% (n = 36), excessive menstruation during puberty – 27.8% (n = 22), secondary amenorrhea(SA) – 26.6% (n = 21). Pathological menarche(PM) was noted by 52.5% (n = 63) of the examined. 81.7% (n = 63) of respondents noted a change in eating behavior over the past few months. More than half of these children had dyshormonal disorders or met the criteria of metabolic syndrome – 61.7% (n = 74) (Table II).

Higher maternal education was associated with higher menstrual cycle self-control among the sample (OR 1.60; 95% CI 1.15–2.17). Girls with menarche aged <12 years are more likely to have menstrual cycles > 6 days (OR 1.73; 95% CI 1.19–2.51) and dysmenorrhea (OR 1.87; 95% CI 1.11–3.16 ) than girls with menarche ≥12 years. One of the problems in the subjects was a significant level of MDs against the background of prolonged stress. Such a prevalence of this problem may be associated primarily with a hormonal response to stress, as well as with limited motor activity caused by a long stay in shelters, lack of usual physical exertion, sports, eating disorders with irregular eating, overeating high-calorie food or fast food after forced starvation. A detailed analysis was conducted with a cohort of selected medical records of adolescents with confirmed MS. Therefore,

another component of MS in adolescents can be considered menstrual irregularities. Among menstrual disorders of girls with MS and obesity, oligomenorrhea prevailed – 36.5 % (n = 27). Secondary amenorrhea was noted in 28.3 % (n = 21) of girls with MS. Excessive menstruation was observed much more often of girls with MS – 17.6 % (n = 13) and dysmenorrhea of 17.6 % (n = 13). The presented MDs were significantly different from the parameters of girls with normal weight with a high degree of reliability ($p < 0.05$).

It was found that the frequency of menstrual cycle disorders in the subjects was 65.8% (n = 79). Among menstrual cycle disorders: dysmenorrhea – 45.6% (n = 36), among which 49% took painkillers, and 65% independently monitor their menstrual cycle, excessive menstruation – 27.8% (n = 22), secondary amenorrhea – 26.6% (n = 21). 71.7% (n = 86) of the examinees noted a change in eating behavior over the past few months. Higher maternal education was associated with higher menstrual cycle self-control among the sample (OR 1.60; 95% CI 1.15–2.17). Girls with menarche aged <12 years are more likely to have menstrual cycles >6 days (OR 1.73; 95% CI 1.19–2.51) and dysmenorrhea (OR 1.87; 95% CI 1.11–3.16 ) than girls with menarche ≥12 years.

One of the problems in the subjects was a significant level of metabolic disorders against the background of prolonged stress. Such a prevalence of this problem may be associated primarily with a hormonal response to stress, as well as with limited motor activity caused by a long stay in shelters, lack of usual physical exertion, sports, eating disorders with irregular eating, overeating high-calorie food or fast food after forced starvation. Almost half of these children had dyshormonal disorders or met the criteria of metabolic syndrome – 45.3% (n = 39).

## DISCUSSION

MDs refer to a range of conditions that can affect a woman's menstrual cycle. These disorders can include heavy or irregular periods, painful cramps, and premenstrual syndrome (PMS ) [12]. They can also include more serious conditions such as endometriosis and polycystic ovary syndrome [13]. The causes of MDs can be complex and may include hormonal imbalances, structural issues within the reproductive system, and certain medical conditions. Stress-induced menstruation abnormalities are one of the most prevalent health issues for females living in war-torn environments [14].

Secondary amenorrhea (SA) is a common reproductive health concern that affects a significant proportion of women. It is defined as the absence of menstrual periods in a woman who has previously had regular menstrual cycles. SA was found to be extremely common in our adolescent sample, affecting 26.6% of the population. This is astronomically high when compared to the typical 3-4% of reproductive-age women affected [13]. The cause of our sample population's high rate of SA could be stress-induced anovulation. This condition, also known as functional hypothalamic amenorrhea (FHA), is a common cause of SA. It is caused by reproductive dysfunction, which is similar to that caused by malnutrition, excessive exercise, severe emotional stress, and chronic diseases. SA is a serious issue that can lead to long-term reproductive and emotional problems such as infertility and reduced quality of life. It can also cause bone loss and increase the risk of osteoporosis. Furthermore, SA can be a sign of serious underlying medical conditions such as polycystic ovary syndrome, thyroid disorders, and pituitary tumors. As a result, it is critical to address and treat SA promptly to avoid further complications [13].

Subsequently, our study discovered that 27.8% of the sample population reported having excessive menstruation during puberty, which is a significantly higher percentage than the estimated prevalence of 9%-14% in healthy women [15]. War-induced stress may be a factor in this high rate of excessive menstruation. High levels of stress hormones, such as cortisol, caused by war-related stressors can disrupt the body's balance of estrogen and progesterone, resulting in abnormal uterine bleeding. Furthermore, displacement and a lack of access to healthcare during a war can contribute to excessive menstruation by making it difficult for individuals to receive proper medical treatment for underlying causes of heavy bleeding.

Pathological menarche (PM) is a condition in which a girl's first menstrual period occurs at an unusually young age. This condition was prevalent in 52.5% of our sample population, which is comparable to 48% of adolescent girls whose abnormal first menstrual period was associated with stress and unhealthy living conditions in rural Bangladesh [16]. War-related stress can cause an increase in the levels of stress hormones such as cortisol, which can disrupt the body's balance of estrogen and progesterone and lead to the earlier onset of menarche. Additionally, displacement and lack of access to healthcare can also contribute to PM as it can make it difficult for individuals to receive proper medical treatment for underlying causes of early onset of menarche [16].

A recent study of adolescent Ghanaian schoolgirls discovered that 68.1% had dysmenorrhea, a condition characterized by severe pain during menstruation [17]. According to the study, this high prevalence may be

related to the participants' high levels of stress. This correlation is strengthened by the fact that 45.6% of our sample population reported having dysmenorrhea, indicating a strong connection between stress and the condition. War-related stress can still contribute to this condition by altering hormone levels and disrupting the normal functioning of the menstrual cycle. Dysmenorrhea has a significant physical and emotional impact, causing pain, discomfort, fatigue, emotional distress, and an increased risk of infection and other complications if left untreated. It can also be a symptom of serious underlying medical conditions like endometriosis, uterine fibroids, or adenomyosis. Therefore, it is important to treat dysmenorrhea timely and effectively to prevent any further complications [17].

The high rate of MS in our sample population (61.7%) is also cause for concern, given that several studies have shown a strong connection between stress and MSs [18]. Stress from war can raise the levels of stress hormones like cortisol, which can disrupt the body's glucose and insulin balance, resulting in high blood sugar levels. Furthermore, during war, lack of access to healthcare and adequate nutrition can all exacerbate the development of MS. MS has a significant physical and emotional impact, increasing the risk of heart disease, stroke, diabetes, and emotional distress, as well as increasing the risk of infection and other complications if untreated. Furthermore, MS can be a symptom of more serious underlying medical conditions like obesity, polycystic ovary syndrome, and thyroid disorders. As a result, it is very important to treat MS timely and effectively in order to avoid further complications.

The fact that 65.8% of the adolescents in this study have some form of MDs indicates significant disruptions or changes in their menstrual cycle. When compared to other war-related findings conducted by Hannoun *et al.,* where 35% of women surveyed reported experiencing menstrual abnormalities as a result of war-related stressors [14], our findings are astronomically high with 65.8%. This high occurrence of MDs in Ukraine highlights the devastating effects of the war, as well as the fact that war-related stressors have a significant impact on the menstrual cycle, and that interventions are required to address this issue.

In addition, studies have found that people living in war-torn areas have a higher prevalence of eating disorders, as a results of stressors of the war. According to Antoine et al., stress caused by war is a major contributor to the development of eating disorders. This was demonstrated in a sample of 300 Lebanese students, with 71% reporting eating disorders during times of war [19]. Furthermore, Wiksten et al. discovered a connection between menstrual disorders and various types of eating disorders, with 68% of adolescent girls diagnosed with menstrual disorders also being diagnosed with eating disorders. This may explain why a large proportion (81%) of adolescent girls in Ukraine's war-torn population developed eating disorders, leading to an increase in MDs. One of the most common types of eating disorders, anorexia nervosa, can be cause in a significant decrease in body weight and fat, which can give a disruption in the menstrual cycle, including amenorrhea (absence of menstrual periods) and oligomenorrhea (infrequent or light menstrual periods). Another type of eating disorder, bulimia nervosa, can disrupt the menstrual cycle and cause hormonal imbalances. Furthermore, the psychological stressors of war can result in MDs on their own. These combined effects of eating disorders and war-related stress can have a significant impact on the physical and mental health of individuals living in war-affected areas [20].

Addressing this issue requires a multifaceted approach that considers both the physical and emotional effects of war-related stressors. Medical treatment, counseling and support services, nutritional assistance, education and awareness, and access to health care are all possible measures. These interventions should be tailored to the specific needs and cultural context of the adolescent population and implemented in collaboration with local health care providers and organizations. It is also extremely important to reduce the root cause of war and displacement, which causes stress in the first place. The study notes the need for additional interventions to address the problem of war-related medical illness among adolescents. Understanding the specific causes and risk factors for these disorders in the context of war-related stress is critical, as is developing interventions such as counseling, medical treatment, and support services to help people suffering from war-related medical conditions.

Limitations of the study were the inability to conduct a random sample and the underrepresentation of adolescent girls in Ukraine (fewer participants compared to war-affected adolescent girls). Volunteer bias can underestimate or overestimate prevalence estimates, affecting the association between menstrual irregularities and war-related stress to a lesser extent.

## CONCLUSIONS

Timely detection and adequate correction of psycho-emotional and metabolic disorders in girls under stressful conditions contributes to the prevention of menstrual and reproductive disorders.

## REFERENCES


1. Padda J, Khalid K, Hitawala G, et al. (July 21, 2021) Depression and Its Effect on the Menstrual Cycle. Cureus 13(7): e16532. doi:10.7759/cureus.16532
2. Saboor Aftab SA, Kumar S, Barber TM. The role of obesity and type 2 diabetes mellitus in the development of male obesity-associated secondary hypogonadism. Clin Endocrinol (Oxf). 2013;78(3):330-7. doi: 10.1111/cen.12092.
3. Desroches S, Lamarche B. The evolving definitions and increasing prevalence of the metabolic syndrome. Appl. Physiol., Nutr. Metab. 2007;32(1):23-32. doi: 10.1139/h06-095.
4. Ritchie SA, Connell JMC. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. Nutr. Metab. Cardiovasc. Dis. 2007;17(4):319–6. doi:10.1016/j.numecd.2006.07.005.
5. Agudelo GM, Bedoya G, Estrada A, et al. Variations in the prevalence of metabolic syndrome in adolescents according to different criteria used for diagnosis: which definition should be chosen for this age group? Metabolic Syndrome and Related Disorders. 2014; 12(4):202-9. doi:10.1089/met.2013.0127.
6. Friend A, Craig L, Turner S. The prevalence of metabolic syndrome in children: a systematic review of the literature. Metabolic Syndrome and Related Disorders.2013;11:71-80.
7. Cook S, Weitzman M, Auinger P, et al. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. Arch. Pediatrician Adolescent Med. 2013;157:821-7. doi:10.1001/ARCHPEDI.157.8.821
8. Zelinska NB. Metabolic syndrome in children. Health of Ukraine. 2013;6: 48-51.
9. Fleming R, Hopkinson ZE, Wallace AM, et al. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double-blind placebo-controlled trial. The Jornal of Clinical Endocrinology and Metabolism. 2002; 87(2):569-74. doi:10.1210/jcem.87.2.8261.
10. Tatarchuk TF, Kosey NV, Regeda SI, et al. The role of reproductive health disorders in the development of metabolic syndrome in women. Journal of the National Academy of Medical Sciences of Ukraine. 2019;25(1):77-87.
11. Sartor BM, Dickey RP. Polycystic ovarian syndrome and the metabolic syndrome. Am. J. Med. Sci. 2005;330(6):336-42. doi: 10.1097/00000441-200512000-00012.
12. Lim SS, Kakoly NS, Tan JWJ, et al. Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. Obes. Rev. 2019;20(2):339-52. doi: 10.1111/obr.12762.
13. Fazleen NE, Whittaker M, Mamun A. Risk of metabolic syndrome in adolescents with polycystic ovarian syndrome: a systematic review and meta-analysis. Diab. Metab. Syndr. 2018; 12(6):1083-90. doi: 10.1016/j.dsx.2018.03.014.
14. Zimmet P, Alberti KG, Kaufman FT, et.al. IDF Consensus. The metabolic syndrome in children and adolescents – the IDF consensus report. Pediat Diabetes. 2007;5:299-306. doi: 10.1097/00000441-200512000-00012.
15. Reisinger C, Nkeh-Chungag BN, Fredriksen PM, Goswami N. The prevalence of pediatric metabolic syndrome — a critical look on the discrepancies between definitions and its clinical importance. International Journal of Obesity. 2021;45:12-24.
16. Malitha JM, Islam MA, Islam S, et al. Early age at menarche and its associated factors in school girls (age, 10 to 12 years) in Bangladesh: a cross-section survey in Rajshahi District, Bangladesh. J Physiol Anthropol. 2020 Mar 23;39(1):6. doi: 10.1186/s40101-020-00218-w.
17. Acheampong K, Baffour-Awuah D, Ganu D, et al. Prevalence and Predictors of Dysmenorrhea, Its Effect, and Coping Mechanisms among Adolescents in Shai Osudoku District, Ghana. Obstet Gynecol Int. 2019 May 20;2019:5834159. doi: 10.1155/2019/5834159.
18. Janczura M, Bochenek G, Nowobilski R, et al. The Relationship of Metabolic Syndrome with Stress, Coronary Heart Disease and Pulmonary Function--An Occupational Cohort-Based Study. PLoS One. 2015 Aug 14;10(8):e0133750. doi: 10.1371/journal.pone.0133750.
19. Aoun A, Garcia FD, Mounzer C, et al. War stress may be another risk factor for eating disorders in civilians: a study in Lebanese university students. Gen Hosp Psychiatry. 2013 Jul-Aug;35(4):393-7. doi: 10.1016/j.genhosppsych.2013.02.007.
20. Wiksten-Almströmer M, Hirschberg AL, Hagenfeldt K. Menstrual disorders and associated factors among adolescent girls visiting a youth clinic. Acta Obstet Gynecol Scand. 2007;86(1):65-72. doi: 10.1080/00016340601034970.


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ORIGINAL ARTICLE

# CRIMINAL OFFENCES RELATED TO ILLICIT TRAFFICKING IN FALSIFIED MEDICINES: INVESTIGATION PROBLEMS

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## ABSTRACT

**The aim:** Formulate recommendations for improving the efficiency of detection and investigation of trafficking in falsified medicines, application of criminalistics knowledge. To analise the contemporary condition and the latest trends in combating this type of crimes and to justify the need for creation of a complex criminalistic methodic investigation.

**Materials and methods:** Analysis of the applicable laws governing trade in medical products in Ukraine; judgments of courts of Ukraine for the period from 2013 to 2022; results of generalization of 128 criminal proceedings; active employee survey results (205 respondents) etc. Over the course of the present research, we have used general scientific and specialised research methods.

**Results and Conclusions:** Increasing the effectiveness of combating the illegal circulation of falsified falsified medicines is a complex problem that encompasses a whole system of directions, requiring the combined efforts of international bodies and organizations, various scientists. One of the priority directions for the introduction of an effective mechanism for combating the distribution of falsified medicines is the development of a complex criminalistic methodic investigation.

**KEY WORDS:** criminalistics, methodics of investigation, falsification of medicines, criminalistic means of combating, specialised knowledge

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## INTRODUCTION

Nowadays falsification and contribution of falsified medicines have become a global-scale problem[1]. Today, it have acquired the characteristics of a separate sector of the shadow economy and "promising" criminal business, which is essentially transnational organized crime [2]. Pharmaceutical market is the third largest sector of international shadow economy only behind firearms and drug trafficking. The WHO experts assess the total value of the illicit global pharmaceutical market in $30 bln [3]. These criminal activities are currently acquiring the characteristics of international (transnational) crime [4], as they are often committed in several countries at once and require the strengthening of international cooperation in the field of detection, investigation and prevention criminal offenses related to illicit trafficking in falsified medicines [5, 6].

The root cause of the globalization of falsification and trafficking in falsified medicines is often cited in the literature [7, 8] as the inadequacy of the legislative framework to ensure a reliable system of means of countering these criminal manifestations and the lack of effective mechanisms for the detection, investigation and prevention of such criminal activity. Unfortunately, today there is no single approach to understanding falsified medicines and an efficient mechanism for combating trafficking in fraudulent medicines both on domestic and on international level, there is no productive international cooperation in the field, no proper data exchange, no unified database on the detected and registered facts with falsified falsified medicines and all of the above makes the coorperation between law-enforcement authorities of different countries much more difficult.

We can circle out several circumstances that encourage the increase in this type of crimes: a) development of international trade and border transparency while national legislations of most countries have not been brought into compliance with the international international law, which makes it difficult to effectively combat criminals who operate on a transnational scale; b) high profitability of this type of illegal activities compared to "traditional" crime [9]. Moreover, criminals use the latest tools and echniques of falsification and illegal distribution of falsified medicines, first of all, by using ICT, various webpages, social media etc. These distribution technologies make it possible for criminals to respond immediately to potential threats, in particular, by quickly opening an illegal online pharmacy,

changing its IP address or urgently closing the outlet once certain legal risks arise [10].

Falsification and illicit trafficking of falsified medicines have become the plague of the 21st century and they are spreading not at the local level, but at the global and international levels, thus posing a significant threat to the global health system [11]. Production of fraudulent medicines and illegal distribution of falsified medicines Jürgen Stock, Secretary General of International Criminal Police Organization, made a witty remark that it is an utter contempt to human life to be involved in trafficking in fraudulent medicines at the time of a real crisis of the global public health system [12].

Furthermore, a wide use of the potential of online trade in medical products that started rapidly growing during the COVID-19 pandemic only contributes to rapid and uncontrollable distribution of fraudulent medicines and trafficking in registered and unregistered pharmaceuticals, veterinary medicines and medical products. Today, Ukraine hosts a diversified system of illegal online pharmacies trading in pharmaceuticals of unknown origin that are not subject to quality assurance tests, control of origin, conditions of storage and transportation as set forth by the Law of Ukraine "On Pharmaceuticals". This type of illegal online activities has grown exponentially since 2020 after the legislation was adopted to permit the online retail trade in pharmaceuticals not restrained by a proper control system [13].

The current situation indicates the latency of manifestations of criminal activity related to the falsification of medicinal products and the illegal circulation of falsified medicines the professional skill of criminals, as well as the insufficient efficiency of state, law enforcement, and judicial bodies. Thus, the analysis of court practice under Art. 321-1 of the Criminal Code of Ukraine shows the inadequate severity of punishment for falsification and illicit trafficking of falsified medicines because it is imposed unfairly. We have analysed 28 sentences under Art. 321-1 of the Criminal Code of Ukraine for the period from 2013 to 2020, of which 2 sentenses were acquittals and 29 persons were convicted (26 sentences). Only 28 persons were sentenced to up to 5 years in prison, then released from prison and put on probation under Art. 75 of the Criminal Code of Ukraine. As we can see, no one charged with falsification of medicinal products and illicit trafficking of falsified medicines has indeed spent time in prison in Ukraine. On the one hand, it shows that Art. 321-1 of the Criminal Code of Ukraine is unenforceable and it is not enforced in practice; on the other hand, Ukrainian courts are exceptionally lenient on these types of criminals, as evidenced by their regular decisions to release criminals from prison [14]. It should be noted that unfortunately, the situation has not improved in 2021-2022 and it only emphasises the low efficiency of legaslation and government agencies, law-enforcement bodies and judiciary in the field of combating falsification of medicinal products and illicit trafficking of falsified medicines.

Practice shows that only separate instances of falsification of medicinal products are uncovered today, although we are aware of criminal cases when investigators uncovered hundreds of earlier episodes of criminal activities during investigation. This category of latent crimes encompasses the following large schemes: illegal smuggling of large quantities of falsified medicines, large-scale vaccine and stolen medical alcohol smuggling schemes as well as trafficking in falsified medicines and other related crimes. All of the above interferes with the social and law-enforcement functions of the state, as the state is unable perform the quality assurance of pharmaceutical and provide proper response to socially dangerous activities related to illicit trafficking of falsified medicines.

Moreover, the absence of a single criminalistics investigation methodic for falsified medical products-related crimes calls for development of efficient guidelines for crime detection, investigation and prevention as well as for formulation of a complex criminalistics investigation methodic for this type of criminal offenses and for increased efficiency of practical application of specialised and criminalistics knowledge in combating trafficking of falsified medicines using criminalistics techniques and methods.

Therefore, there is a need in creation and introduction of an efficient criminal law and criminalistics mechanism for combating of illicit trafficking of falsified medicines that pose a global threat to population's health, may cause death or inflict serious harm to human health. It is crucial that such a mechanism exist on international, regional and national levels [15]. The need arises for activisation of harmonisation and convergence of the national legislation and Western European rules and regulations and international pharmaceutical standards [16, 17], in particular, concerning efficient combating of falsified medicines-related criminal offenses and illicit trafficking of falsified medicines. As a candidate for the EU membership and an active participant in international cooperation, Ukraine undertakes to comply with international requirements for pharmaceutical safety, quality assurance and effectiveness on all stages of trade and to contribute to and strengthen international cooperation in pharmaceutical sphere.

## THE AIM

The aim of the article is to study the contemporary condition and the latests trends in combating of

falsification of medicinal products and illicit trafficking of falsified medicines in Ukraine, to analyse the challenges of formulation and implementation of an effective criminal law and criminalistics mechanism for combating this type of crimes on domestic and internatuional level as well as to make suggestons on imprival of such mechanism and formulation of a complex criminalistics investigation methodic for this category of criminal offenses. Formulate recommendations for improving the efficiency of detection and investigation of illicit trafficking in falsified medicines, application of specialised and criminalistics knowledge in combating transnational organised crime with due regard tointernational experience and contemporary needs of investigation activities and court practice.

## MATERIALS AND METHODS

The research included study and analysis of the applicable criminal legislation of Ukraine and laws governing trade in medical products in Ukraine; the WHO guidelines on combating trafficking in falsified medicines [3]; Council of Europe Convention on the Counterfeiting of Medical Products and Similar Crimes Involving Threats to Public Health dated 28.10.2011 [11]; statistical information for 2013-2022 published by the Office of the Prosecutor General of Ukraine [14,18]; results of generalization and analysis of 128 criminal proceedings of such crimes, Ukrainian court sentences delivered in 2013-2022 under Art. 321-1 of the Criminal Code of Ukraine; active employee survey results (205 respondents) etc.; outcomes of generalisation and analysis of the published investigation and court records; international experience of combating trafficking in falsified medicines. Methodological framework of the research is a dialectical scientific cognition method that reflects the interconnection between the theory and practice as well as concepts of criminalistics. Over the course of the present research, we have used general scientific and specialised research methods, in particular, dialectical, analytical, statistical, induction and deduction, systemic and structural analysis.

## RESULTS AND DISCUSSION

Falsification and illicit trafficking of falsified medicines significant losses to the public budget, pose a fairly significant threat to the population's life and health, criminalise the pharmaceutical market, negatively affect the nation's health and pose a real threat to economic, social and national security of the state. The presence of falsified medicines market in Ukraine poses a threat to the Ukrainian's life and health and negatively affects the image of lead Ukrainian pharmaceutical producers [18]. Every civilised country undertakes to create an efficient public healthcare system for its citizens with the use of safe and top-quality medical products as its essential part. This obligation is based both on the requirements of international law and on the national constituitional norms and principles[19].

At the same time, the significant growth and wide scale of criminal activities are mostly explained by contemporary social and economic and political problems plaguing the society, imperfections in domestic and international legislation [20], improper organisation of the judiciary and law-enforcement agencies and certain difficulties in combating illicit trafficking of falsified medicines. At the same time, it is important to note that mechanisms of trafficking in falsified medicines are fairly diverse today and they are constrantly changing depending on the circumstances. Lately, this mechanism has changed significantly due to changes in social life, pandemic and spread of COVID-19 [21], declaration of martial law in Ukraine and the start of the Russian military aggression and waging war [22].

It is important to note that in order to combat these negative phenomena, the Ukrainian legislation provides for criminal responsibility for falsification of medicines and illicit trafficking of falsified medicines (Art. 321-1 of the Criminal Code of Ukraine). Practice shows that this type of crimes is usually combined with other related crimes (smuggling of drugs, phychotropic substances, their analogs or precursors or falsified medicines) (Art. 305 of the Criminal Code of Ukraine); violation of the prescribed procedure for pre-trial investigation of clinical tests and state registration of medicinal products (Art. 321-1 of the Criminal Code of Ukraine). At the same time, these elements of criminal offenses have the main common feature – the subject of a criminal offense, which is falsified medicines [12].

Having analysed these articles of the Criminal Code of Ukraine, the criminal-law classification of criminal offenses and the practice of combating illicit trafficking of falsified medicines as a certain type of criminal activity, we have substantiated the necessity and need for the formulation of a specific complex criminalistics investigation methodic with: a) a common subject of a criminal offense, i.e. falsified medicines; b) a similar objective aspect of the commission of such falsified medical product-related crime; c) complex criminalistics investigation methodics, in particular, the peculiarities of identifying signs of such criminal offenses, the subject of the investigation, investigative situations, tactics, the organisation of the investigation and the application of specialised knowledge. In this case, we are talking about the need to develop a complex criminalistics

investigation methodic in the field criminal offenses related to illicit trafficking in falsified medicines.

It is evident that illicit trafficking of falsified medicines unites all the types of related criminal offenses associated with a certain cycle of operations: from their manufacture and falsification or illegal distribution of falsified medicinal products, for the violation of which the legislation of Ukraine provides for criminal liability. There is a common subject of a criminal offense (falsified medicines) in related and tightly related crimes and there is illicit trade in this object.

It is believed that criminal offenses provided for by Articles 305, 321-1, 321-2 of the Criminal Code of Ukraine should be included in this complex criminalistics investigation methodic. The adjacency of the above elements occurs crimes in the creation of two separate pairs: a) Art. 321-1 and 305 of the Criminal Code of Ukraine; b) Art. 321-1 and 321-2 of the Criminal Code of Ukraine, as they create two pairs of elements of a crime having the properties that partially coincide with the properties of other element of a crime that is included in this pair [12]. They form a certain set of criminal offenses related to the falsification of medicinal products, which are united by both criminal law and criminalistics criteria [23] and, in turn, require the development of corresponding methodical and criminalistics recommendations and the construction of a complex criminalistics methodic investigation.

As for the common subject of a criminal offense, a falsification of medicinal products in accordance with Art. 2 of the Law of Ukraine «On Medicinal Products» is a medicinal product that is intentionally labeled non-identically (inconsistently) with the information (one or several of them) about a medicinal product with the corresponding name entered in the State Register of Medicinal Products of Ukraine (DRLZU), as well as a medicinal product, which is deliberately forged in another way and does not correspond to the information (one or more of them), including the composition, about the medicinal product with the corresponding name, which is entered in the DRLZ of Ukraine. However, such a definition suffers from a number of flaws as it does not specify all the properties that could be falsified.

At the same time, it is worth paying attention to the definition suggested by the WHO that defines a falsified medicines as a medical product that deliberately/fraudulently misrepresents its identity, composition or sourse [24]. Based on the above definition, a pharmaceutical is considered falsified medicinal products, if it: is inadequately packaged; is inadequately marked; has non-compliant composition (with or without an active substance or other auxiliary components). Misrepresentation of origin means placing a wrong manufacturer; a wrong country of origin; a wrong permit holder or requestor on the package. Misrepresentation of history involves provision of untrue or incomplete information about distribution methods or using illegal distribution chains.

A special attention should be paid when including low-quality and counterfeit medicines in the subject of these criminal offenses. The definition of falsified medicines as quoted from the Law of Ukraine «On Medicinal Products» completely absorbs the definition of counterfeit medicinal products. The classification of medicines as "counterfeit" seems to specify the manifestation of falsification by indicating the element that is subject to falsification, namely, the trademark or origin of pharmaceuticals. At the same time, with regard to low-quality medicinal products, formally they are not absorbed into the category of falsified medicinal products, and therefore do not fall under the definition of the subject of criminal encroachment. Therefore, in our opinion, the definition of falsified medicinal products contained in the Law of Ukraine «On Medicinal Products» includes counterfeit medicinal products, but does not absorb the definition of low-quality medicinal products. In this regard, the proposal of scientists is valid [25] regarding the need to improve the concept of falsified medicinal products, bringing it to international standards and establishing a clear relationship between them and the concepts of low-quality and counterfeit medicinal products.

It is also interesting to bear in mind that international practice now understands this term as encompassing not only falsified medicines but also medical products and medical equipment. Meanwhile, if the concept of "falsified medicines" is defined in the special Law of Ukraine «On Medicinal Products», it is only possible to promote the full implementation of the provisions of the MEDICRIME Convention in Ukraine after the definitions of fraudulent medicines and falsified medical equipment are incorporated in the law in the form of a specific law [26]. Pondering on this idea, other scholars claim that despite the fact that Ukraine has assumed internation legal obligations by entering into and ratifying the MEDICRIME Convention, the Criminal Code of Ukraine only provides for criminal penalty for production of fraudulent medicines and trafficking in fraudulent medicines for human consumption, effectively leaving unpunished production of fraudulent medicines and trafficking in falsified medicines for veterinary use, medical products and other medicines [7]. This indicates the need to bring the concept of falsified medicines into compliance with contemporary needs of practice and international standards.

As we mentioned earlier, an important feature of this group of criminal offenses is the methods of production

of falsification of medicines and illicit trafficking of falsified medicines product. In this regard, it is important to state that when committing such criminal offenses, the criminals deliberately mislead the end consumer by misrepresenting such pharmaceuticals for the purposes of getting more money for pharmaceuticals that cost much less and are of inferior quality [27]. It means that production of falsified medicines is effectively a form of deception: putting a lower quality pharmaceutical into a more expensive packaging, artificial improvement of the product appearance to make it look similar to expensive (branded) products etc [1]. Such deception is associated not only with the production of falsified medicines but also with their sale. Therefore, from the criminalistics point of view, production of falsified medicines and trafficking in falsified medicines is a system of interdependent actions that include preparation, aimed at creating false (false) information about the composition of medicinal products, their manufacturer, properties and characteristics that determine their selection and application to achieve a criminal purpose and involve their trafficking, and the outcome of such criminal activities is characterised by a cause-and-effect relationship between such activities and the occurrence of criminal implications [28] (i.e. death of a person, other serious consequences, long-term harm to someone's health etc.).

As for the illicit trafficking in falsified medicines, it should be understood as illegal acts representing a certain cycle of operations: illegal production and manufacture of falsified medicines and trade, sale, collection, display, accounting, storage, carrying, shipment, transportation, use, seisure, destruction or import and export of falsified medicines into a country/out of the country. The most common forms of committing these crimes are: production; manufacture; acquisition; transportation; forwarding; storage; sale of pharmaceuticals knowing them to be fraudulent. Most often, investigators and judges deal with a combination of two or more of the specified forms of active criminal behavior.

The most common methods of smuggling falsified medicines (Article 305 of the Criminal Code of Ukraine) are: a) smuggling falsified medicines across borders without customs clearance; b) hiding falsified medicines from customs control. The object of this criminal offense is falsified medicines that are smuggled across the customs border of Ukraine without customs clearance or hidden from customs control.

It is important to note that during the study of the correlation of adjacent elements of the crimes as set forth by Art. 321-1 and 321-2 of the Criminal Code of Ukraine, we can come to the conclusion that producers of falsified medicines directly aim at the falsification of the subject of the crime (falsified medicines), while commission of acts as set forth by Art. 321-2 of the Criminal Code of Ukraine provides for falsification of the results of preclinical studies and clinical trials of pharmaceuticals, meaning production (execution of a forged document that looks similar to the real one) and alteration (introducing partial changes to the text or details of an already existing document) of the final a document or materials of conducted studies that influenced the results. Also, during the commission of the crime as set forth by Art. 321-2 of the Criminal Code of Ukraine, it is possible to violate the order of state registration of pharmaceuticals (as a form of an objective aspect), while production of falsified medicines or trafficking in fraudulent medicines does not presuppose any actions aimed at state registration of such pharmaceuticals at all. If there is an attempt to register falsified medicines in accordance with the procedure established by the applicable legislation and at the same time there is a violation of the applicable legislation, then we can be talking about a body of crime as set forth by Art. Art. 321-1 and 321-2 of the Criminal Code of Ukraine [29].

Regarding the investigation of the targets of these crimes, it should be noted that they partially match. So, in contrast to the crimes provided for in Article 321-1 of the Criminal Code of Ukraine, the target of deliberate violation of the established procedure of preclinical study, clinical trials of medicinal products, falsification of their results as well as violation of the established procedure for the state registration of medicinal products are exclusively medicinal products (within the meaning of Article 2 of the Law of Ukraine "On Medicinal Products"). Having analyzed the concept of a falsified medicinal product earlier in this article, it becomes obvious that a falsified medicinal product is also a medicinal product but with certain dangerous qualities [12]. In addition, in contrast to Article 321-1 of the Criminal Code of Ukraine, Article 305 of the Criminal Code of Ukraine, in addition to falsified medicinal products, also has other targets of crime (narcotic drugs, psychotropic substances, their analogues or precursors).

Based on the above, the illegal circulation of falsified medicinal products acquires a comprehensive nature, forming a certain kind of system by committing several criminal offenses in aggregate. Therefore, during their investigation, an investigator (prosecutor) has to resort to various types of group and non-specific methods of investigation, which increases the amount of work and requires additional knowledge and the ability to apply comprehensive methodical and criminalistic recommendations. However, since the crimes under consideration are very multifaceted, it is impossible to assign comprehensive complex methodic of their

investigation to only one category of methodics. From our point of view, complex criminalistics methodic of investigating the illegal circulation of falsified medicinal products belong to the non-specific ones, since the basis of such methods are the sphere in which illegal actions are committed and corpus delicti of a certain crime, taking into account criminalistic signs and criteria for their division and classification. The formation of such complex criminalistics methodic should be intended for a specific addressee – the investigator (a party to criminal proceedings). When building such methods, it is necessary to proceed from a descriptive approach to a certain standardization and unification [30].

As practice shows, the investigation process is significantly complicated by the existing difficulties in conducting expert research and using expertise (67.8% of the surveyed respondents indicated this) as well as the need to develop separate criminalistic methodic (this was noted by 71.2%) [31], which requires a separate study of this issue. In this regard, it can be seen that the effectiveness and completeness of determining all the circumstances of the illegal circulation of falsified medicinal products largely depends on the correct use of expertise by the investigator in the process of pre-trial investigation [32]. It is obvious that such specificity is caused by the occurrence of certain difficulties faced by investigators when detecting, recording and removing traces, as well as conducting a complex of procedural and non-procedural actions, which significantly affects the choice of forms of using expertise [33-35] as well as the variability of issues that need to be resolved in such situations [36].

In criminal procedural activity, special knowledge is used in three forms: when involving specialists during individual investigative (search) or judicial actions, in the form of consultations and clarifications by specialists and within the scope of the forensic examination. During the administration of justice, forensic examination provides great assistance to the investigation and the court [37]. As practice shows, among the main forms of using expertise during the investigation of the circulation of falsified medicinal products, the most common are: forensic examination (96.9% of criminal proceedings); involvement of specialists during investigative (search) actions or security measures (76.6%); receiving consultations and explanations from specialists (71.1%).

Forensic examinations can be appointed both at the initial and subsequent stages of the investigation. The analysis of the files of criminal proceedings showed that forensic examinations during the investigation of this category of criminal offenses were appointed from the moment of entering information into the Unified Register of Pre-Trial Investigations: a) 5 days – 4.7%; b) 15 days – 22.7%; c) within a month – 57.0%; d) more than a month – 15.6%. As you can see, the overwhelming majority of forensic examinations are appointed by officers of investigative units within a month after commencement of the pre-trial investigation, which led to the creation of certain prerequisites for the loss or destruction of crime traces and evidentiary information. The investigator is often not aware of the possibility of appointing certain forensic examinations. This not infrequently leads to delay in pre-trial investigation and investigative and judicial errors [38].

It is especially important to involve a specialist in conducting investigative (search) and judicial actions [39] In the vast majority of cases, signs of falsified medicinal products were detected precisely with the use of special technical means, in particular, such as verifiers, special microscopes, fluorescent irradiators, diffraction films, etc. Falsification of medicinal products was detected with the help of infrared and ultraviolet irradiators based on the fluorescent glow of packaging materials: labels, film, blisters, containers, instructions paper, etc. Hidden protective marks on the packaging is detected with the help of irradiators and the application of special diffraction films. Protective stickers and holograms are identified using verifiers. At the same time, as the generalization of the files of criminal proceedings showed, in 36.6% of cases, technical means were not used, which requires clarifying the reasons and finding ways to eliminate them. It is obvious that such proposed recommendations and their application in practice will contribute to the quality and effectiveness of the investigation of the studied category of criminal offenses and court hearing.

## CONCLUSIONS

Thus, in modern realities, there is a need to create and implement an effective criminal law and criminalistic mechanism to combat the distribution of falsified medicinal products, both at the international, regional and national levels. There is a need to intensify the processes of harmonization, convergence of domestic legislation and pan-European rules and international standards in the field of pharmaceutical activity, in particular with regard to effective counteraction to the illegal circulation of falsified medicinal products. At the same time, Ukraine, as a candidate for membership of the European Union, is obliged to fulfill international requirements to ensure the safety, quality and effectiveness of medicinal products at all stages of their circulation, to promote and strengthen international cooperation in pharmaceutical activities.

The current state of the practice of combating the illegal circulation of falsified medicinal products cause an urgent need for the development of complex crimi-

nalistic investigation methodic, which have: a) a common subject of a criminal offense, i.e. falsified medicines; b) a similar objective aspect of the commission of such falsified medical product-related crime; c) complex criminalistics investigation methodics, in particular, the peculiarities of identifying signs of such criminal offenses, the subject of the investigation, investigative situations, tactics, the organisation of the investigation and the application of specialised knowledge. In this case, we are talking about the need to develop a complex criminalistics investigation methodic in the field criminal offenses related to illicit trafficking in falsified medicines. It is considered that these complex criminalistics methodic should include related corpus delicti of criminal offenses provided for by Articles 305, 321-1 and 321-2 of the Criminal Code of Ukraine, which have the main common feature – the subject of the crime, which is falsified medicinal products and their illegal circulation, as a certain cycle of operations – from production to their sale to a specific consumer, is illegal, the violation of which is subject to criminal liability under the legislation of Ukraine. They form a set of criminal offenses related to the falsification of medicinal products, which are united by both criminal law and criminalistic criteria and, in turn, require the development of appropriate methodological and criminalistic recommendations and building complex criminalistic methodics.

The effectiveness of combating the falsification of medicinal products and the illegal circulation of falsified medicines is a complex problem that covers the whole system of measures and areas that require the combined efforts of public authorities, different ministries and agencies, law enforcement agencies and scientists in order to direct such joint activities to the solution of emerging practical tasks. Criminalistics should intensify its powerful scientific potential and modern capabilities and use them in technical and criminalistic, tactical and criminalistic as well as methodical and criminalistic areas in order to ensure effective prevention and combat against modern challenges of this type of transnational crime.

## REFERENCES


1. Pashkov V, Soloviov A, Olefir A. Legal Aspects of Counteracting the Trafficking of Falsified Medicines in the European Union. Wiadomości Lekarskie. 2017; 70(4): 843–849.
2. Cherniavskyi SS, Holovkin BM, Chornous YM et al. International cooperation in the field of fighting crime: Directions levels and forms of realization. Journal of Legal, Ethical and Regulatory Issues. Substandard and falseified medicinal products. World Health Organization.2019;22(3):1-11.
3. Substandard and falseified medicinal products. World Health Organization. http: // www.who.int/medicines/ services/counterfeit/en / [date access 26.09.2022].
4. Rakovska Yu. Fal'syfikat likars'kykh zasobiv yak nayprybutkovishyy vyd transnatsional'noyi zlochynnoyi diyal'nosti. [Counterfeit medicines as the most profitable type of transnational criminal activity]. Customs business. 2014; 1(21): 148-154 (in Ukrainian).
5. Aleksieiev OH. Perspective and current state of international standards influence on prevention and treatment of diseases through the prism of developing high-quality and safe medicines. Zaporozhye medical journal. 2022;24(4):448-453.
6. Tykhonova OV, Kholostenko AV, Herasymenko LV et al. Comparative analysis of combating economic crimes in ukraine and european union. International Journal of Management. 2020;11(3): 624–632.
7. Gutorova NO. Kryminal'na vidpovidal'nist' za fal'syfikaciju medychnoi' produkcii'. [Criminal liability for falsification of medical products]. Poltava legal journal. 2021; 2: 9-21. (in Ukrainian).
8. Shevchuk O, Shevchuk V, Matyukhina N, Zatenatskyi D. Testing of drugs in the implementation of customs control in Ukraine: legal aspects. Georgian Medical News. 2020; 1(298): 165-169.
9. Latysh KV, Demidova YE. Corruption offenses in medications circulation: investigation problems. Wiad. Lek. 2021;74(11): 2896-2900. doi: 10.36740/WLek202111206.
10. Lytvyn AA, Prjahin JeV. Metodyka rozsliduvannja kryminal'nyh pravoporushen', vchynjuvanyh u sferi obigu likars'kyh zasobiv: monografija. [Methods of investigation of criminal offenses committed in the field of medicinal products: monograph]. Lviv. 2021, p.15-16. (in Ukrainian)
11. Korolenko IV. Fal'syfikacija likars'kyh zasobiv abo obig fal'syfikovanyh likars'kyh zasobiv kontent: analiz nacional'nogo zakonodavstva. Kryminal'ni pravoporushennja proty publichnogo zdorov'ja v projekti Kryminal'nogo kodeksu Ukrai'ny: materialy nauk.-prakt.vebinaru, 25 travnja 2021 r.; NDI vyvchennja problem zlochynnosti im. akademyka V. V. Stashysa. [Falsification of medicinal products or circulation of falsified medicinal products content: analysis of national legislation. Criminal offenses against public health in the draft Criminal Code of Ukraine: materials of the scientific and practical webinar, May 25, 2021; research institute for the study of crime problems named after Academician V. V. Stashis]. Kharkiv: Pravo. 2021, p.55-58. (in Ukrainian).
12. Kovalenko IA. Falsyfikatsiia ta obih falsyfikovanykh likarskykh zasobiv: kryminalno-pravove doslidzhennia: monohrafiia [Falsification and both falsified medicinal products: criminal and legal research: monograph]. Ye. L. Streltsova ed. Odesa: Vydavnychyi dim «Helvetyka». 2018, p. 34 (in Ukrainian).

13. Gutorova NO. Chornyj onlajn rynok likars'kyh zasobiv pid chas pandemii' COVID-19: pravovi zasoby protydii'. [The Online Black Market of Medicines During the COVID-19. Pandemic: legal remedies]. Law Forum. 2021; 68(3): 15-24. (in Ukrainian).
14. Gutorova NO. Kryminal'na vidpovidal'nist' za fal'syfikaciju medychnoi' produkcii'. [Criminal liability for falsification of medical products]. Poltava legal journal. 2021; 2: 9-21. (in Ukrainian).
15. Gutorova N, Zhytnyi O, Soloviov O. Falsification of Medical Products: Criminal Law Mechanism Combating Threats to Public Health. Wiad. Lek. 2019; 72 (5 ): 856-864. doi:10.36740/WLek201905124.
16. Aleksieiev OH. Farmatsevtychnyi sektor Ukrainy: suchasnyi stan pravovoho rehuliuvannia [Pharmaceutical sector of Ukraine: current state of legal regulation]. Current issues in pharmacy and medicine: science and practice. 2020; 13(1): 115-121.
17. Demidova LM. Vaccination against infectious diseases: international standards of patient's rights. Wiad. Lek. 2019;72(12): 2518– 2523. doi: 10.36740/WLek201912220.
18. Lohvynenko BO, Sezonov VS, Frantsuz-Yakovets TA. Tendencies for the falsification of medicinal products in Ukraine: general analysis and areas of counteraction. Wiad. Lek. 2019; 12: 2478-2484. doi: 10.36740/WLek201912214.
19. Shevchuk V, Shevchuk O, Zuy V, Chub O. Legal regulation of procurement of narcotic drugs in Ukraine with involvement of international specialized organizations. Georgian Medical News. 2018; 11(284): 143-149.
20. Batyrgareieva VS, Babenko AM, Kaija S. Corruption in medical sphere of Ukraine: current situation and ways of prevention. Wiad Lek. 2019; 72 (9):1814-1821.
21. Mykhailichenko TO, Horpyniuk OP, Rak VY. Medical Confidentiality Disclosure in Conditions of Epidemic Threats. Wiad. Lek. 2021; 74(11): 2877. doi: 10.36740/WLek202111203.
22. Konovalova V O, Shevchuk VM. Modern criminalistics in the conditions of war: problems of adaptation and reload. Modern research in world science: Proceedings of the 5th International scientific and practical conference. 2022, p. 896-903.
23. Shevchuk VM. Methodological problems of the conceptual framework development for innovation studies in forensic science. Journal of the National Academy of Legal Sciences of Ukraine. 2020; 27(2): 170-183. doi: 10.37635/jnalsu.27(2).2020.170-183.
24. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. http://ec.europa.eu/health//si... health/files/files/ eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdh [date access 04.12.2023].
25. Mel'nychuk VM. Kvalifikacija fal'syfikacii' likars'kyh zasobiv ta obigu fal'syfikovanyh likars'kyh zasobiv. [Qualification of falsification of medicinal products and circulation of falsified medicinal products]. Bulletin of the Academy of Advocacy of Ukraine. 2014; 29: 130-135. (in Ukrainian).
26. Solovjov OS. Konvencija MEDICRIME: dosvid ta osoblyvosti implementacii' polozhen' konvencii' v Ukrai'ni. [The MEDICRIME Convention: experience and peculiarities of the implementation of the provisions of the convention in Ukraine]. Management, economics and quality assurance in pharmacy. 2020; 1(61): 50-56. (in Ukrainian).
27. Nikolaienko RA. Oznaky zlochyniv, pov'iazanykh iz vyhotovlenniam ta poshyrenniam falsyfikovanykh likarskykh zasobiv za sposobamy operatyvno-znachymoi povedinky na stadii yikh vyrobnytstva. [Signs of crimes related to the manufacture and distribution of counterfeit drugs by methods of operationally significant behavior at the stage of their production]. Pravo i suspilstvo, 2018; 3 (2): 276–281. (in Ukrainian).
28. Shevchuk O, Shevchuk V, Kompaniiets I et al. Features of ensuring the rights of drug addicts for rehabilitation in Ukraine and the European Union: Comparative Legal Aspect. Juridical Tribune – Tribuna Juridica. 2022; 12(2): 264 – 282. doi: 10.24818/TBJ/2022/12/2.07.
29. Orlovskyi R, Us O, Shevchuk V. Committing a Criminal Offence by an Organized Criminal Group. Pakistan Journal of Criminology. 2022;14, 2: 33-46.
30. Shepitko VY, Shepitko MV. The role of forensic science and forensic examination in international cooperation in the investigation of crimes. Journal of the National Academy of Legal Sciences of Ukraine. 2021; 28 (1): 179–186. doi: 10.37635/jnalsu.28(1).2021.179-186.
31. Shevchuk VM, Parfylo IV, Sokolenko MO. Falsification of medicines and contribution of falsified medicines in Ukraine : criminalistic means of detection and counteraction. Wiad. Lek. 2021; 74 (11): 2946-2953. doi: 10.36740/WLek202111215.
32. Kharytonov SO, Haltsova VV, Bondarenko OO. Divulgence of confidentiality of adoption: criminal legal and medical aspects. Wiad. Lek. 2021; 74(11): 3085-3091. doi: 10.36740/WLek202111238.
33. Yaremchuk VO. The use of medical knowledge in the crime investigation. Wiad. Lek. 2019; 72(1): 103–106.
34. Shevchuk V, Shevchuk O, Matyukhina N, Zatenatskyi D. Testing of drugs in the implementation of customs control in Ukraine: legal aspects. Georgian Medical News. 2020; 1 (298): 165-169.
35. Komziuk A, Orlovskyi R. Contemporary forms and methods of counteracting narcotization of the youth. Amazonia Investiga, 2020; 9 (28): 377-385.
36. Zhuravel VA, Konovalova VE, Avdeyeva GK. Reliability evaluation of a forensic expert's opinion: World practices and Ukrainian realities. Journal of the National Academy of Legal Sciences of Ukraine. 2021; 28 (2): 252-261.
37. Shepitko VY, OIkhovsky VO, Shepitko MV. The process of scientific knowledge integration in crime prevention and trends of medical criminalistics development in ukraine in XIX – early XX century. Wiad. Lek. 2020; 73 (1):176 -179. doi: 10.36740/WIek202001133.

38. Parfylo IV. Problemy zastosuvannja special'nyh znan' pry rozsliduvanni fal'syfikacii' ta obigu fal'syfikovanyh likars'kyh zasobiv. [Problems of applying special knowledge in the investigation of falsification and circulation of falsified medicinal products]. Actual problems of the state and law. 2020; 86: 154-168. (in Ukrainian).
39. Ackermann VR, Kurapka VE, Malewski H, Shepitko V. Schaffung eines einheitlichen europaisehen Kriniinalistischen Raumes: Die Tatigkeit offentlicher Organisationen zur Starkung der internationalen Beziehungen. Kriminalistik. 2020; 6: 355-363.

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ORIGINAL ARTICLE

# ROLE OF DIMETHYL FUMARATE (NRF2 ACTIVATOR) IN REDUCING OF CIPROFLOXACIN-INDUCED HEPATOTOXICITY IN RATS VIA THE NRF2/HO-1 PATHWAY

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## ABSTRACT

**The aim**: The present study aims to study the effect of DMF on ciprofloxacin-induced liver damage as assessed by liver function and liver pathology and to study this effect if it is thought to activate the Nrf2 antioxidant defense mechanism.

**Materials and methods:** G1 (control), G2 (ciprofloxacin group), G3 and G4 (two DMF groups rats treated with DMF 50mg and 100mg), and G5 and G6 (two DMF groups rats treated with DMF 50mg and 100mg) (two ciprofloxacin Plus DMF at 50 mg and 100 mg). The tests included study of liver function, Nrf2 analysis, and anti-oxidant enzyme analysis.

**Results**: The serum blood Nrf2, HO-1, and tissue anti-oxidant enzymes all increased after ciprofloxacin treatment. The serum levels of Nrf2 and HO-1 were higher in the ciprofloxacin plus DMF groups, but anti-oxidant enzymes were lower. DMF increased Nrf2 expression in rats when ciprofloxacin caused hepatotoxicity.

**Conclusions**: DMF lowers experimental hepatotoxicity in vivo. This effect is thought to activate the Nrf2 antioxidant defense mechanism.

**KEY WORDS:** Nrf2, ciprofloxacin, HO-1, anti-oxidants

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## INTRODUCTION

Fluoroquinolones are a class of antibiotics that have a broad spectrum of activity against Gram-negative and Gram-positive bacteria. It is well accepted by patients, although it has been linked to many side effects, including unfavorable central nervous system effects and oxidative stress [1]. Oxidative stress not only causes of liver damage by causing of permanent damage to lipids, proteins, and DNA, but it also affects biological functioning through modifying pathways. Since these pathways of control gene transcription, protein expression, cell death, and hepatic stellate cell activation, so, the oxidative stress is one of the most important pathophysiological mechanisms behind the onset and progression of many liver illnesses [2]. Ciprofloxacin's hepatotoxicity results could be due to oxidative stress in the liver, induced by the drug's production of reactive radicals, which causes protein depletion in hepatocytes due to nucleic acid loss and DNA damage. This may lead to a significant decrease of mitochondrial number and its degeneration, what is responsible for energy production [3]. Many naturally occurring antioxidants are controlled by a family of transcription factors, including the nuclear factor-erythroid 2 related factor 2 (Nrf2). The antioxidant response element (ARE) is located in the promoters of several chemoprotective genes, including those that involved in the response to oxidative stress, and Nrf-proteins bind to it. The binding of Nrf2 to ARE boosts the transcription of numerous antioxidant genes, such as Super-Oxide Dismutase (SOD), Catalase (CAT), and Glutathione (GST) [4, 5]. Ciprofloxacin-induced hepatotoxicity was characterized by the elevation of liver damage hallmarks: Alanine aminotransferase (ALT), aspartate transferase (AST), and alkaline phosphatase (ALP). Amino-transferase is the most specific and routinely utilized indicator of hepatocellular necrosis. High levels of these enzymes may indicate liver damage. Anti-oxidant enzymes such SOD, and GSH, mainly derived from hepatocytes, biliary epithelial cells, liver tubules, pancreas, and intestine [6]. Elevated levels of serum enzyme activity have been considered as a sensible marker of hepatic disorders. The NRF2 field developed from biochemical and molecular discoveries on chemical transcription factors of hepatic detoxication enzymes, as well as

**Table I.** Distribution of anti-oxidant enzymes among study groups.

| Groups/ Markers | Nrf2 ng/g of protein | HO-1pg/ g of protein | Catalase (U/l) | SOD (U/l) | GSH (U/l) | *p-value |
|---|---|---|---|---|---|---|
| G1 | 23.67 ± 0.72 | 15.39 ± 0.52 | 14.82 ± 0.29 | 19.97 ± 0.32 | 22.37 ± 0.94 | 0.00 |
| G2 | 32.49 ± 0.43 | 16.34 ± 0.82 | 6.69 ± 0.35 | 11.84 ± 0.35 | 13.97 ± 0.51 | |
| G3 | 42.66 ± 0.64 | 19.31 ± 0.60 | 14.83 ± 0.34 | 19.87 ± 3.25 | 22.50 ± 0.47 | |
| G4 | 43.45 ± 1.99 | 19.94 ± 0.74 | 14.88 ± 0.25 | 19.81 ± 0.12 | 22.92 ± 0.69 | |
| G5 | 38.03 ± 0.56 | 18.47 ± 0.66 | 12.31 ± 0.25 | 17.26 ± 0.18 | 19.23 ± 0.40 | |
| G6 | 39.02 ± 0.50 | 18.95 ± 0.52 | 12.93 ± 0.09 | 19.48 ± 0.21 | 21.23 ± 0.56 | |

Each value is a mean of six animals ± SD, *=one-way ANOVA

subsequent characterization of the modulation of drug/toxicant-induced hepatotoxicity [7]. As a result, using of the Nrf2 pathway to stimulate the production of cytoprotective genes could be employed to treat liver diseases.

## THE AIM

The aim of the study was to see, if DMF could protect the liver in an acute Cipro-induced hepatotoxicity chemical model.

## MATERIALS AND METHODS

The hepatoprotective effects of DMF against Cipro were examined, because it has been found, that DMF activate Nrf2. Hepatotoxicity was studied in rats.

### ANIMALS AND STUDY DESIGN

Six groups of 36 Sprague Dawley male rats will be formed. For a period of 30 days, each group has six rats. Drug preparation: Dimethyl fumarate dissolves in DMSO and is given intravenously at doses of 50 and 100 mg/kg, respectively. The animals were maintained in the animal house at the University of Kufa's Faculty of Medicine. The University of Kufa's Animal Care and Research Committee accepted the experiment, and the investigation followed the Laboratory Animals Guide Care. The animals has unlimited access to clean water and will be divided into the following groups: G1: DMSO is given for 30 days, G2**:** administered medication (ciprofloxacin) once daily by oral delivery at a dose of 100 mg/kg for 30 days [8], G3**:** IP administration of DMF at a dosage of 50 mg/kg once daily for a period of 30 days [9], G4**:** IP administration of DMF at a dosage of 100 mg/kg once daily for a period of 30 days [10], G5: For 30 days, ciprofloxacin 100 mg/kg was administered orally once daily, adding DMF IP at a dosage of 50 mg/kg starting on day 10 [11, 12], and G6: For 30 days, ciprofloxacin 100 mg/kg was administered orally once daily, adding DMF IP at a dosage of 100 mg/kg starting on day 10. Animals will be sacrificed by heart puncture under ketamine (25 mg/kg) and xylazine (5 to 10 mg/kg) anesthesia at the end of the experiment [13]. The animals were euthanized so that blood and liver tissues can be collected for further analysis [14].

### MEASUREMENT OF OXIDANT PARAMETERS

Two commercial detection kits were used to assess the amounts of CAT, SOD, and GSH enzymes, as well as Nrf2 (*Nanjing Jiancheng Bioengineering Institute*) according to the manufacturer's procedure and a recent study [15].

### STATISTICAL ANALYSIS

The data are presented as means with standard deviations (SD). The significance of differences in multiple group comparisons was established using the SPSS program 26.0 and one-way analysis of variance (ANOVA).

## RESULTS

### DMF-ASSOCIATED MINIMIZING OF THE OXIDATIVE STRESS AND INCREASING OF THE PRODUCTION OF ANTIOXIDANT ENZYMES IN LIVER TISSUES

DMF administration has previously been seen to improve the expression of Nrf2 and its downstream protein such as HO-1 [16, 17]. To investigate is the DMF's reno-protective impact in ciprofloxacin-induced hepatotoxicity is linked to Nrf2 activation (researchers increased the gene expression of Nrf2 and HO-1). According to our findings, DMF greatly protected the kidney against ciprofloxacin-induced damage via the Nrf2-HO-1 pathway. The levels of Nrf2 and HO-1 in tissue were considerably higher in the treated group than in the untreated done (Table I, Figure 1).

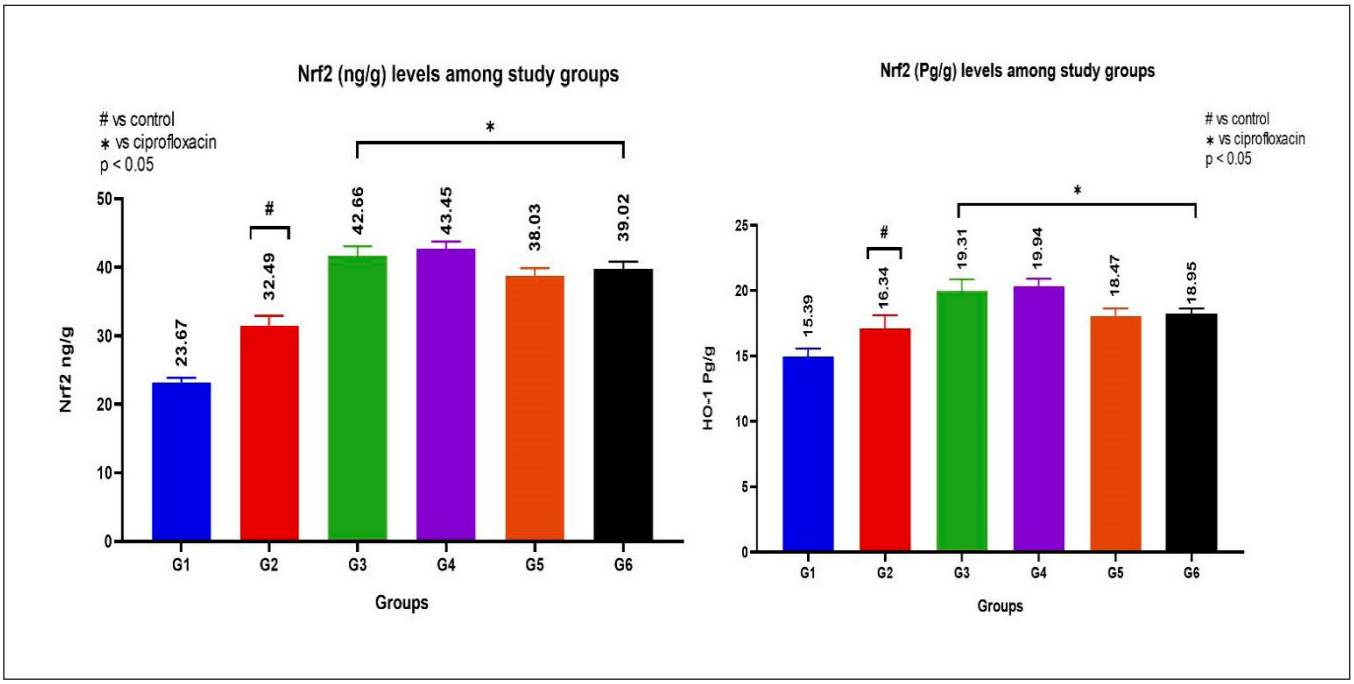


**Fig. 1.** Represent the Nrf2 and HO-1 enzyme tissue levels among groups.

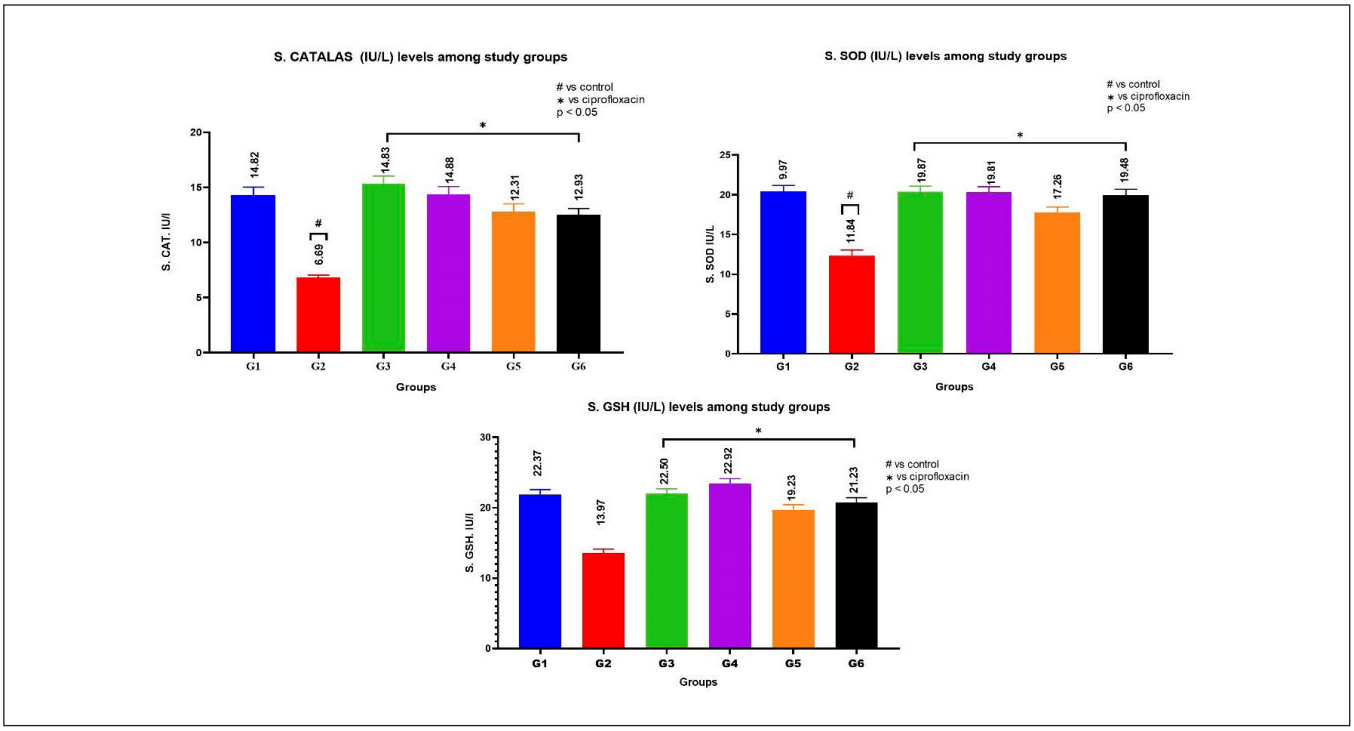


**Fig. 2.** Representation of the anti-oxidant enzymes serum levels (U/L) among study groups.

The antibacterial ciprofloxacin lowered the activity of the CAT, SOD, and GSH enzymes, but this effect was reduced by DMF treatment. Furthermore, the levels of antioxidant enzymes in the serum were altered in six groups, as shown in Table I and Figure 2.

The levels of ciprofloxacin in serum were considerably lower (P<0.05) in the G2 group than in the G1 group. In the ciprofloxacin plus DMF groups, DMF significantly increased these decreases in anti-oxidant levels, while anti-oxidant levels did not differ significantly between the control and ciprofloxacin plus DMF groups. In addition, there is no statistically significant difference (p>0.05) between the DMF groups with both G5 and G6 groups. There is, however, a significant increase (p<0.05) when we compared treated groups with the G2.

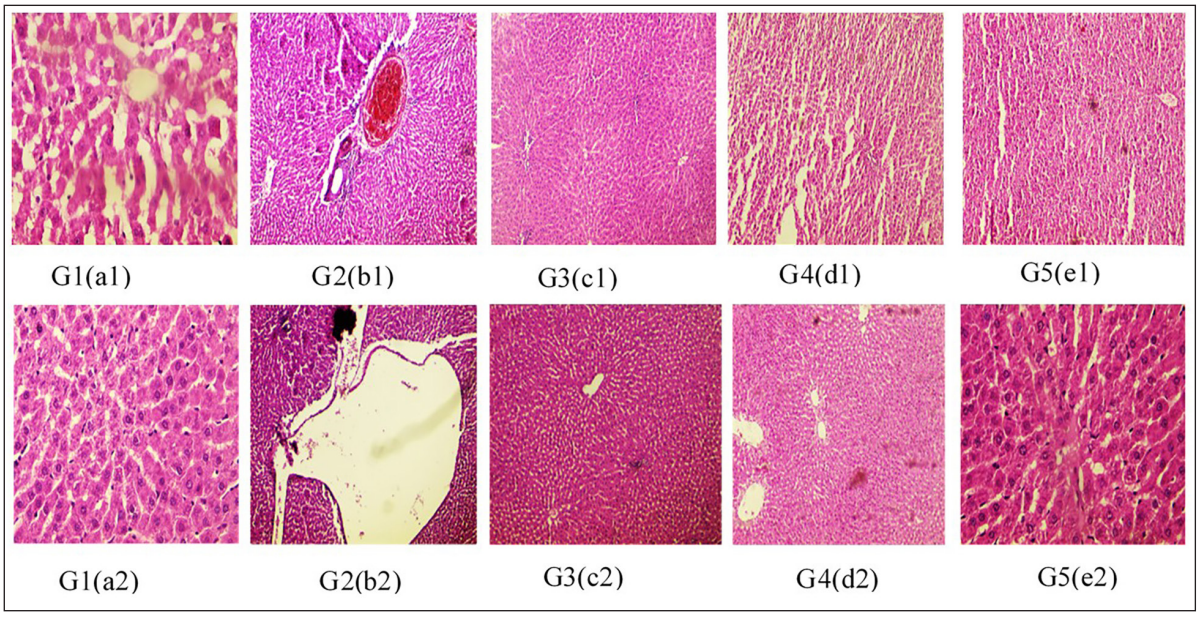


**Fig. 3.** Representative histologic samples from several groups, G1(a1, a2), G2(b1,b2), G3(c1,c2), G4(d1,d2), and G5 (e1, e2). Magnification: X40.

### DMF-ASSOCIATED REDUCTION IN LIVER TISSUE DAMAGE

The degenerative alterations in liver slices from all groups are depicted in Figure 3. The liver sections of the control and DMF groups of rats showed no significant histological changes. The liver sections from the ciprofloxacin group had substantial damage, including epithelial necrosis, and hemorrhagic foci. The development of these lesions and tissue damage is dramatically reduced in the ciprofloxacin plus DMF group. According to this liver pathological finding, DMF may prevent ciprofloxacin induce liver damage in rats.

## DISCUSSION

The liver seems to be the major organ for maintaining homeostasis. Drugs are thought to be a primary cause of liver failure, and the majority of idiosyncratic drug reactions resulting in negative consequences, including liver transplantation. It has been reported, that the fundamental mechanism, that causing by ciprofloxacin-induced ALF is the oxidative stress. Indeed, the main signal in the evolution of several liver illnesses is an oxidant/antioxidant imbalance [18, 19]. DMF protects the cells from harmful influence, that caused by nuclear Nrf2 upregulation, inflammation and oxidative stress modulation, and its down-regulation [20]. According to our findings, using of ciprofloxacin caused the immediate liver injury: the rats' liver function had deteriorated, and histological damage had occurred. Furthermore, the ciprofloxacin group had significantly higher levels of ROS in liver tissue. In contrast, providing of DMF without an inducible agent, boosted of an anti-oxidative enzyme activity via increasing the expression of the antioxidant transcription factor Nrf2, demonstrating that DMF has a protective role in the liver. This protection, demonstrated after induction, drastically reduced of liver damage and decreased ROS levels in the ciprofloxacin plus DMF group. The reduced CAT, SOD, and GSH enzymes in the liver tissues of the ciprofloxacin group in this study also indicated the role of oxidative damage in the ciprofloxacin inducing liver damage in animals. In rats without damage, treatment with DMF elevated antioxidant enzyme activity to protect against oxidative damage, which can be seen in figure 3. Furthermore, in rats with damage, DMF treatment immediately scavenged ROS and unregulated anti-oxidant enzymes. DMF's cytoprotective characteristics are tightly associated with the removal of excess ROS. Previous research by Naguib et al. 2021 reported that Nrf2 could have therapeutic potential in the treatment of hepatotoxicity by inhibiting oxidative stress-induced hepatocytes cell membrane disruption during ciprofloxacin-induced changes [21]. In addition, Xu D et al. showed that Nrf2 increased autophagy in hepatocytes results in increased clearance of damaged mitochondria, reduced mtDNA release, and reduced ROS production, resulting in a reduction in DAMP-induced inflammatory responses and consequent secondary hepatocytes injury [21]. Finally, we have reported DMF's antioxidant properties, which are consistent with our findings. In addition, DMF improved the viability of ciprofloxacin-induced injuries.

## CONCLUSIONS

According to our findings, DMF improves ciprofloxacin and induces liver damage as assessed by liver function and liver pathology. The anti-oxidant protein Nrf2 nuclear translation was dramatically enhanced by DMF. These favorable effects are mostly due to improved antioxidant defense in the liver and activation of the Nrf2 pathway. DMF may thus be an effective treatment for CIN prevention, while more research and randomized clinical trials are needed to prove this.

## REFERENCES


1. Valko M, Leibfritz D, Moncol J et al. Free radicals and antioxidants in normal physiological functions and human disease. The international journal of biochemistry & cell biology. 2007;39(1):44-84.
2. Cho H-Y, Reddy SP, Kleeberger SR. Nrf2 defends the lung from oxidative stress. Antioxidants & redox signaling. 2006;8(1-2):76-87.
3. Adikwu E, Brambaifa N. Ciprofloxacin cardiotoxicity and hepatotoxicity in humans and animals. 2012; 3(2): 207-213. doi: 10.4236/pp.2012.32028.
4. Masubuchi N, Makino C, Murayama N. Prediction of in vivo potential for metabolic activation of drugs into chemically reactive intermediate: correlation of in vitro and in vivo generation of reactive intermediates and in vitro glutathione conjugate formation in rats and humans. Chemical research in toxicology. 2007;20(3): 455-464.
5. Al-Mudhafer R, Abbas Al-Huseini L, Hassan S et al. Bardoxolone Ameliorates Cerebral Ischemia/ Reperfusion Injury in Male Rats. Africa Health Research Organization. 2019;22:122-130.
6. Taguchi K, Kensler TW. Nrf2 in liver toxicology. Arch Pharm Res. 2020;43(3): 337-349.
7. Hashim M, Al-Cekal S, Al-Khamas A. Determination of the effect of ciprofloxacin and gentamicin alone and in combination to induce nephrotoxicity in experimental rats. Annals of Tropical Medicine and Public Health. 2020;23:487-496.
8. Soliman MM, Nassan MA, Ismail TA. Origanum Majorana extract modulates gene expression and hepatic and renal changes in a rat model of type 2 diabetes. Iranian Journal of Pharmaceutical Research: IJPR. 2016;15:45-54.
9. Armstrong JM, Avant RA, Charchenko CM et al. Impact of anabolic androgenic steroids on sexual function. Translational Andrology and urology. 2018;7(3):483–489. doi: 10.21037/tau.2018.04.23.
10. Abdelsalam HM, Diab AA, Zahra MH et al. Therapeutic effects of Origanum majorana and propolis against nephrotoxicity induced by adenine. Biol Eng Med. 2019;4:1-9.
11. Cho H, Hartsock MJ, Xu Z et al. Monomethyl fumarate promotes Nrf2-dependent neuroprotection in retinal ischemia-reperfusion. J Neuroinflammation. 2015;12: 239. doi:10.1186/s12974-015-0452-z.
12. Hu Y, Dietrich H, Metzler B et al. Hyper expression and Activation of Extracellular Signal–Regulated Kinases (ERK1/2) in Atherosclerotic Lesions of Cholesterol-Fed Rabbits. Arteriosclerosis, thrombosis, and vascular biology. 2000;20(1):18-26.
13. Adekunl A, Adelusi T, Fatoki J et al. A Diet-induced Atherosclerosis in Rabbit Model Provides an Insight into Essential Elements Concentrations in Cardiovascular Disease. British Journal of Medicine and Medical Research. 2013;3(3):517.
14. Hassan SM, Jawad MJ, Ahjel SW et al. The Nrf2 activator (DMF) and covid-19: is there a possible role? Medical Archives. 2020;74(2): 134–138.
15. Hadi NR, Hassan SM, Jawad MJ, Alawaida W. Cerebral Ischemia-Reperfusion Injury. Cerebral Ischemia-Reperfusion Injury. 2021;1-63. doi:10.9734/bpi/mono/978-93-91473-00-6.
16. Sasaki A, Koike N, Murakami T et al. Dimethyl fumarate ameliorates cisplatin-induced renal Tubulointerstitial lesions. Journal of toxicological pathology. 2019;32(2):79-89.
17. Chalasani N, Björnsson E. Risk factors for idiosyncratic drug-induced liver injury. Gastroenterology. 2010;138(7):2246-2259.
18. Naguib YM, Azmy RM, Samaka RM et al. Pleurotus ostreatus opposes mitochondrial dysfunction and oxidative stress in acetaminophen-induced hepato-renal injury. BMC Complementary and Alternative Medicine. 2014;14(1): 494. doi: 10.1186/1472-6882-14-494.
19. Abbas Al-Huesini LM, Al-Mudhaffer RH et al. DMF Ameliorating Cerebral Ischemia/Reperfusion Injury in Meal Rats. Systematic Reviews in Pharmacy. 2019;10(1):206-213.
20. Naguib Y, Motawea S, Ameen O. Replenishing glutathione counters ciprofloxacin-induced acute liver failure via a possible gene modifying mechanism. Bulletin of Egyptian Society for Physiological Sciences. 2021;41:525-536.
21. Xu D, Chen L, Chen X et al. The Triterpenoids CDDO-Imidazolide ameliorates mouse liver ischemia-reperfusion injury through activating the Nrf2/HO-1 pathway enhanced Autophagy. Cell death & disease. 2017;8(8):e2983-e2983.



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ORIGINAL ARTICLE

# VARIANTS OF THE FORMATION AND COURSE OF DRUG-RESISTANT EPILEPSY IN CHILDREN WITH GENETIC POLYMORPHISMS OF *CYP2C9, CYP2C19, CYP3A4*

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## ABSTRACT

**The aim:** To clarify the frequency with which various variants of the formation and course of drug-resistant epilepsy occur in children with genetic polymorphisms of cytochromes *CYP2C9, CYP2C19, CYP3A4*.

**Materials and methods:** The genotyping of *CYP2C9*2, CYP2C9*3, CYP2C19*2, CYP3A4*1B* by the allele-specific polymerase chain reaction was performed in 116 children with drug-resistant epilepsy aged from 2 to 17 years. Thirty cases (boys-15; girls-15) with a follow-up period of more than 5 years were analyzed in detail.

**Results:** Of 30 cases analyzed, polymorphisms were not detected in 8 (26.67%) children, and 22 (73.33%) had polymorphisms of the *CYP2C9, CYP2C19* and *CYP3A4* genes associated with a slow metabolism of AED. In children with polymorphisms of the *CYP450* genes, the wave-like course of the disease with the periods of remission and its failures was characteristic, while for children with a presumably normal metabolism there was the initial resistance to the treatment with AED.

**Conclusions:** Individual changes in the AED metabolism affect the course of drug-resistant epilepsies. For patients with a slow metabolism of AED the wave-like course of the disease and the "slipping off" phenomenon were more characteristic.

**KEY WORDS:** children, drug-resistant epilepsy, cytochrome P450, allelic polymorphism, the course variants

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## INTRODUCTION

Epilepsy is a chronic disease of the nervous system manifested by recurrent seizures. About 60 million people in the world with epilepsy are forced to constantly take antiepileptic drugs (AED); moreover, 30-40% of them never reach remission [1, 2].

Despite the great successes achieved in the study of epileptogenesis, antiepileptogenesis, the occurrence of seizures depending on the specific etiology, the availability of models for the study of epilepsy, as well as models of drug resistance, to date, the mechanisms of the formation of resistance to AED remain not fully elucidated and are the subject of close attention of researchers [3-5].

In clinical practice, there are several variants of resistance to AED: 1) the initial resistance when the patient from the moment of the onset and further never reaches remission; 2) the slow drug resistance, when at the beginning of the treatment epileptic seizures can be stopped, but then they relapse and become uncontrollable; 3) the wave-like course of epilepsy when there is an alternation between controlled and uncontrolled periods during the disease; 4) epilepsies initially resistant to the treatment with AED, but react to it after a while [3].

Studies of recent decades have proven that an important role in the effectiveness of the treatment of epilepsy, the nature of the response to the use of AED is played by the genetic characteristics of patients, in particular the activity of cytochrome *P450* enzymes providing the metabolism of xenobiotics [6]. Of the existing enzymes of this system in the human body, the following ones are the most important in the AED biotransformation: *CYP2C9, CYP2C19, CYP2D6, CYP3A4*, they are encoded by the corresponding genes – *CYP2C9, CYP2C19, CYP2D6, CYP3A4* [7-10].

The individual characteristics of metabolism are of particular importance when dealing with the treatment of drug-resistant epilepsies with the use of several AED simultaneously. Mutations in key nucleotides with the replacement of one nucleotide by another in the sequence of deoxyribonucleic acid (DNA) can lead to

the emergence of new functional variants of xenobiotic biotransformation. Such variants accelerate or slow down the metabolic activity of enzymes compared with the original "wild" type. The genetic characteristics of patients can make changes in the interactions of AED with each other, affect the metabolic rate of certain xenobiotics, the effectiveness of the antiepileptic therapy, cause undesirable side reactions in patients and possibly lead to the development of drug resistance [11-13].

## THE AIM

The aim of the study was to investigate the frequency with which various variants of the formation and course of drug-resistant epilepsy occur in children with genetic polymorphisms of cytochromes *CYP2C9, CYP2C19, CYP3A4*, to determine their potential role in the formation of drug resistance by studying the anamnesis and long-term observation of patients.

According to the working hypothesis, the presence of appropriate genetic polymorphisms in children with resistant forms of epilepsy contributes to the formation of resistance to antiepileptic therapy and the wave-like course of the disease.

## MATERIALS AND METHODS

The pharmacogenetic testing was performed in 116 children, including 63 boys (B) — 54.31% and 53 girls (G) — 45.69% aged 2 to 17 years, Slavic nationality, residents of Ukraine suffering from refractory epilepsy. Patients of earlier age were excluded from the study due to the fact that the cytochrome P450 enzyme system in children, especially under the age of one year, was not fully formed and its function was unstable [14, 15]. At the time of hospitalization, the children had repeated epileptic seizures; they took two or more AED. Patients and/or their parents signed an informed consent to participate in the study. We used in our study following methods: clinical anamnestic, clinical neurological, neurophysiological (electroencephalography), neuroimaging (nuclear magnetic resonance imaging of the brain), genetic (allele-specific polymerase chain reaction), methods of mathematical statistics.

Epilepsy was diagnosed according to the recommendations of the International Antiepileptic League, and the anticonvulsant therapy was selected and depended on the type of seizures or epileptic syndromes, the age and sex of the child, concomitant diseases, the effectiveness of the antiepileptic therapy used earlier.

The features of the onset and course of the disease as a variant of the formation of drug-resistant epilepsies were studied in the anamnestic study and observation of patients. For this purpose, all available accounting forms of medical documentation were used (extracts from medical histories, outpatient cards, advisory opinions), as well as diaries of attacks kept by parents in an arbitrary form. Further, 30 cases (B-15; G-15) out of all the examined were analyzed in detail with a follow-up period of more than 5 years (a period of time when it is already possible to speak about variants of the course of the disease).

To clarify the potential role of individual characteristics of AED metabolism in the occurrence of the treatment resistance, and the course of drug-resistant epilepsies, genotyping of *CYP2C9*1*, *CYP2C9*2*, *CYP2C9*3*, *CYP2C19*1*, *CYP2C19*2*, *CYP3A4*1A*, *CYP3A4*1B* by allele-specific polymerase chain reaction (PCR) was performed. The DNA of the genome was isolated from the clinical material (whole blood leukocytes) using a "DNA-sorb-B" reagent. Allelic variants of genes were determined using "SNP-express" diagnostic kits. The separation of amplification products was carried out by horizontal electrophoresis in 3% agarose gel.

Single nucleotide polymorphisms in genes were determined using allele-specific primers. Allelic variant *2 of the *CYP2C9* gene (rs1799853) is characterized by the replacement of cytosine (C) with thymine (T) in position 430 – *C > T*. Allelic variant *3 of the *CYP2C9* gene (rs1057910) is characterized by the replacement of adenine (A) with cytosine (C) in position 1061 – *A > C*.

Polymorphic variant *2 of the *CYP2C19* gene (rs4244285) is distinguished by the presence of adenine (A) instead of glycine (G) in position 681 – *G > A*; variant *3 of the *CYP2C19* gene (rs4986893) has the same replacement of glycine (G) with adenine (A) G > A, but in position 636.

Polymorphism *1B of the *CYP3A4* gene (rs2740574) is determined by the replacement of adenine (A) with glycine (G) A > G in position 392.

The results obtained were analyzed using Statistica – 7 program. Differences between groups were assessed Student's coefficient. Statistical significance was set at $P<0.05$. The mean values (M) and its deviations (±m) were calculated.

## RESULTS

In the total group of 116 patients, individual single nucleotide polymorphisms and their combinations were detected in 75 children (64.66%). Isolated polymorphisms of the *CYP2C19* gene were detected in 39 patients (33.62±4.46%), the *CYP2C9* gene – in 17 examined persons (14.66±3.30%), the *CYP3A4* gene – in 5 children (4.31±1.89%). In 14 patients (12.07±3.04%), the presence of polymorphism combinations of several different genes was found.

**Table I.** The nature of epileptic seizures (N = 30)

| The nature of epileptic seizures | Children with drug-resistant epilepsy | | | | p |
|---|---|---|---|---|---|
| | With polymorphisms CYP450, (N = 22) | | Without polymorphisms CYP450, (N = 8) | | |
| | Abs. qty | M±m% | Abs. qty | M±m% | |
| Focal | 5 | 22.73± 9.14 | 3 | 37.50± 18.30 | > 0.05 |
| Focal and secondary generalized | 15 | 68.18± 10.16 | 4 | 50.00± 18.90 | > 0.05 |
| Absences | 1 | 4.55± 4.55 | 0 | 0 | > 0.05 |
| Polymorphic | 1 | 4.55± 4.55 | 1 | 12.50± 12.50 | > 0.05 |

**Table II.** Variants of the formation and course of drug-resistant epilepsies

| Variants of the formation and course of drug-resistant epilepsies (the observation period is more than 5 years) | Epilepsy in children with the P450 gene polymorphisms, (N = 22) | | Epilepsy in children without the P450 gene polymorphisms, (N = 8) | | p |
|---|---|---|---|---|---|
| | Abs. qty | M±m % | Abs. qty | M±m% | |
| The resistance from the moment of the onset, the course without remission, possible short-term reduction in the number of seizures | 6 | 27.27± 9.72 | 4 | 50.00±18.90 | > 0.05 |
| The delayed drug resistance | 3 | 13.64± 7.49 | 3 | 37.50±18.30 | > 0.05 |
| The wave-like course | 12 | 54.55± 10.87 | 1 | 12.50± 12.50 | < 0.05 |
| The persistent achievement of control | 1 | 4.55± 4.55 | 0 | 0.00 | > 0.05 |

Thirty (30) children with drug-resistant epilepsies who were observed by us for more than 5 years, depending on the genetic testing results, were divided into two groups. Group 1 included 22 children (B-13, G-9; 73.33±8.21%), in whom polymorphisms of *CYP2C9, CYP2C19, CYP3A4* genes affecting the individual AED metabolism, slowing it down, were detected. Group 2 consisted of 8 children (B-2, G-6; 26.67±8.21%) with no polymorphisms of *CYP450* genes, suggesting the normal AED metabolism. Thus, in our long-term follow-up in children with drug-resistant epilepsies, the presence of polymorphisms of genes controlling the AED metabolism was almost 3 times more common than their absence (73.33±8.21% vs. 26.67±8.21%).

The analysis of the pharmacogenetic testing results showed that polymorphisms of *CYP450* genes occurred with different frequency. Thus, polymorphisms of *CYP2C9*2, CYP2C9*3* were detected in 6 out of 22 children (27.27±9.72%), *CYP2C19*2* in 15 (68.18±10.16%), and *CYP3A4*1B* in 3 patients (13.64±7.49%). The *CYP2C19*3* polymorphism was not detected among the children who were included in the analysis. A combination of 2 different single nucleotide polymorphisms was recorded in 3 patients (13.64±7.49%), and 3 polymorphisms – in 1 (4.55±4.45%) patient. All polymorphisms identified were associated with a slow metabolism. Thus, the results obtained indicate that the polymorphism of genes providing the AED metabolism was common in children with drug-resistant epilepsy observed for a long time, in 73.33±8.21% of cases, with the most common polymorphism being *CYP2C19*2*, the *CYP3A4*1B* variant and a combination of genetic polymorphisms were rarely detected, and the polymorphism *CYP2C19*3* was absent.

The study of the clinical features of epilepsy showed that in both groups symptomatic epilepsy significantly prevailed: in group 1 – in 21 children (95.45±4.55%) and in group 2 – in 7 children (87.50±12.50%) compared to other forms. Idiopathic epilepsy was recorded only in 1 (4.55±4.55%) child among children of group 1, and cryptogenic epilepsy in 1 child (12.50±12.50%) of group 2.

The most often cause of epilepsy in children of group 1 were in decreasing order: neuroinfections – in 12 children (54.55±10.87%); ante/perinatal lesions – in 9 children (40.91±10.73%); a hereditary pathology with

epileptic seizures as one of the symptoms – in 2 children (9.09±6.27%); craniocerebral injuries occurred in 2 children (9.09±6.27%), while 3 patients (13.64±7.49%) from this group had a combination of several etiological factors.

Among the children of group 2, the etiology of epilepsy was as follows: an ante/perinatal pathology – in 5 children (62.50%); neuroinfections – in 3 children (37.50%); traumatic brain injuries – in 2 children (25.00%); a hereditary pathology – in 2 patients (25.00%). The combination of several etiological factors in this group was more common – in 4 patients (50.00%).

Among the etiological factors in both groups, early organic brain lesions and neuroinfections prevailed. However, if in children of group 2 it was possible to assume the impact of several etiological factors that could make a significant contribution to the occurrence of drug-resistant epilepsies significantly more often ($p < 0.05$), then in children of group 1 the occurrence of the disease could only be associated with one etiological factor and the presence of a slow metabolism.

Peculiarities of the phenotype of epileptic seizures in children observed for a long time are presented in Table I.

Thus, no differences were found between the groups in terms of the type of epileptic seizures. Focal and focal epileptic seizures with secondary generalization prevailed in both groups. Among focal seizures, frontal attacks were most often diagnosed, less often temporal seizures with a frequency from one in several months to hundreds per day without a significant difference in both observation groups. The tendency to seriality in 17 patients (56.67±9.20%) and the state flow in 8 patients (26.67±8.21%) was found among 30 children, without significant differences in the groups. The nature of epileptic seizures (focal onset, localization of the focus, the possibility of generalization) was confirmed by EEG diagnostics.

Epilepsy started at an early age in both groups. Almost a third of patients in group 1 (31.82±10.16%) and a quarter of patients in group 2 (25.00±16.37%) had it before the 1st year, and the overwhelming majority of children of both groups had it before the age of 7: group 1 – in 77.28±9.14%, and group 2 – in 75.00±16.37% of cases. The results obtained confirm the fact that the onset of epilepsy at an early age, in particular before one year, is one of the predictors of the unfavorable course of the disease and the formation of drug resistance.

In most cases, the children observed in both groups had various neurological and mental disorders, indicating lesions of the central nervous system.

Neurological symptoms insignificantly prevailed in group 1, and mental disorders dominated in group 2 where behavioral disorders were significantly more common ($p < 0.05$).

Using magnetic resonance imaging (MRI) the structural changes in the brain were revealed in 12 patients (54.55±10.87%) of group 1 and 4 patients (50.00±18.90%) in group 2.

The examined children in most cases are forced to take more than two AED: in group 1 – 86.36±7.49%, and in group 2– 87.50±12.50%. When clarifying the treatment effectiveness and selecting the therapy the following data became known: in group 1 patients responded positively to the first AED in 8 cases (36.36±10.50%), among them in 4 patients (18.18±8.42%) the seizures completely stopped for up to 6 months, and in 4 children (18.18±8.42%) their number decreased by more than 50 %; in patients of group 2, in 2 cases (25.00%) the seizures stopped after taking the first AED for a period of up to 6 months and then resumed again, while in other patients their number decreased slightly, by less than 50%.

Due to the severe course of the disease, which was resistant to the drug treatment with AED, there was the selection of the therapy with a large number of samples, in most cases there were more than 5 of them in both groups (in group 1 – 54.55±10.87% and in group 2 – 75.00±16.37%).

Analyzing the course of drug-resistant epilepsies we identified certain characteristic features for each group. For patients of group 2 with a presumably normal AED metabolism, the resistance was characteristic from the moment of the onset (in 50±18.90% of cases), and in children with the presence of polymorphisms in the genes controlling the *CYPP450* enzyme system, the wave-like course of the disease (in 54.55±10.87% of patients) prevailed when a good response to the introduction of another AED with a further increase in the dose was replaced by worsening in the form of an increase in the frequency and/or severity of epileptic seizures.

Table II shows the variants of the formation and course of drug-resistant epilepsies in children over a follow-up period of more than 5 years.

The significantly ($p < 0.05$) more frequent wave-like course of the disease in the group of patients with polymorphisms draws attention, no difference between the groups in the frequency of other variants is observed. A characteristic feature of the wave-like course of drug-resistant epilepsies was the presence of a kind of the "slipping off" phenomenon: when prescribing another AED a positive effect was initially obtained; it was leveled after a while, despite a further increase in dose, without the influence of any exo- or endogenous provoking factors. The presence of the "slipping off" phenomenon was significantly more often observed in

children of group 1 compared to group 2 (54.55±10.87% vs. 12.50±12.50%, $p < 0.05$), and if a child from group 2 had only an increase in seizures, then for children of group 1 a combination of increased frequency of seizures and the appearance of undesirable side effects (8 children – 36.36±10.50% of the total number of patients in group 1) was characteristic, requiring the AED withdrawal.

## DISCUSSION

The current studies prove the importance of genetic characteristics of patients in the treatment of various diseases, in a positive or negative response to the therapy. To date, there are no studies on the effect of polymorphisms of genes encoding enzymes of the cytochrome *P450* system, which are involved in the AED biotransformation, on the formation and course of drug-resistant epilepsies since, in addition to conducting the pharmacogenetic testing, a long-term monitoring of these patients is necessary for a reliable assessment of the course of the disease. Four variants of the onset and outcome of the drug-resistant epilepsy are theoretically substantiated and described in the works of Löscher W. et al. 2020 [5]. In order to confirm the frequency with which a particular variant of the occurrence and course of drug-resistant epilepsy occurs, how the genetic features of the metabolism affect these variants, it is necessary, in addition to the pharmacogenetic testing, to monitor patients for a long time. Currently, many population pharmacogenetic studies have been conducted in different countries to identify polymorphisms of the *CYP2C9, CYP2C19*, and *CYP3A4* genes that control the AED metabolism among various ethnic groups, while studies of gene polymorphisms in patients with drug-resistant epilepsies are rare [16-19]. The relationship between the genetic features of the drug metabolism in patients suffering from epilepsy and the occurrence of side effects has been proven [20]. At the same time, there are only isolated studies confirming a reliable link between drug-resistant epilepsy and genetic polymorphisms of *CYP450* [21]. There is no research studying the features of the course of drug-resistant epilepsies, depending on the presence or absence of an AED metabolic disorder genetically determined.

Our study has shown that the presence of single nucleotide polymorphisms of cytochromes *CYP2C9, CYP2C19, CYP3A4* is characteristic in children with drug-resistant epilepsies. Thus, among patients with drug-resistant epilepsies, who were under our supervision for more than 5 years, genetic polymorphisms of *CYP450* were recorded in 73.33±8.21% of cases. Therefore, it can be assumed that in most children with drug-resistant epilepsies, in addition to etiological factors, disorders of the AED metabolism play an important role in the occurrence and course of the disease.

We identified biological markers of a slow metabolism of AED in children with drug-resistant epilepsies: *CYP2C9*2, CYP2C9**3 in 6 of 22 patients (27.27±9.72%), *CYP2C19*2* in 15 patients (68.18±10.16%), and *CYP3A4*1B* in 3 patients (13.64±7.49%); a combination of two different single nucleotide polymorphisms were recorded in 3 patients (13.64±7.49%); a combination of 3 polymorphisms – in 1 patient (4.54±4.45%). The specific weight of the effect of each of them is different, and their importance in drug-resistant epilepsy is unknown.

The analysis of the clinical features, age of the onset, data from additional research methods in groups with both the presence and absence of polymorphisms of genes encoding cytochrome *P450* enzymes has shown no significant difference in the groups.

In both observation groups of children with drug-resistant epilepsies (with and without polymorphisms), symptomatic epilepsies significantly prevailed (95.45±4.55% and 87.50±12.50%, respectively). Moreover, the occurrence of epilepsy in children of group 2 (without polymorphisms) compared to patients of group 1 can more often be associated with the action of several etiological factors (50.00±18.90% vs. 13.64±7.49%, $p < 0.05$), whereas in children (with polymorphisms) of group 1 the occurrence of the disease could be associated with only one etiological factor and the presence of a slow metabolism caused by genetic polymorphisms of the *CYP P450* system genes.

Individual changes in the AED metabolism affect the course of drug-resistant epilepsies. For patients with a slow metabolism, the wave-like course of the disease was more characteristic, with periods of remission and its failures, and for children with a normal metabolism, the initial resistance to the treatment with AED was more common.

## CONCLUSIONS

Single nucleotide polymorphisms of CYP2C9, CYP2C19, CYP3A4 cytochromes were found in 73.33±8.21% of children with drug-resistant forms of epilepsy who have been under observation for 5 years or more. The markers of slow AEP metabolism were determined: CYP2C9*2, CYP2C9*3 in 6 of 22 patients (27.27±9.72%), CYP2C19*2 in 15 patients (68.18±10.16%) and CYP3A4*1B in 3 patients (13.64±7.49%. In children with polymorphisms, the wave-like course of the disease is determined significantly more often (54.55±10.87% vs. 12.50±12.50%, $p < 0.05$). A characteristic feature of the wave-like course of drug-resistant epilepsies was the presence of a peculiar phenomenon of "slippage":

when another AED was prescribed, a positive effect was initially obtained; after some time, it leveled off, despite a further increase in the dose, without the influence of any exo- or endogenous provoking factors. Obviously, the results obtained do not give an unambiguous answer to the question of the degree of significance of the factor of the presence of polymorphisms of the *CYP P450* system genes in the occurrence, formation and progression of drug-resistant epilepsies in children, but, at the same time, they demonstrate the expediency of further research in this direction with an expansion of the spectrum of polymorphisms studied and a comprehensive assessment of genetic and clinical indicators.

Wider introduction of the pharmacogenetic testing will make it possible to assume the course of drug-resistant epilepsy in each individual child, will help in developing new treatment regimens with wider application of individualized approaches to therapy, reducing undesirable side effects and treatment costs, improving the quality of life of patients and their families.

## REFERENCES


1. Kwan P, Arzimanoglou A, Berg AT et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia. 2010; 5:1069–1077.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000; 342:314–319.
3. Schmidt D, Löscher W. Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. Epilepsia. 2005; 46:858–877.
4. Tang F, Hartz AMS, Bauer B. Drug-Resistant Epilepsy: Multiple Hypotheses, Few Answers. Front. Neurol. 2017; 8:301. doi: 10.3389/fneur.2017.00301.
5. Löscher W, Potschka H, Sanjay M et al. Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. Pharmacological Reviews. 2020;72(3);606-638.
6. Steinlein OK. Gene polymorphisms and their role in epilepsy treatment and prognosis. Naunyn Schmiedebergs Arch Pharmacol. 2010; 382:109–118. doi: 10.1007/s00210-010-0531-8.
7. Cárdenas-Rodríguez N, Carmona-Aparicio L, Pérez-Lozano DL et al. Genetic variations associated with pharmacoresistant epilepsy (Review) Mol. Med. Rep. 2020;21:1685–1701. doi: 10.3892/mmr.2020.10999.
8. Peng J, Pang N, Wang Y et al. Next-generation sequencing improves treatment efficacy and reduces hospitalization in children with drug-resistant epilepsy. CNS Neurosci. Ther. 2019; 25:14–20. doi: 10.1111/cns.12869.
9. Liu X, Ou S, Xu T et al. New differentially expressed genes and differential DNA methylation underlying refractory epilepsy. Oncotarget. 2016;7: 87402–87416. doi: 10.18632/oncotarget.13642.
10. López-García MA. Influence of genetic variants of CYP2D6, CYP2C9, CYP2C19 and CYP3A4 on antiepileptic drug metabolism in pediatric patients with refractory epilepsy. Pharmacol Rep. 2017;69(3):504-511.
11. Goldstein DB, Need AC, Singh R, Sisodiya SM. Potential genetic causes of heterogeneity of treatment effects. Am. J. Med. 2007;120:21–25. doi: 10.1016/j.amjmed.2007.02.004.
12. Striano P, Vari MS, Mazzocchetti C et al. Management of genetic epilepsies: From empirical treatment to precision medicine. Pharmacol Res. 2016;107:426–429. doi: 10.1016/j.phrs.2016.04.006.
13. Lakhan R, Kumari R, Singh K et al. Possible role of CYP2C9 & CYP2C19 single nucleotide polymorphisms in drug refractory epilepsy. Indian J Med Res. 2011; 134:295–301.
14. Connor EM, Smoyer WE, Davis JM et al. Meeting the demand for pediatric clinical trials. Sci Transl Med. 2014;6(227):227fs11. doi: 10.1126/scitranslmed.3008043.
15. Drug metabolism and disposition in children. Fundam Clin Pharmacol. 2003; 17:281–299.
16. Seven M, Batar B, Unal S et al. The effect of genetic polymorphisms of cytochrome P450 CYP2C9, CYP2C19, and CYP2D6 on drug-resistant epilepsy in Turkish children. Mol Diagn Ther. 2014; 18:229–236. doi: 10.1007/s40291-013-0078-8.
17. Kumari R, Lakhan R, Garg RK et al. Pharmacogenomic association study on the role of drug metabolizing, drug transporters and drug target gene polymorphisms in drug-resistant epilepsy in a north Indian population. Indian J Hum Genet. 2011;17(1):32–40. doi: 10.4103/0971-6866.80357.
18. Kesavan R, Kukreti R, Adithan C, Indian J. Genetic polymorphism of drug refractory epilepsy. Med Res. 2011;134(3):253–5.
19. Patsalos PN. Antiepileptic drug interactions: a clinical guide. Springer. 2016, p.389.
20. Louis EK. Truly "rational" polytherapy: Maximizing efficacy and minimizing drug interactions, drug load, and adverse effects. Curr Neuropharmacol. 2009; 7:96–105.
21. Seven M, Batar B, Unal S et al. The Effect of Genetic Polymorphisms of Cytochrome P450 CYP2C9, CYP2C19, and CYP2D6 on Drug-Resistant Epilepsy in Turkish Children. Molecular Diagnosis & Therapy. 2014; 18(2):229–236.

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ORIGINAL ARTICLE

# MORPHOLOGICAL ASSESSMENT OF THE LUNGS IN POST-COVID-19 SYNDROME: ANALYSIS OF AUTOPSY MATERIAL

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## ABSTRACT

**The aim** was to reveal the morphological features of the lungs in post-COVID-19 syndrome.

**Materials and methods:** The material of the study was autopsy material – fragments of the lung tissue from 96 deceased (59 men and 37 women). During the lifetime, all patients had in anamnesis COVID-19 of varying severity, and after the treatment of this infection, they had various manifestations of respiratory failure until death. The average duration of the post-COVID-19 period was 148.6±9.5 days. Based on the severity of COVID-19 in anamnesis, all cases were divided into three groups. Group 1 included 39 cases with mild COVID-19 in anamnesis. Group 2 included 24 cases with moderate severity of COVID-19 in anamnesis. Group 3 included 33 cases with severe COVID-19 in anamnesis. Histological, histochemical, morphometric and statistical research methods were used.

**Results:** Morphological features of the lungs in post-COVID-19 syndrome were the presence of pneumosclerosis; focal-diffuse immune cells infiltration; emphysematous and atelectatic changes; degenerative-desquamatic changes in the alveolar epithelium; metaplastic changes of connective tissue; dystrophic calcification; dystrophic, metaplastic and dysplastic changes in the epithelial layer of bronchial tree; hemodynamic disorders. Pneumosclerosis, focal-diffuse immune cells infiltration, alterative changes in the alveolar epithelium, emphysematous and atelectatic changes, hemodynamic disorders increased with an increase the severity of COVID-19. Metaplastic changes of connective tissue, dystrophic calcification, dystrophic, metaplastic and dysplastic changes in epithelial layer of bronchial tree did not depend on the severity of the infection.

**Conclusions:** The changes identified by the authors help to explain pulmonary manifestations of post-COVID-19 syndrome. They should be the basis for the oncological alertness formation among doctors, the development of rehabilitation and treatment measures for such category of patients.

**KEY WORDS:** lungs, morphology, autopsy, post-COVID-19 syndrome

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## INTRODUCTION

After the COVID-19 pandemic, doctors of many specialties are now faced with a major global concern – post-COVID-19 syndrome [1]. The post-COVID-19 syndrome, according to some scientists, is the hidden part of a metaphorical iceberg that requires immediate interdisciplinary research [2].

Post-COVID-19 syndrome, according to the World Health Organization, includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of SARS-CoV-2 infection, lasting for at least 2 months and not attributable to alternative diagnoses [3]. Post-COVID-19 syndrome has an official disease status in the International Classification of Diseases (10th revision), where it is designated as a «post-COVID-19 condition» under the code U09.9 [4]. The impact of post-COVID-19 syndrome is enormous for patients, the healthcare system and economic development [5].

The prevalence of post-COVID-19 syndrome has varied across and within many countries: UK – 1.6-71%, Germany – 35-77%, China 49-76%, Africa – 68%, India –22%, Bangladesh – 16-46%, Denmark – 1%, Italy – 5-51%, USA – 16-53%, Norway – 61% [6].

The mechanism of the post-COVID syndrome is a debatable and not fully understood issue. Post-COVID-19 syndrome, according to many scientists, is a complex and multifactorial syndrome involving aberrant immune responses, virus-specific pathophysiological alterations, inflammatory damage in response to the acute infection and mechanisms of viral persistence in certain tissues, SARS-CoV-2 interactions with host microbiome/virome communities, clotting/coagulation issues and dysfunctional brainstem/vagus nerve signaling [7, 8].

Post-COVID-19 symptoms vary in intensity and duration and are not linear or sequential [9]. Post-COVID-19 syndrome may manifest by neurological, respiratory, car-

**Table I.** Pathological anatomy diagnoses and causes of death in the studied cases.

| Pathological anatomy diagnosis | Cause of death | Number of cases | |
|---|---|---|---|
| | | Absolute | Relative (%) |
| Myocardial infarction | Acute cardiac insufficiency | 39 | 40.6 |
| Atherosclerotic cardiosclerosis | Chronic cardiac /cardiopulmonary insufficiency | 34 | 35.4 |
| Cerebral infarction | Dislocation of the brain stem | 12 | 12.5 |
| Deep vein thrombophlebitis of the lower extremities | Thromboembolism of the pulmonary artery | 7 | 7.3 |
| Gangrene of the intestine | Intoxication | 4 | 4.2 |

diovascular, hematologic, gastrointestinal and other symptoms, but the most common are respiratory disorders [1, 10]. Respiratory disorders include external respiration dysfunction, dyspnea, cough, reduced exercise tolerance, post-COVID-19 interstitial lung disease, pain in the intercostal space, pulmonary hypertension, etc. [1, 11, 12].

In the available literature, we did not find comprehensive morphological studies aimed at identifying the morphofunctional state of the lungs in patients with post-COVID-19 syndrome, which would make it possible to understand the morphological substrate of clinically observed signs of respiratory disorders in this category of patients.

## THE AIM

The purpose was to reveal the morphological features of the lungs in post-COVID-19 syndrome.

## MATERIALS AND METHODS

The material of the study was autopsy material – fragments of the lung tissue from 96 deceased (59 men and 37 women). Autopsies were performed on the basis of pathoanatomical department of Public nonprofit organization of the Kharkiv District Council «Regional Clinical Hospital» (Ukraine). During the lifetime, all patients had in anamnesis COVID-19 of varying severity, and after the treatment of this infection, they had various manifestations of respiratory failure until death. The average duration of the post-COVID-19 period was 148.6±9.5 days. In all cases, it was found the presence of immunoglobulin G antibodies to SARS-CoV-2 in diagnostic titers.

Based on the severity of COVID-19 in anamnesis, all cases were divided into three groups. Group 1 included 39 cases with mild COVID-19 in anamnesis. Group 2 included 24 cases with moderate severity of COVID-19 in anamnesis. Group 3 included 33 cases with severe COVID-19 in anamnesis.

An analysis of the causes of death and pathological anatomy diagnoses is given in Table I. In most cases the cause of death was acute cardiac or chronic cardiac/cardiopulmonary insufficiency.

Autopsy material was fixed in a 10% solution of neutral buffered formalin according to the generally accepted technique and embedded in paraffin. Serial sections of 3-4 μm thick were made from paraffin blocks. The slides were stained with hematoxylin and eosin, picrofuchsin according to van Gieson, according to Mallory. The slides were studied using an Olympus BX-41 microscope. A morphometric study was carried out using the Olympus DP-soft version 3.1 software.

The obtained digital data were statistically processed, using the Statistica 10.0 program. The average indicators in the groups were compared, using the nonparametric Mann-Whitney U test. Differences were considered significant at $p<0.05$.

## RESULTS

Survey microscopy of the slides in all cases revealed pneumosclerosis, characterized by the excessive growth of connective tissue fibers perivascular and directly in the vessels walls of various calibers, around the bronchi and bronchioles or directly in their walls, in the interalveolar septa with its thickening, in the alveoli lumen (Fig. 1).

The results of a morphometric study also indicated sclerotic changes in the lungs. In all groups, in the lungs during morphometric study, the specific volume of the parenchyma, including the system of the bronchial tree and the system of the acini, and the stroma, represented by connective tissue fibers with vessels located between them, were determined (Fig. 2). In the direction from group 1 to group 3, the specific volume of the parenchyma decreased ($p<0.05$), and the specific volume of the stroma increased ($p<0.05$). These changes indicated an increase of pneumosclerosis with an increase of the infection severity.

Among the connective tissue fibers during Mallory staining a decrease in the number of elastic fibers and an increase in the number of collagen fibers in the direction from group 1 to group 3 were revealed, which also indicated about the sclerotic changes. In group 3, in a significant number of fields of vision, elastic fibers were practically not detected.

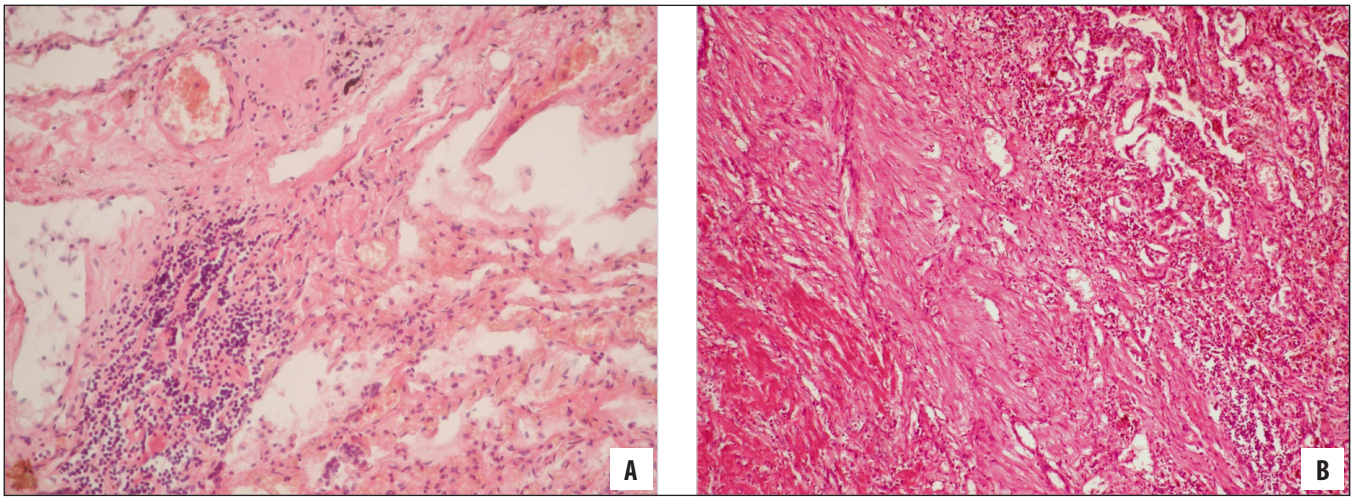


**Fig. 1.** Sclerotic changes in the lungs in groups 1 (a) and 3 (b). Immune cells infiltration in foci of pneumosclerosis. Stained with hematoxylin and eosin, a) ×200, b) ×100.

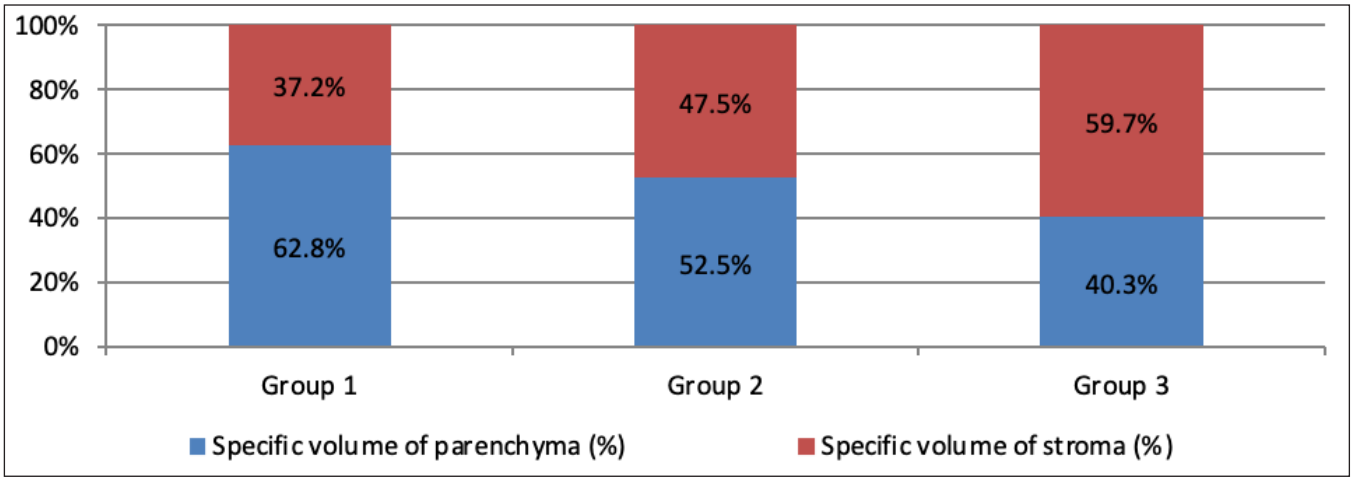


**Fig. 2.** The average values of the specific volumes of parenchyma and stroma in the lungs in groups 1-3.

In the foci of pneumosclerosis in all groups, focal-diffuse infiltration by immune cells was noted, which increased in the direction from group 1 to group 3 (Fig. 1).

Also, in the areas of pneumosclerosis, metaplastic changes of the connective tissue were detected, characterized by the presence of hyaline cartilage (Fig. 3), bone and adipose tissues (Fig. 4). These changes were identified in group 1 in 8 cases (20.5%), in group 2 – in 6 cases (25%), in group 3 – in 9 cases (27.3%). Comparative analysis did not reveal significant ($p>0.05$) differences between the numbers of cases with this microscopic finding in all groups.

Against the background of the changes described above in the areas of pneumosclerosis, foci with dystrophic calcification were also detected in group 1 in 7 cases (17.9%), in group 2 – in 4 cases (16.7%), in group 3 – in 6 cases (18.2%) (Fig. 5). The severity of dystrophic calcification did not depend on the severity of the infection.

In the deformed bronchial tree, due to sclerotic changes, we noted various general pathological processes in the epithelial layer. In all cases of groups 1-3, dystrophic changes in the epithelium were determined. Also in the epithelial layer in 8 cases (20.5%) of group 1, in 5 cases (20.8%) of group 2 and in 7 cases (21.2%) of group 3 metaplastic and dysplastic changes sometimes with the formation of adenomatous structures were detected (Fig. 6). The severity of the identified changes in the epithelium of the bronchial tree did not depend on the severity of COVID-19.

Microscopic examination of the lungs in all groups revealed focal degenerative-desquamatic changes in the alveolar epithelium, as well as unchanged alveoli, alveoli with ephysematous and atelectatic changes (Fig. 7). Alterative changes in the alveolar epithelium increased with an increase the severity of COVID-19. Morphometry identified that with an increase of the COVID-19 severity, the specific volume of unchanged alveoli (group 1 – (72.5±1.54)%, group 2 – (60.9±2.11)%,

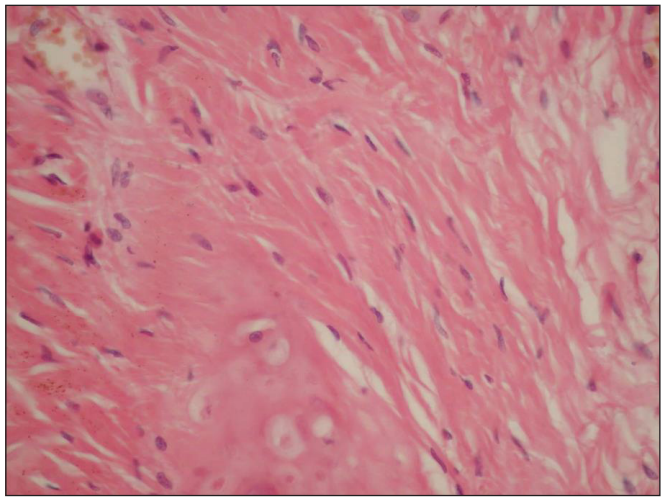

**Fig. 3.** Hyaline cartilage in the area of pneumosclerosis. Stained with hematoxylin and eosin, ×400.

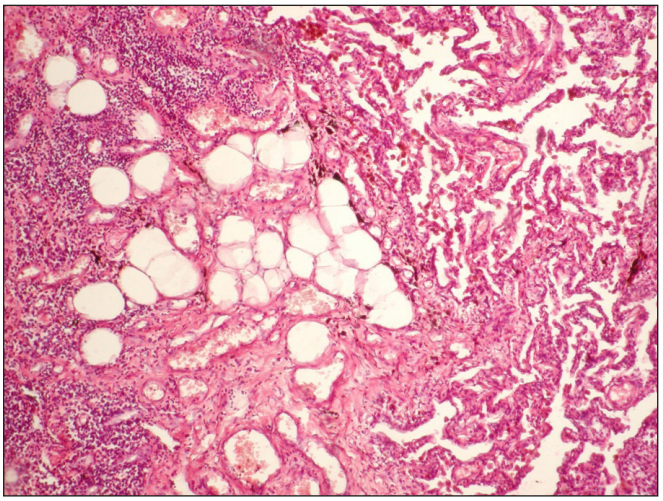

**Fig. 4.** Adipose tissue in the area of pneumosclerosis. Stained with hematoxylin and eosin, ×100.

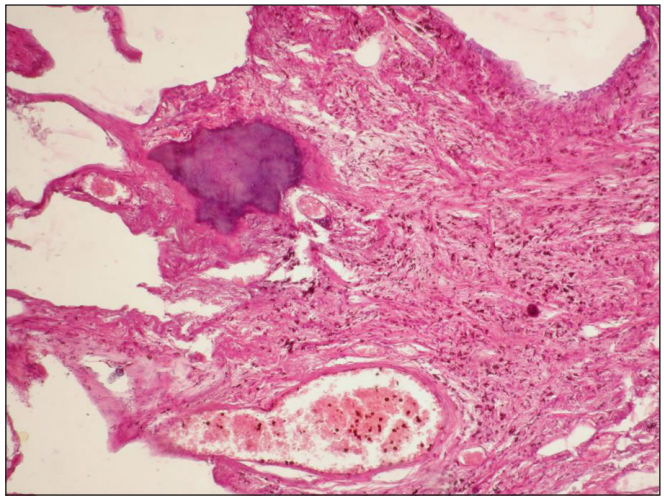

**Fig. 5.** Dystrophic calcification in the area of pneumosclerosis. Stained with hematoxylin and eosin, ×100.

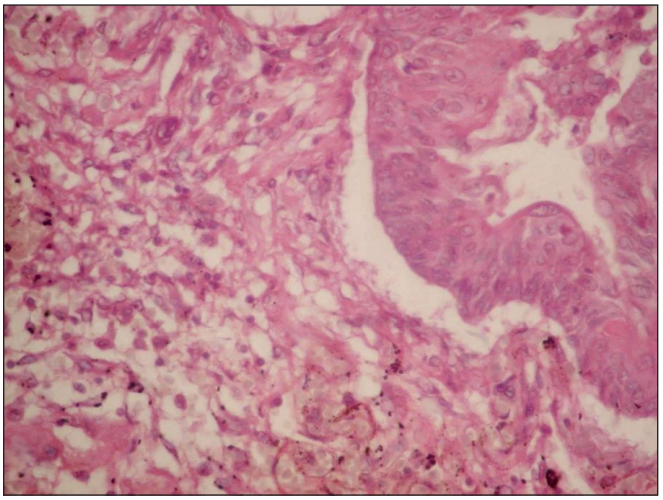

**Fig. 6.** Metaplastic and dysplastic changes in the epithelial layer of the bronchial tree in group 3. Stained with hematoxylin and eosin, ×400.

group 3 – (51.8±2.43)%) decreased ($p<0.05$), and the specific volume of emphysematous and atelectatically changed alveoli taken together (group 1 – (27.5±1.54)%, group 2 – (39.1±2.11)%, group 3 – (48.2±2.43)%) increased ($p<0.05$) (Fig. 8).

In all cases of groups 1-3, against the background of the described changes, we detected hemodynamic disorders that increased in the direction from group 1 to group 3 and were characterized by edema, vascular plethora, thrombosis, small-focal hemorrhages with hemosiderin deposition (Fig. 9).

## DISCUSSION

The authors for the first time on autopsy material carried out a comprehensive morphological study of the lungs in post-COVID-19 syndrome, which makes it possible to explain the respiratory manifestation of this syndrome. This study revealed morphological changes in the parenchyma and stroma of the lungs in post-COVID-19 syndrome. Some preliminary results of this study were published by the authors earlier [13]. In this article, the authors publish the final results of the study.

The pneumosclerosis identified by the authors is the outcome of COVID-19, which has also been noted by many scientists [14]. Such pathological process is characterized by the replacement of parenchymal elements with connective tissue, the substitution of elastic fibers with collagen fibers, followed by a decrease in lung compliance, compression of the bronchial tree, which leads to the development of ventilation and parenchymal respiratory failure resulting in decreased quality of life, increased morbidity and mortality [15]. The authors noted an increase of pneumosclerosis with an increase the severity of the infection.

Sclerosis from the point of view of the reversibility of

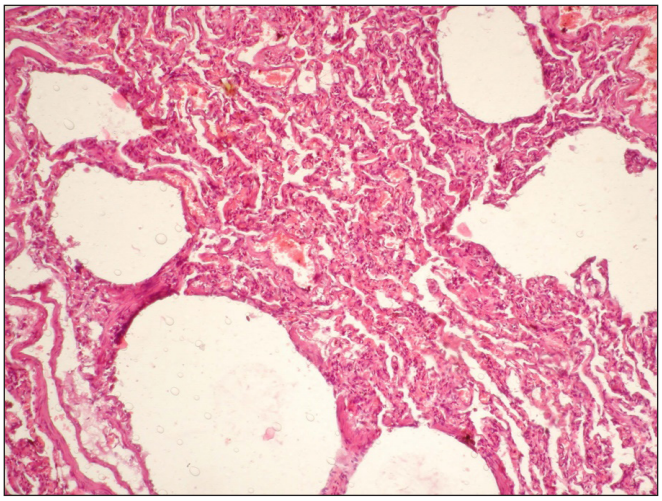

**Fig. 7.** Emphysematous and atelectatic changes in lung tissue in group 2. Stained with hematoxylin and eosin, ×100.

the process can be reversible (labile), partially reversible (stable), irreversible (progressive). In our study, among the connective tissue fibers, a decrease in the number of elastic fibers and their complete disappearance, an increase in the number of collagen fibers were revealed, which, from our point of view, indicates the irreversibility of the sclerotic process in such category of patients.

The pathogenesis of pulmonary fibrosis in post-COVID-19 period is a complex and not fully understood issue [15]. Most scientists associate the development of pneumosclerosis after COVID-19 with transforming growth factor beta (TGF-β), which is a multifunctional cytokine with profibrogenic, antiinflammatory and immunosuppressive effects that are elevated after COVID-19 [2].

Interestingly, one of the factors contributing to the development of pneumosclerosis is mechanical ventilation, which was used in the treatment of respiratory distress syndrome. Due to mechanical ventilation shear forces not only induce secretion of TGF-β but also activate collagen synthesis and inhibit collagenase production [2].

Some scientists assign the leading role in the development of pneumosclerosis after COVID-19 to endothelial-mesenchymal and epithelial-mesenchymal transformation. In the development of the latter, vascular endotheliocytes, alveolar epithelium (type II pneumocytes) can take part [16].

One of the factors triggering the endothelial-mesenchymal and epithelial-mesenchymal transformation can be hypoxemia [17].

Some scientists note the role of CD44 and metalloproteinase-9 in the development of pneumosclerosis after COVID-19. CD44 with hyaluronic acid activates the Phosphatidylinositol 3 Kinase/Protein Kinase B pathway, which induces the reduction in cellular apoptosis, increasing the survival of fibroblasts and myofibroblasts. Metalloproteinase-9 is expressed by alveolar epithelial cells, neutrophils, macrophages, and fibroblasts being able to activate TGF-β1, which contributes to the increase in the active TGF-β pool [18].

The infiltration by immune cells revealed by the authors in the foci of pneumosclerosis, which increased in parallel with sclerotic changes, indicates the participation of these cells in the development of pneumosclerosis.

In the foci of pneumosclerosis, the authors identified dystrophic calcification in 17 cases of groups 1-3, which is due to ongoing physicochemical changes in tissues, followed by the absorption of calcium salts from the blood and tissue fluid [19]. Also, in the areas of pneumosclerosis in 23 cases of groups 1-3, metaplasia of the connective tissue was noted with the formation of adipose, bone and cartilage tissues. In this case, before

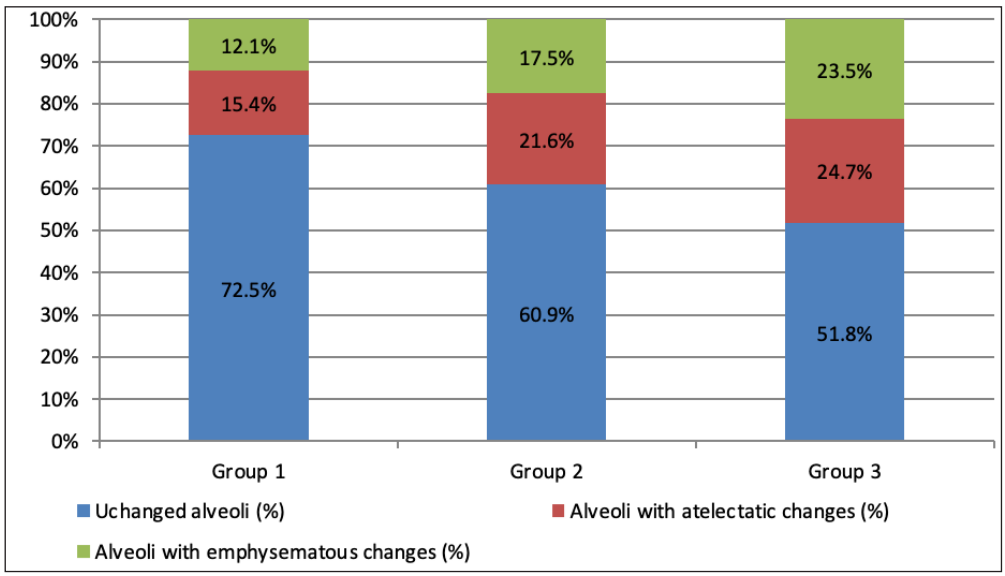


**Fig. 8.** The average values of the specific volumes of unchanged alveoli, alveoli with emphysematous and atelectatic changes in the lungs in groups 1-3.

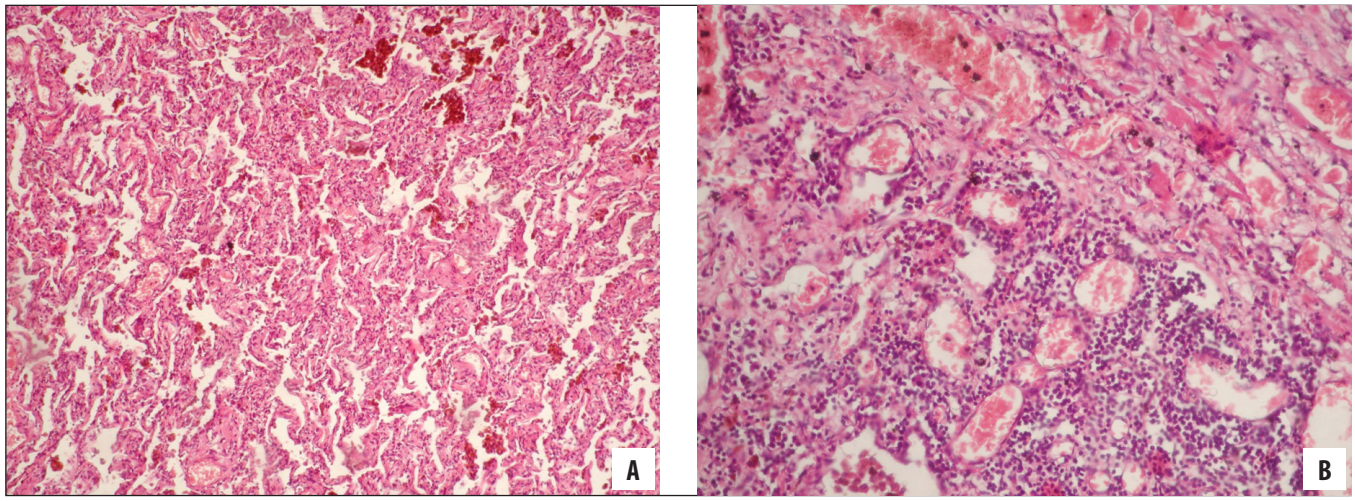


**Fig. 9.** Hemodynamic changes in the lungs in groups 2 (a) and 3 (b). Stained with hematoxylin and eosin, a) ×100, b) ×200.

the formation of adipose, bone, and cartilage tissues, proliferation of young cells of the connective tissue was noted, followed by differentiation into adipocytes, chondrocytes, and osteocytes. The changes in the connective tissue identified by the authors did not depend on the severity of the infection.

The sclerotic changes in the lungs identified by the authors led to a decrease of the parenchymal component, and with an increase of the severity of the infection, this pattern increased, which, accordingly, would lead to an increase the respiratory failure signs.

In all cases of groups 1-3, hemodynamic disorders were detected which depended on the severity of the infection and were characterized by edema, vascular plethora, thrombosis, small-focal hemorrhages with hemosiderin deposition. Similar changes have been described by scientists in the lungs during COVID-19 [20, 21].

Many scientists use the term COVID-19-associated interstitial lung disease (ILD) to describe pneumosclerosis as an outcome of COVID-19. Some scientists describe pulmonary aspergillosis as a manifestation of respiratory disorders of post-COVID-19 syndrome [22]. In our study, pulmonary aspergillosis was not detected. In our previous studies, we described chronic atrophic rhinosinusitis in patients in post-COVID-19 period caused by the association of bacteria and fungi. Among fungi, there were Aspergillus, Candida, Mucor and Coccidioides [23].

Sclerotic changes in the lungs were combined with damage of the parenchymal component. Damage of the latter was characterized, firstly, by focal degenerative-desquamative changes of the alveolar epithelium, which, together with the above described sclerotic changes of the basement membranes, leads to a violation of the morphofunctional state of the air-blood barrier and the development of parenchymal respiratory failure. Secondly, changes of the parenchymal component were characterized by a decrease of the specific volume of unchanged alveoli and an increase of the specific volume of emphysematous and atelectatically changed alveoli. The authors found an increase of these changes with increasing severity of COVID-19.

Also, changes of the parenchymal component of the lungs were characterized by damage of the epithelial layer of the bronchial tree, deformed due to sclerosis. In all cases of groups 1-3 the authors noted dystrophic changes. In 20 cases of groups 1-3 metaplastic and dysplastic changes sometimes with the formation of adenomatous structures were detected in the epithelial layer of the deformed bronchial tree. The changes in the bronchial epithelium identified by the authors did not depend on the severity of COVID-19.

Metaplasia and dysplasia are precancerous conditions [24, 25]. Therefore, the dysplastic and metaplastic changes identified by the authors in the epithelial layer of the bronchial tree, which did not depend on the severity of COVID-19, indicate that these patients are more likely to develop lung cancer in the future. It's just a hypothesis that requires years of research.

Some scientists in their studies also suggest that COVID-19 may be a risk factor for lung cancer [26].

There are studies in the literature that found that pneumosclerosis, immune cells infiltration, dysplastic and metaplastic changes in the epithelium of the bronchi are the basis for the development of peripheral lung cancer ("cancer in the scar") [27]. There are epigenetic and genetic alterations, abnormal expression of microRNAs, cellular and molecular aberrances such as an altered response to regulatory signals, delayed apoptosis or reduced cell-to-cell communication, along with the activation of specific signaling transduction

pathways, all these characterize the pathogenesis of pneumosclerosis and lung cancer [27].

Sadigov A. et al. showed in their studies that lung cancer most common was found at three months after lung infection, and most commonly incidence of lung cancer was observed in patients after surviving severe COVID-19 infection with severe acute respiratory distress syndrome in whom was developed massive and non-resolving fibrosis with history of cigarette smoking and most commonly type of the lung cancer was squamous cell lung cancer [28].

## CONCLUSIONS

1. Morphological features of the lungs in post-COVID-19 syndrome are the presence of pneumosclerosis; focal-diffuse immune cells infiltration; emphysematous and atelectatic changes; degenerative-desquamatic changes in the alveolar epithelium; metaplastic changes of connective tissue; dystrophic calcification; dystrophic, metaplastic and dysplastic changes in the epithelial layer of bronchial tree; hemodynamic disorders.
2. Pneumosclerosis, focal-diffuse immune cells infiltration, alterative changes in the alveolar epithelium, emphysematous and atelectatic changes, hemodynamic disorders increased with an increase the severity of COVID-19. Metaplastic changes of connective tissue, dystrophic calcification, dystrophic, metaplastic and dysplastic changes in the epithelial layer of bronchial tree did not depend on the severity of the infection.
3. The changes identified by the authors help to explain pulmonary manifestations of post-COVID-19 syndrome. They should be the basis for the oncological alertness formation among doctors, the development of rehabilitation and treatment measures for such category of patients.

## REFERENCES


1. Montani D, Savale L, Noel N, et al. COMEBAC Study Group. Post-acute COVID-19 syndrome. Eur Respir Rev. 2022;31(163):210185.
2. Oronsky B, Larson C, Hammond TC, et al. A review of persistent post-COVID syndrome (PPCS). Clin Rev Allergy Immunol. 2023;64(1):66-74.
3. Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: an overview. Diabetes Metab Syndr. 2021;15(3):869-875.
4. Soriano JB, Murthy S, Marshall JC, et al. WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis. 2022;22(4):e102-e107.
5. Yan MZ, Yang M, Lai CL. Post-COVID-19 syndrome comprehensive assessment: from clinical diagnosis to imaging and biochemical-guided diagnosis and management. Viruses. 2023;15(2):533.
6. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J. 2022;43(11):1157-1172.
7. Pierce JD, Shen Q, Cintron SA, Hiebert JB. Post-COVID-19 syndrome. Nurs Res. 2022;71(2):164-174.
8. Visco V, Vitale C, Rispoli A, et al. Post-COVID-19 syndrome: involvement and interactions between respiratory, cardiovascular and nervous Systems. J Clin Med. 2022;11(3):524.
9. Antoniou KM, Vasarmidi E, Russell AM, et al. European Respiratory Society statement on long COVID follow-up. Eur Respir J. 2022;60(2):2102174.
10. Fernández-Plata R, Higuera-Iglesias AL, Torres-Espíndola LM, et al. Risk of pulmonary fibrosis and persistent symptoms post-COVID-19 in a cohort of outpatient health workers. Viruses. 2022;14(9):1843.
11. Esendağli D, Yilmaz A, Akçay Ş, Özlü T. Post-COVID syndrome: pulmonary complications. Turk J Med Sci. 2021;51(SI-1):3359-3371.
12. Song WJ, Hui CKM, Hull JH, et al. Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. Lancet Respir Med. 2021;9(5):533-544.
13. Myroshnychenko M, Sukhorukov I, Dyadyk O, et al. Morphological features of the lungs in post-COVID-19 period. Medicina (Kaunas). 2023;59 (Supplement 1):43.
14. Rai DK, Sharma P, Kumar R. Post-COVID-19 pulmonary fibrosis. Is it real threat? Indian J Tuberc. 2021;68(3):330-333.
15. Hama Amin BJ, Kakamad FH, Ahmed GS, et al. Post COVID-19 pulmonary fibrosis; a meta-analysis study. Ann Med Surg (Lond). 2022;77:103590.
16. Eapen MS, Lu W, Gaikwad AV, et al. Endothelial to mesenchymal transition: a precursor to post-COVID-19 interstitial pulmonary fibrosis and vascular obliteration? Eur Respir J. 2020;56(4):2003167.
17. Vishnupriya M, Naveenkumar M, Manjima K, et al. Post-COVID pulmonary fibrosis: therapeutic efficacy using with mesenchymal stem cells – How the lung heals. Eur Rev Med Pharmacol Sci. 2021;25(6):2748-2751.
18. Vaz de Paula CB, Nagashima S, Liberalesso V, et al. COVID-19: immunohistochemical analysis of TGF-β signaling pathways in pulmonary fibrosis. Int J Mol Sci. 2021;23(1):168.
19. KazymyrkoVK, Silantieva TS, Ivanitska LN, et al. Calcification of arteries in patients with atherosclerosis: causes and mechanisms of development. Likars'ka Sprava. 2021;3-4:17-35.

20. Sastry S, Cuomo F, Muthusamy J. COVID-19 and thrombosis: the role of hemodynamics. Thromb Res. 2022;212:51-57.
21. Gencer S, Lacy M, Atzler D, et al. Immunoinflammatory, thrombohaemostatic, and cardiovascular mechanisms in COVID-19. Thromb Haemost. 2020;120(12):1629-1641.
22. Zubairi ABS, Shaikh A, Zubair SM, et al. Persistence of post-COVID lung parenchymal abnormalities during the three-month follow-up. Adv Respir Med. 2021;89(5):477-483.
23. Myroshnychenko MS, Kalashnyk-Vakulenko YM, Kapustnyk NV, et al. Rhinosinusitis in patients in post-COVID-19 period: etiology, clinical and morphological characteristics. Wiad Lek. 2022;75(8 pt 2):1945-1953.
24. Giroux V, Rustgi AK. Metaplasia: tissue injury adaptation and a precursor to the dysplasia-cancer sequence. Nat Rev Cancer. 2017;17(10):594-604.
25. Thébaud B, Goss KN, Laughon M, et al. Bronchopulmonary dysplasia. Nat Rev Dis Primers. 2019;5(1):78.
26. Tao SL, Wang XM, Feng YG, et al. Is the presence of lung injury in COVID-19 an independent risk factor for secondary lung cancer? Med Hypotheses. 2020;143:110074.
27. Sapalidis K, Sardeli C, Pavlidis E, et al. Scar tissue to lung cancer; pathways and treatment. J Cancer. 2019;10(4):810-818.
28. Sadigov A, Akhundov S, Agayeva A. Risk factors for lung cancer in individuals with COVID-19 without cancer history. Respiratory Care. 2021;66 (Suppl. 10):3566906.

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*The Authors declare no conflict of interest*

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ORIGINAL ARTICLE

# THE FEATURES OF LIMITED PROTEOLYSIS IN PLACENTAL FIBRINOID IN COMBINATION WITH INFLAMMATION AND IRON DEFICIENCY ANEMIA OF PREGNANT WOMEN

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## ABSTRACT

**The aim:** To establish the features of limited proteolysis in fibrinoid of the chorionic and basal plates of the placenta in acute and chronic chorioamnionitis, as well as basal deciduitis on the background of iron deficiency anemia in pregnant women.

**Materials and methods:** The histochemical procedure was performed using the ninhydrin-Schiff response to free amino groups of proteins by the method of A. Yasuma and T. Ichikava, and Bonheg bromophenol blue.

**Results:** With iron deficiency anemia of pregnant women, the relative units of optical density in the chorionic plate were 0.312±0.0026, and with basal one – 0.310±0.0024 (with indicators of physiological pregnancy 0.285±0.0024 and 0.289±0.002.1). In the observations of acute chorioamnionitis, the quantitative indicators were 0.311±0.0024, chronic one – 0.311±0.0024, and with inflammation on the background of anemia of pregnant women – 0.315±0.0031 and 0.339±0.0036, respectively. With acute basal deciduitis – 0.316±0.0027, chronic one – 0.326±0.0034, and with inflammation of the basal plate of the placenta on the background of anemia of pregnant women – 0.320±0.0031 and 0.341±0.0038, respectively.

**Conclusions:** With anemia of pregnant women, the processes of limited proteolysis are intensified in accordance with the indicators of optical density of histochemical staining in the fibrinoid of the chorionic and basal plates of the placenta compared with physiological pregnancy. In case of acute and chronic forms of chorioamnionitis and basal deciduitis, quantitative indicators of optic density of histochemical staining increase compared with physiological pregnancy. Comorbid anemia of pregnant women activates the processes of limited proteolysis only in the chronic form of chorioamnionitis and basal deciduitis.

**KEY WORDS:** placental insufficiency, chorioamnionitis, basal deciduitis, protein amino groups, free radical processes

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## INTRODUCTION

Many scientific papers have been devoted to the problem of inflammation of the manure and iron deficiency anemia (IDA) of pregnant women due to the high frequency of these conditions. However, it is important to investigate their interaction, in order to expand and supplement the information base of the pathomorphology of placental insufficiency, which is a common morphological manifestation for these conditions.

After analyzing domestic and foreign literature, we noticed that the morphology of chorioamnionitis (ChA) and basal deciduitis (DB) on the background of iron deficiency anemia in pregnancy is not given much attention, the study of which is essential to establish morpho-functional features and optimize diagnosis and development of complications and diseases of newborn. You can try to predict pathological changes in the placenta in advance by finding data on pathophysiological and morphological changes in the interaction of these conditions in the human body in many other inflammatory processes in the absence of pregnancy, however, it is not necessary to unequivocally assert their regularity in the placenta in case of IDA during pregnancy, because the placenta, with its inherent features (absence of lymphatic vessels and nerve endings, immunological signs [1–3], circulatory properties in the fetal part of the placenta (venous blood flows in arteries, and arterial blood flows in veins) [1], can dramatically change the morphology of manure inflammation. Uncertainty on the above issues complicates the pathological diagnosis of the placenta and needs to be resolved.

It is known that many pathological processes, as a rule, increase the level of oxygen free radicals, which oxidize the amino groups of proteins, change the properties of these macromolecules [4]. Intensification of oxidative modification of proteins may be accompanied by enhanced processes of limited proteolysis [5], which is associated with fundamental life processes: intracellular protein breakdown and regulation of

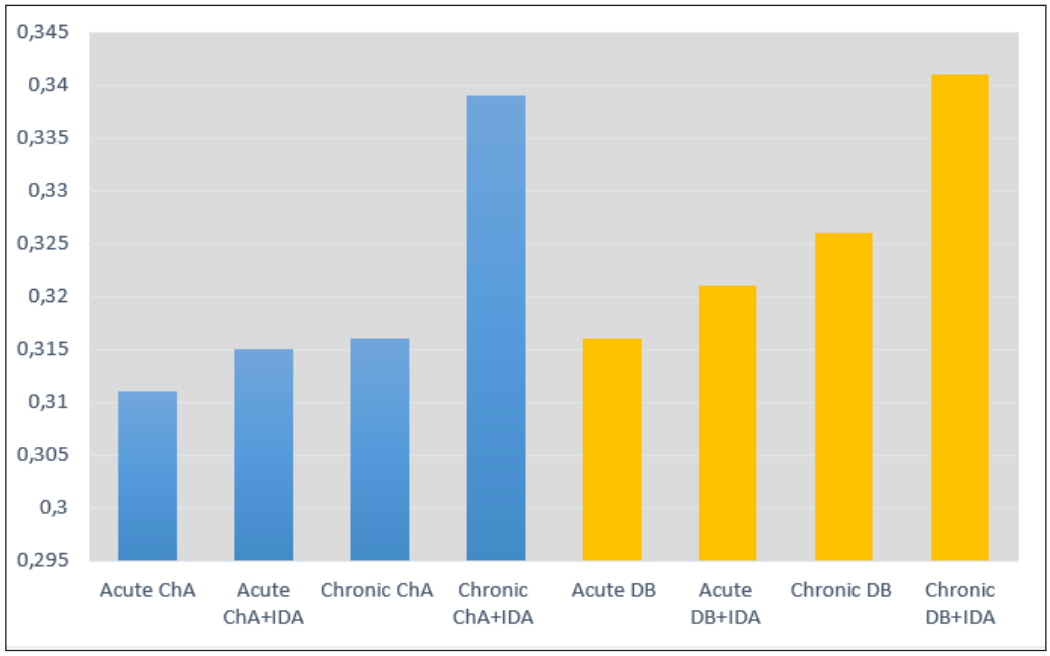


**Fig. 1.** Comparison of optical density of histochemical staining for free amino groups of proteins in the fibrinoid of the chorionic and basal plates of the placenta in inflammation on the background of IDA during pregnancy

their elimination, nutrition, morphogenesis, protective reactions, and adaptive rearrangements of metabolism [6]. In this aspect, our previous publications highlight our findings on the study of nitroperoxides [7] and determine the degree of oxidative modification of proteins in inflammation of manure in combination with iron deficiency anemia in pregnance [8]. However, the features of limited proteolysis in the combination of these conditions have not yet been elucidated and are promising in order to fully understand the histochemical properties of proteins in placental structures.

## THE AIM

To establish the features of limited proteolysis in fibrinoid of the chorionic and basal plates of the placenta with iron deficiency anemia of pregnant women, in acute and chronic chorioamnionitis, as well as basal deciduitis on the background of iron deficiency anemia in pregnant women by means of histochemical method in combination with computer microdensitometry.

## MATERIALS AND METHODS

198 placentas from parturients at 37 – 40 weeks of gestation were studied. Including, for comparison, the placenta during physiological pregnancy and the observation of iron deficiency anemia of pregnant women without inflammation of the manure. The number of observations in specific study groups is given in the tables (Table I and Table II). The study of fibrinoid in chorioamnionitis was studied in the chorionic, and in basal deciduitis - in the decidual plate of the placenta.

To achieve the goal and solve the tasks set in this study, the following were carried out: histochemical (histochemical technique using ninhydrinoschiffian reaction to free amino groups of proteins by the method of A. Yasuma and T. Ichikava, histochemical method for total protein with bromophenol blue according to Bonheg, morphometric (in ImageJ computer program environment) and statistical research methods (an odd Student's test and Shapiro-Wilk test).

Pieces of placenta were fixed for 24 to 48 hours in neutral Lilly-buffered 10% formalin solution, followed by ethanol dehydration and paraffin pouring according to standard procedures. On serial histological sections of 5 μm thick there were performed 2 methods: 1) histochemical technique using ninhydrinoschiffian reaction to free amino groups of proteins by the method of A. Yasuma and T. Ichikava, which allows to assess the degree of limited proteolysis, resulting in "opening" hidden amino groups of proteins; 2) histochemical method for total protein with bromophenol blue according to Bonheg.

Digital copies of the image were obtained using a Delta Optical Evolution 100 microscope (planachromatic lenses) and an Olympus SP-550UZ digital camera. The obtained images were analyzed in the computer program ImageJ (1.48, W. Rasband, National Institutes of Health, USA) [9].

Quantitative measure of total protein and limited proteolysis was the value of relative optical density (relative units of optical density) in units of optical density (from 0 - no color, absolute transparency, to 1 - maximum color, absolute opacity, based on logarithmic transformations) in gradations from "0" to "255").

**Table I.** Optical color density (relative to optical density) in the fibrinoid of the basal and chorionic plates in physiological pregnancy and iron deficiency anemia of pregnant women (M ± m)

| Structures | Study Group | |
|---|---|---|
| | Observation of physiological pregnancy (n=20) | Observation of iron deficiency anemia of pregnant women without inflammation of the manure (n=21) |
| Fibrinoid of chorionic plate | 0.285±0.0024 | 0.312±0.0026<br>p<0.001 |
| Fibrinoid of basal plate | 0.289±0.0021 | 0.310±0.0024<br>p<0.001 |

Note: p – the probability of the difference between the two means between physiological pregnancy and the study group

**Table II.** Optical color density (relative to optical density) in fibrinoid of the chorionic and basal plates of the placenta with a combination of different forms of inflammation of manure and iron deficiency anemia of pregnant women (M ± m)

| Study Group | Observation of inflammation of the manure | Observation of inflammation of the manure |
|---|---|---|
| Chorioamnionitis acute (fibrinoid of the chorionic plate is studied) | 0.311±0.0024<br>$p_1$<0.001<br>(n=23) | 0.315±0.0031<br>$p_2$>0.05<br>(n=21) |
| Chorioamnionitis chronic (fibrinoid of the chorionic plate is studied) | 0.316±0.0024<br>$p_1$<0.001<br>(n=20) | 0.339±0.0036<br>$p_2$<0.001<br>(n=21) |
| Basal deciduitis acute (fibrinoid of the basal plate is studied) | 0.316±0.0027<br>$p_1$<0.001<br>(n=16) | 0.320±0.0031<br>$p_2$>0.05<br>(n=15) |
| Basal deciduitis chronic (fibrinoid of the basal plate is studied) | 0.326±0.0034<br>$p_1$<0.001<br>(n=21) | 0.341±0.0038<br>$p_2$<0.001<br>(n=20) |

Note: $p_1$ - the probability of the difference between the two means between physiological pregnancy and the study group; $p_2$ - the probability of the difference between the two means between inflammation of the studied placental plate and inflammation in combination with IDA of pregnant women

Arithmetic mean and its error were calculated, discrepancies in mean tendencies were checked using an odd Student's test after a positive test of the sample for normality of distribution in it according to Shapiro-Wilk test (computer program PAST 3.14, free license, O. Hammer, 2016) [10]. The critical value of the level of significance (p) was accepted at p≤0.05, which could indicate the influence of iron-deficiency anemia of pregnant women on the morphology of placental inflammation. If a value of p>0.05 was obtained, the difference between the values was considered unreliable.

All studies were performed in compliance with the Council of Europe Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (March 18, 1986) "Ethical Principles for Medical Research Involving Human Subjects", approved by the Declaration of Helsinki (1964 - 2013), ICH GCP (1996), EEC Directives #609 (dated 24.11.1986), Orders of the Ministry of Health of Ukraine #690 dated 23.09.2009, #944 dated 14.12.2009, #616 dated 03.08.2012. The Commission on Bioethics of the Bukovinian State Medical University of Ukraine found no violations (Minutes #4 of December 19, 2019).

All the procedures and experiments of this study respect the ethical standards of the Helsinki Declaration of 1975, as revised in 2008 (5), as well as the national law. Informed consent was obtained from all the patients included in the study.

## RESULTS

Specific histochemical staining in fibrinoid, endothelial cells and placental decidual cells was identified on the obtained histological preparations using the ninhydrinoschiffian reaction to free amino groups of proteins by the method of A. Yasuma and T. Ichikava. Previously, we have conducted research using this technique in endothelial cells of the chorionic and basal plates of the placenta [11]. This part of the paper is devoted to the quantitative assessment of the degree of limited proteolysis by determining the optical density of histochemical staining in fibrinoid in chorioamnionitis and basal deciduitis on the background of IDA in pregnancy.

Thus, according to the quantitative indicators of the stoichiometric study using the ninhydrin-Schiff reaction

**Table III.** Optical density of staining for total protein according to Bonheg in fibrinoid (relative units of optical density) of basal and chorionic plates of the placenta during physiological pregnancy and iron deficiency anemia of pregnant women (M±m)

| Structures | Study Group | |
|---|---|---|
| | Observation of physiological pregnancy (n=20) | Observation of iron deficiency anemia of pregnant women without inflammation of the manure (n=21) |
| Fibrinoid of chorionic plate | 0.412±0.0114 | 0.421±0.0102<br>p>0.05 |
| Fibrinoid of basal plate | 0.408±0.0104 | 0.416±0.0110<br>p>0.05 |

Note: p – the probability of the difference between the two means between physiological pregnancy and the study group

**Table IV.** Optical color density for total protein according to Bonheg (relative units of optical density) in placental fibrinoid with a combination of different forms of inflammation of manure and iron deficiency anemia of pregnant women (M±m)

| Study Group | Observation of inflammation of the manure | Observation of inflammation of the manure |
|---|---|---|
| Chorioamnionitis acute (fibrinoid of the chorionic plate is studied) | 0.410±0,0110<br>$p_1$>0.05<br>(n=23) | 0.412±0.0112<br>$p_2$>0.05<br>(n=21) |
| Chorioamnionitis chronic (fibrinoid of the chorionic plate is studied) | 0.414±0.0109<br>$p_1$>0.05<br>(n=20) | 0.417±0.0114<br>$p_2$>0.05<br>(n=21) |
| Basal deciduitis acute (fibrinoid of the basal plate is studied) | 0.407±0.0106<br>$p_1$>0,05<br>(n=16) | 0.405±0.0104<br>$p_2$>0.05<br>(n=15) |
| Basal deciduitis chronic (fibrinoid of the basal plate is studied) | 0.404±0.0104<br>$p_1$>0.05<br>(n=21) | 0.401±0.0102<br>$p_2$>0.05<br>(n=20) |

Note: $p_1$ – the probability of the difference between the two means between physiological pregnancy and the study group; $p_2$ – the probability of the difference between the two means between the study group and inflammation without anemia

to free amino groups of proteins by the method of A. Yasuma and T. Ichikava, which are given in the table (Table I and Table II), we can see that in case of IDA in pregnancy relative units of optical density increase on average with the same intensity in both the chorionic and basal plates of the placenta (0.312±0.0026, p<0.001 and 0.310±0.0024, p<0.001, respectively).

When studying the processes of limited proteolysis in the observations of acute and chronic chorioamnionitis (0.311±0.0024 and 0.316±0.0024), the obtained indicators showed an intensive increase in quantitative parameters relative to physiological pregnancy (0.285±0.0024), where p<0.001. Only in chronic inflammation on the background of IDA in pregnancy the processes of limited proteolysis in the fibrinoid of the chorionic plate of the placenta (0.339±0.0036, p<0.001) were intensified.

Regarding the fibrinoid of the placental basal plate, these tables convincingly show that in both acute (0.316±0.0027) and chronic (0.326±0.0034) basal deciduitis the processes of limited proteolysis were higher compared to observations of physiological pregnancy (p<0.001), with the highest indicators of chronic inflammation. Iron deficiency anemia of pregnant women affects the intensification of processes only in chronic inflammation of the basal plate of the placenta (0.341±0.0038, p<0.001).

Visualization of the comparative characteristics between acute and chronic inflammation of both the chorionic and basal plates of the placenta can be performed using the figure (Fig. 1). When comparing, we can see a clear pattern of growth of the processes of limited proteolysis both in acute and chronic chorioamnionitis and basal deciduitis concerning the placentas of physiological pregnancy in the corresponding plates of the placenta. However, the obtained quantitative indicators of the relative units of optical density of histochemical staining in the observations of basal deciduitis are higher than in the observations of chorioamnionitis. Iron-deficiency anemia of pregnant women has the greatest effect on the intensification of the processes of limited proteolysis in chronic inflammation, with the highest indicators in chronic basal deciduitis.

Iron-deficiency anemia of pregnant women has the greatest effect on the intensification of the processes of limited proteolysis in chronic inflammation, with the highest indicators in chronic basal deciduitis.

## DISCUSSION

Our data on the increase on average with the same intensity of relative units of optical density of histochemical staining for free amino groups of proteins in both the chorionic and basal plates of the plate in anemia of pregnant women do not contradict the results of other researchers, which demonstrate that the processes of limited proteolysis intensify under the conditions of IDA of pregnant women. In particular, the authors found an increase in the processes of limited proteolysis in the trophoblast cytoplasm of the chorionic villi of the placenta in combination with premature maturation of the chorionic tree and iron deficiency anemia [12]. According to a team of other authors, according to a histochemical study of iron-deficiency anemia of pregnant women in fibrinoid with type II and type IV calcium deposits (fine-grained deposits), both in the zone of the chorionic tree and in the basal plate of the placenta, a sharp increase in the processes of limited proteolysis was established in comparison with the observations without anemia [13].

The expected results were obtained in acute and chronic chorioamnionitis, as well as basal deciduitis, which indicate the intensification of limited proteolysis. Thus, the most limited proteolysis, according to the optical density of a specific color, increases with inflammation of the basal plate of the placenta compared with the indicators of physiological pregnancy and IDA of pregnant women without inflammation. These quantitative indicators are the highest in the chronic form. Slightly less, but with a high statistical probability, limited proteolysis is enhanced by inflammation of the chorionic plate. It should be noted that inflammation of the manure in combination with IDA was characterized by higher average figures than without anemia, only in chronic inflammation of both the chorionic and basal plates of the placenta, where $p<0.001$.

To substantiate the obtained results, it is necessary to focus on the essence of histochemical method for free amino groups of proteins by the method of A. Yasuma and T. Ichikava. The peculiarity of this technique is that it detects only free groups of proteins. Therefore, this technique shows the number of unhidden (free) amino groups of proteins rather than the total amount of protein. If there is a loss of proteins of a higher degree of structural organization (denaturation of proteins), the hidden amino groups of proteins become free - available for oxidation by ninhydrin [14]. Therefore, in order to be able to interpret the obtained data on limited proteolysis, there was conducted a quantitative determination of total protein (using the method with bromophenol blue according to Bonheg) in fibrinoid of the chorionic and basal plate of the placenta in acute and chronic chorioamnionitis and basal deciduitis in case of IDA and without it. The results of the study are shown in table (Table III and Table IV).

When comparing these figures, it is obvious that in case of iron deficiency anemia of pregnant women without inflammation, as in all forms of inflammation of the manure, the results are on average statistically close to the placental physiological pregnancy. The same tendency is observed at a combination of an inflammation with IDA of pregnant women.

Therefore, if the total amount of protein does not change, which indicates the fact of sufficient regeneration of proteins in cells, and the color in the ninhydrin-Schiff reaction increases, it means that the protein loses its ability to perform its functions and denaturation of proteins appears. Thus, histochemical determination of limited proteolysis is one of the subtle methods of establishing one of the forms of alteration of structures.

In addition, the results obtained are important for a full understanding of free radical processes, which, according to various authors, are activated in both inflammation of the manure and iron deficiency anemia of pregnant women. Thus, the identified features of limited proteolysis complement the previously obtained and substantiated data on chemiluminescent study of nitroperoxides in placental structures [7] and processes of oxidative modification of proteins in the inflammatory focus [8] in combination with inflammation of manure and iron deficiency anemia of pregnant women, which reflects a logical connection between the processes: increase in nitroperoxides, followed by intensification of oxidative modification of protein activity, with increasing activity of limited proteolysis processes. This gives reason to believe that the key factor in the formation of morphological features of placental inflammation is the intensification of free radical processes, and iron deficiency additionally significantly modifies these processes, which in turn enhances proteolysis.

## CONCLUSIONS

1. Iron deficiency anemia of pregnant women intensifies the processes of limited proteolysis according to the optical density of histochemical staining for free amino groups of proteins in the fibrinoid of the chorionic ($p<0.001$) and basal plate ($p<0.001$) of the placenta in comparison with physiological pregnancy.

2. In acute and chronic forms of chorioamnionitis ($p<0.001$ / $p<0.001$) and basal deciduitis ($p<0.001$ / $p<0.001$), the processes of limited proteolysis are intensified according to quantitative indicators of the optical density of histochemical staining in comparison with physiological pregnancy.
3. Comorbid iron deficiency anemia of pregnant women activates the processes of limited proteolysis only in the chronic form of chorioamnionitis ($p<0.001$) and basal deciduitis ($p<0.001$) in comparison with inflammation without anemia.

## REFERENCES


1. Baergen RN, Burton GJ, Kaplan CG. Benirschke`s pathology of the human placenta. 7th ed. Berlin: Springer-Verlag. 2022, p.939.
2. Bonney EA. Immune regulation in pregnancy: a matter of perspective? Obstet Gynecol Clin North Am. 2016;43(4):679–98. doi: 10.1016/j.ogc.2016.07.004.
3. Faas MM, de Vosa P. Uterine NK cells and macrophages in pregnancy. Placenta. 2017;56:44–52. doi: 10.1016/j.placenta.2017.03.001.
4. Gubsky Yui. Cell death: free radicals, necrosis, apoptosis: monograph. Vinnitsa: New Book. 2015, p.360.
5. Davydenko IS, Hrytsiuk MI, Davydenko OM. Metodyka kil'kisnoyi otsinky rezul'tativ histokhimichnoyi reaktsiyi z bromfenolovym synim dlya vstanovlennya spivvidnoshennya mizh amino- ta karboksyl'nymy hrupamy v bilkakh [Methods for quantifying the results of histochemical reactions with bromophenol blue to establish the relationship between amino and carboxyl groups in proteins]. Bulletin of Marine Medicine. 2017;4(77):141-8. (in Ukrainian).
6. Schopper S, Kahraman A, Leuenberger P et al. Measuring protein structural changes on a proteome-wide scale using limited proteolysis-coupled mass spectrometry. 2017;12(11):2391-2410.
7. Ilika VV, Davydenko IS. Chemilyuminestsentne doslidzhennya nitroperoksydiv u strukturakh platsenty pry khorionamnioniti ta bazal'nomu detsyduyiti z zalizodefitsytnoyu anemiyeyu vahitnykh [Chemiluminescent studying of nitro-peroxides in placental structures in chorionamnionitis and basal deciduitis in pregnant women with iron deficiency anemia]. Ukrainian Journal of Medicine, Biology and Sports. 2018;3(5):36–40. (in Ukrainian).
8. Ilika VV, Davydenko IS, Davydenko OM. Histochemical evaluation of processes of oxidative modification of proteins in fibrinoid of the placental basal plate. Clinical anatomy and operative surgery. 2016;15(4):48–51.
9. Rasband W, Ferreire T. ImageJ user guide 1.48 v. National Institute of Health, USA. 2015, p.140,
10. Hammer Ø. PAST: Paleontological Statistics, Version 4 .11. Reference manual. Oslo: Natural History Museum University of Oslo. 2022, p.302.
11. Ilika VV. Kil'kisni kharakterystyky obmezhenoho proteolizu v endoteliotsytakh krovonosnykh sudyn platsenty pry poyednanni zapalennya poslidu ta zalizodefitsytnoyi anemiyi vahitnykh [Quantitative characteristics of limited proteolysis in endothelial cells of placental blood vessels in a combination of inflammation of manure and iron deficiency anemia in pregnant women]. Ukrainian Journal of Medicine, Biology and Sports. 2018;3(1):36–9. (in Ukrainian).
12. Garvasyuk OV, Davydenko IS. Histokhimichna otsinka protsesiv okysnyuval'noyi modyfikatsiyi bilkiv u fibrynoyidi bazal'noyi plastynky platsenty. [Histochemical features of limited proteolysis and oxidative modification of proteins in the trophoblast of the placenta in combination with premature maturation of the chorionic tree and iron deficiency anemia of pregnant women]. Clinical and experimental pathology. 2017;16(4):24-9. (in Ukrainian).
13. Popovych AI, Davydenko IS, Davydenko OM. Histokhimichna otsinka protsesiv obmezhenoho proteolizu v fibrynoyidi platsenty pry yiyi kal'tsynozi u poyednanni iz zalizodefitsytnoyu anemiyeyu vahitnykh [Histochemical evaluation of limited proteolysis processes in placental fibrinoid in its calcification in combination with iron deficiency anemia of pregnant women]. Ukrainian Journal of Medicine, Biology and Sports. 2017;6(8):34–7. doi: 10.26693/jmbs02.06.034 (in Ukrainian).
14. Bahrii MM, Dibrova VA et al. Methods of morphological research: monograph. Vinnytsia: Nova Khyha. 2016, p.328.



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ORIGINAL ARTICLE

# PECULIARITIES OF THE COURSE OF PULMONARY EMBOLISM DURING THE COVID-19 PANDEMIC

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## ABSTRACT

**The aim:** A comparative analysis of the course of pulmonary embolism during the COVID-19 pandemic and the era before pandemia

**Materials and methods:** 294 patients with pulmonary embolism (PE) , 1 group – 188 with PE before the pandemic, 2 group -106 during the pandemic. Two subgroups were distinguished in 2 group : 1- with laboratory-excluded coronavirus (acute and in anamnesis) and 2 – with a history of COVID-19. The diagnosis of PE was confirmed by CT. Echocardiography and ultrasound Doppler imaging of the veins of the lower extremities were performed.

**Results:** In 1 group there was a more significant increase in pulmonary artery pressure (44.29 ± 17.04 vs 36.91 ± 16.6, p 0.0023) and a decrease in the E/A ratio of the right ventricle (0.80 ± 0,21 vs 1.28 ± 1.42, p 0.0202). In 2 subgroup of patients with COVID-19 had a significantly higher incidence of Diabetes mellitus (73.7% vs 13.3%, p 0.00001) and significantly lower signs of superficial venous thrombosis of the lower extremities (5.3% vs 33,3%, p 0,0175) and signs of proximal deep vein thrombosis (0% vs 56.7%, p 0.00001) and 3 times less often there was a high risk of adverse disease, right ventricular dysfunction were more pronounced (ratio E/A 0.87 ± 0.25 vs 1.13 ± 0.28, p 0.022).

**Conclusions:** In patients with coronavirus infection, PE was significantly more common in the presence of diabetes mellitus , right ventricular diastole disorders were more common, and superficial and proximal deep vein thrombosis of the lower extremities were less common.

**KEY WORDS:** risk factors, pulmonary embolism, COVID-19

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## INTRODUCTION

Despite advances in the diagnosis and treatment of patients with pulmonary embolism (PE), with the development of scales to determine the risk of venous thromboembolism, stratification of patients with the selection of the group of the negative course of the acute period, widespread introduction of new oral anticoagulants (NOACs), pulmonary embolism remains one of the main causes of cardiovascular death after stroke and myocardial infarction [1, 2]. This is largely due to the increase in the proportion of patients with high risk factors for venous thromboembolism (VTE): prolongation of life expectancy, prevalence of malignant neoplasms, wider joint prosthetics and arthroscopic interventions [3-7]. In addition, the emergence of a coronavirus pandemic, which is able to activate the coagulation system and inhibit fibrinolytic activity by increasing the level of plasminogen activator inhibitor, also affects the risk of developing and the course of VTE [8-11].

Today there are many publications devoted to the study of the frequency, features and treatment of VTE and PE in the period of coronavirus infection [12-18]. Despite reasonable expectations, according to several publications, there is no increase in the incidence of PE, moreover, according to the results of some registers in the pandemic period there is a decrease in the incidence of PE [19, 20]. Perhaps this "paradox" is related to the reduced frequency of patients seeking help due to fear of coronavirus infection. At the same time, the clinical course of PE during the pandemic period was more severe with high hospital mortality, especially of those patients with a combination of active period of infection with thromboembolic complications [21-24].

Given that these publications were foreign, we considered it appropriate to assess the situation with PE during the pandemic on the basis of the register of patients of the MNE "CCH No8" of KCC.

## THE AIM

The aim of the study was to conduct a comparative analysis of the course of PE of those patients treated in

**Table I.** Clinical and anamnestic characteristics of groups of patients with pulmonary embolism before the COVID-19 pandemic and during the pandemic period.

| Indicator | Total n=294 | 1 group (n=188) | 2 group (n= 106) | P level |
|---|---|---|---|---|
| Average age, years (M ± σ) | 63.77±13.86 | 64.51±13.28 | 62.46±14.81 | 0.25 |
| Men, n (%) | 169 (57,5%) | 104 (55,3%) | 65(61,3%) | 0,32 |
| Females, n (%) | 125 (42,5%) | 84 (44,7%) | 41 (38,7%) | |
| **Risk factors for VTE, n (%)** | | | | |
| Fracture of the femoral neck or lower limb in the previous 3 months, n (%) | 11 (3,7%) | 7 (3,7%) | 4 (3,8%) | 0,61 |
| Prosthetics of the hip / knee joint, n (%) | 4(1,4%) | 2(1,1%) | 2(1,9%) | 0,46 |
| Major injury in the previous 3 months, n (%) | 12(4,1%) | 8(4,3%) | 4(3,8%) | 0,55 |
| Previous venous thrombosis or embolic complications, n (%) | 49(16,7%) | 31(16,5%) | 18(17,0%) | 0,91 |
| Previous myocardial infarction, n (%) | 4(1,4%) | 2(1,1%) | 2(1,9%) | 0,46 |
| Spinal cord injury, n (%) | 2(0,7%) | 2(1,1%) | 0 | 0,0001 |
| Arthroscopic knee surgery, n (%) | 1(0,3%) | 1(0,5%) | 0 | 0,64 |
| Chemotherapy, n (%) | 7(2,4%) | 5(2,7%) | 2(1,9%) | 0,51 |
| Chronic respiratory failure, n (%) | 16(5,4%) | 14(7,4%) | 2(1,9%)* | 0,03 |
| Congestive heart failure, n(%) | 23(7,8%) | 12(6,4%) | 11(10,4%) | 0,22 |
| Malignant tumor, n (%) | 49(16,7%) | 29(15,4%) | 20(18,9%) | 0,45 |
| Superficial vein thrombosis, n (%) | 86(29,3%) | 66(35,1%) | 20(18,9%)** | 0,0033 |
| Thrombophilia, n (%) | 7(2,4%) | 2(1,1%) | 5(4,7%) | 0,22 |
| Obesity, n (%) | 42(14,3%) | 31(16,5%) | 11(0,4%) | 0,15 |
| Hypertension, n (%) | 181(61,6%) | 131(69,7%) | 50(47,2%) | 0,0001 |
| Diabetes mellitus, n (%) | 33(11,2%) | 26(13,8%) | 7(6,6%) | 0,09 |
| Varicose veins, n (%) | 27(9,2%) | 20(10,6%) | 7(6,6%) | 0,35 |
| **Distribution of patients by stratification of early risk of death from pulmonary embolism, n (%)** | | | | |
| High | 146(49,7%) | 97(51,6%) | 49(46,2%) | 0,377 |
| Intermediate high | 66(22,4%) | 43(22,9%) | 23(21,7%) | 0,817 |
| Intermediate low | 48(16,3%) | 30(16,0%) | 18(16,9%)) | 0,820 |
| Low | 34(11,6%) | 18(9,6%) | 16(15,1%) | 0,155 |
| **Estimation of the patient's prognosis on the PESI[1] scale (except for high-risk patients), n (%)** | | | | |
| | n =148 | n=91 | n=57 | P level |
| class I | 42(28,4%) | 27(29,7%) | 15(26,3%) | 0,660 |
| class II | 35((23,6%) | 22(24,2%) | 13(22,8%) | 0,849 |
| class III | 31(20,9%) | 18(19,8%) | 13(22,8%) | 0,660 |
| class IV | 24(16,2%) | 15(16,5%) | 9(15,8%) | 0,911 |
| class V | 16(10,8%) | 9((9,9%) | 7(12,3%) | 0,649 |
| Recurrence of pulmonary embolism, n (%) | 3(1,0%) | 2(1,1%) | 1(0,9%) | 0,70 |
| Died, n (%) | 34 (11,6%) | 25 (13,3%) | 9 (8,5%) | 0,29 |

Note. VTE – venous thromboembolism

[1] Original version [8]. Categorical indicators are given as the number of cases and the share, quantitative – in the form of M ± σ.

The difference is statistically significant compared with those in patients of the 1st group: * P <0,05; ** P <0.01; *** P <0.001.

the cardiology departments of the hospital during the year before the pandemic and during the year of the pandemic (provided there is no acute covid infection (COVID-19).

## MATERIALS AND METHODS

The total group included 294 patients with PE, among whom there were 169 men (57.5%) and 125 women (42.5%), whose average age was 63.77 years. The diagnosis

**Table II.** Comparative evaluation of groups based on the results of computed angiography of the pulmonary arteries.

| Signs, n (%) | Total group, n = 294 | 1 group, n=188 | 2 group, n= 106 | P level |
|---|---|---|---|---|
| Right ventricular lesions (RV) | 136 (46,3) | 92 (48,9) | 44 (41,5) | 0,22 |
| Lung trunk thrombus | 23 (7,8) | 15 (8,0) | 8 (7,5) | 0,89 |
| TE of both pulmonary arteries (PA) with their partial occlusion | 131 (44,6) | 86 (45,7) | 35 (33,0) | 0,03 |
| TE lobular branches of PA | 64 (21,8) | 43 (22,9) | 21 (19,8) | 0,54 |
| TE of one lobular branch of PA and segmental branches | 38 (12,9) | 30 (16,0) | 18 (17,0) | 0,82 |

**Table III.** Indicators of echocardiography and computed angiography of the examined groups of patients with pulmonary embolism.

| Indicator | General group (n=294) | 1 group (n=188) | 2 group (n= 106) | P level |
|---|---|---|---|---|
| LAD, cm | 4,07±0,62 | 4,08± 0,54 | 4,05±0,70 | 0,44 |
| RAD, cm | 4,24±0,70 | 4,31±0,72 | 4,18±0,71 | 0,18 |
| LVIDd, cm | 4,80±0,58 | 4,82±0,55 | 4,75±0,65 | 0,32 |
| LVIDs, cm | 3,31±0,59 | 3,29±0,53 | 3,34±0,66 | 0,43 |
| RVDd, cm | 2,97±0,76 | 3,07±0,76 | 2,99±0,79 | 0,19 |
| IVS, cm | 1,03±0,17 | 1,07±0,18 | 1,00±0,14 | 0,0009 |
| LVPW, cm | 1,02±0,13 | 1,04±0,13 | 0,99±0,12 | 0,0094 |
| LVEF,% | 58,23±8,23 | 58,84±6,59 | 57,33±10,12 | 0,91 |
| MPAP, mmHg | 40,06±17,25 | 44,29±17,04 | 36,91±16,6 | 0,0023 |
| E/A RV | 1,20±1,17 | 0,80±0,21 | 1,28±1,42 | 0,0202 |
| Diameter PT, cm | 34,28±14,71 | 34,76±15,91 | 33,42±12,16 | 0,84 |
| Diameter RPA, cm | 26,06±6,66 | 25,50±4,22 | 27,20±9,74 | 0,64 |
| Diameter LPA, cm | 24,86±3,75 | 24,61±3,90 | 25,39±3,43 | 0,34 |

Note of Tables III, V. Categorical indicators are given as the number of cases and the share, quantitative – in the form of M ± σ.
LAD – Left atrial diameter , RAD – Right atrium diameter, LVIDd – Left ventricular internal dimension diastole, LVIDs – Left ventricular internal dimension systole, RVDd – Right ventricular dimension at end – diastole, IVS – Interventricular septum , LVPW – Left ventricle posterior wall, LVEF – Left ventricular ejection fraction , MPAP = Mean pulmonary artery pressure, PT – pulmonary trunk, RPA – right pulmonary artery, LPA – left pulmonary artery, E – Peak velocity of early diastolic transtricuspid flow, A- Peak velocity of late transmitral flow, E/A – Ratio of E to A

of PE was confirmed by computed tomography. All these patients had been treated at the MNE "CCH #8" of KCC from March 2019 to March 2021. At hospitalization, all patients underwent risk stratification to determine therapeutic tactics. In total, 146 patients had a high risk in the group (49.7%), intermediate high – 66 (22.4%), intermediate low – 48 (16.3%) and low – 34 patients (11.6%). Low-risk patients had been hospitalized for a variety of reasons, such as comorbiditiesor inability to control INR when warfarin dose adjustment.

The results of the analysis of risk factors for venous thrombosis show that 11 patients had traumatic and orthopedic problems (fracture of the lower extremity, mainly the thigh), 4 – prosthetics of the knee / hip joint, 1 – arthroscopic intervention on the knee joint. In the anamnesis of the disease, 49 patients had already had previous venous embolic complications. Signs of chronic heart failure (HF) occurred in 23 patients (7.8%), malignant neoplasms in 49 (16.7%). At active detailed search of the source of PE in 86 (29.3%) persons with a history of thrombosis of superficial veins of the lower extremities, and in 7 (2.4%) – signs of thrombophilia (Table I).

According to computed angiography performed on Somatom Definition AS 64 (Siemens, Germany) using intravenous contrast Tomohexol-350, 50 ml according to a standard protocol [25]. The presence of PE according to MCT angiography of PA was defined as the detection of contrast enhancement defects that partially and/or completely blocked the lumen of at least one of the branches of the pulmonary artery. A quantitative assessment was made of the size of the pulmonary trunk and pulmonary arteries and the nature of the spread of damage to the branches of the pulmonary arteries. Thus, in 23 (7.8%) patients a massive thrombus of the pulmonary trunk was detected, in 131 (44.6%) TE of both pulmonary arteries (LA) with their partial occlusion, in 64 (21.8%) – lobular branches of the LA and in 38 (12.9%) – TE of one lobular branch of LA and segmental branches.

**Table IV.** Frequency of detection of limb venous thrombosis in patients with pulmonary embolism.

| Indicator n, (%) | General group, n=294 | 1 group, n=188 | 2 group n= 106 | P level |
|---|---|---|---|---|
| Thrombosis of the upper extremities | 1 (0.3) | 1 (0.5) | 0 | 0.64 |
| Thrombosis of the proximal deep veins | 85 (28.9) | 58 (30.9) | 27 (25.5) | 0.22 |
| Thrombosis of the distal deep veins | 10 (3.4) | 4 (2.1) | 6 (5.7) | 0.1040 |

**Table V.** Clinical and anamnestic characteristics of groups of patients with pulmonary embolism with excluded COVID-19 and those having the disease in the past.

| Indicator | 1 subgroup, n=30 | 2 subgroup, n= 19 | P level |
|---|---|---|---|
| Age, years M ± σ | 62,38±14,54 | 62,79±15,09 | 0,83 |
| Male , n (%) | 19 (63,3) | 11 (57,9) | 0,70 |
| Female , n (%) | 11 (36,7) | 8 (42,1) | |
| **Risk factors for VTE, n (%)** | | | |
| Fracture of the femoral neck or limb, n (%) | 0 | 1 (5,3) | 0,39 |
| Prosthetics of the femoral / knee joint, n (%) | 2 (6,7) | 0 | 0,37 |
| Major injury in the previous 3 months, n (%), n (%) | 1 (3,3) | 0 | 0,61 |
| Previous venous embolic complications, n (%) | 7 (23,3) | 4 (21,1) | 0,57 |
| Previous myocardial infarction, n (%) | 7 (23,3) | 1 (5,3) | 0,10 |
| Spinal cord injury, n (%) | 0 | 0 | |
| Arthroscopic knee surgery, n (%) | 0 | 0 | |
| Chemotherapy, n (%) | 0 | 0 | |
| Chronic respiratory failure, n /% | 1 (1,3) | 0 | 0,61 |
| Congestive heart failure, n (%) | 5(16,7) | 0 | 0,07 |
| Malignant tumor, n (%) | 6(20,0) | 3 (15,8) | 0,51 |
| Superficial vein thrombosis, n (%) | 10 (33,3) | 1 (5,3) | 0,0175 |
| Thrombophilia, n (%) | 1 (1,3) | 1(5,3) | 0,63 |
| Obesity, n (%) | 4 (13,3) | 2(10,5) | 0,57 |
| Hypertension, n (%) | 18(60,0) | 9(47,4) | 0,57 |
| Diabetes mellitus, n (%) | 4(13,3) | 14(73,7) | 0,00001 |
| Varicose veins, n (%) | 5(16,7_ | 5(26,3) | 0,32 |
| **Distribution of patients by stratification of early risk of death from pulmonary embolism, n (%)** | | | |
| High | 19 (63,3) | 6 (31,6) | 0,03 |
| Intermediate high | 3 (10,0) | 5 (26,3) | 0,134 |
| Intermediate low | 5 (16,7) | 4 (21,1) | 0,489 |
| Low | 3 (10,0) | 4 (21,1) | 0,252 |
| **Estimation of the patient's prognosis on the PESI1 scale (except for high-risk patients), n (%)** | | | |
| | n =11 | n= 13 | |
| class I | 3 (27,3) | 3 (23,1) | 0,590 |
| class II | 3 (27,3) | 2 (15,4) | 0,415 |
| class III | 2(18,2) | 2 (15,4) | 0,637 |
| class IV | 1 (9,1) | 3 (23,1) | 0,363 |
| class V | 2(18,2) | 3 (23,1) | 0,834 |
| **The nature of the prevalence of lesions according to MCT angiography of the LA, n (%)** | | | |
| Lesion of the right ventricle, n (%) | 15 (50,0) | 6 (31,6) | 0,17 |
| Pulmonary trunk thrombosis, n (%) | 4 (13,3) | 2(10,5) | 0,57 |
| TE of both PA with their partial occlusion, n (%) | 11(36,7) | 6(31,6) | 0,48 |

**Table V.** (cont.)

| | | | |
|---|---|---|---|
| TE lobular branches of PA, n (%) | 6 (20,0) | 3(15,8) | 0,51 |
| TE of one lobular branch of PA and segmental branches, n (%) | 9 (30,0) | 3 (15,8) | 0,22 |
| **The frequency of thrombosis of the veins of the extremities n, /% detected during hospital treatment** | | | |
| Thrombosis of the upper extremities n (%) | 0 | 0 | |
| Proximal deep vein thrombosis, n (%) | 17(56,7) | 0 | 0,00001 |
| Distal deep vein thrombosis, n (%) | 3 (10,0) | 1(5,3) | 0,4934 |
| Died, n (%) | 13(14,1) | 2/ (0,5) | 0,0148 |
| **Echocardiographic parameters in subgroups of the examined patients** | | | |
| LA, cm | 4,18± 0,68 | 4,16±0,78 | 0,77 |
| RA, cm | 4,39±0,69 | 4,38±0,83 | 0,89 |
| LVIDd, cm | 4,79±0,71 | 4,83±0,59 | 0,75 |
| LVIDs, cm | 3,43±0,76 | 3,33±0,55 | 0,86 |
| RV, cm | 2,98±0,85 | 3,00±0,65 | 0,64 |
| IVS, cm | 1,03±0,18 | 1,02±0,12 | 1,00 |
| LVPW, cm | 1,01±0,12 | 1,04±0,14 | 0,67 |
| EF,% | 57,43±10,77 | 59,53±8,03 | 0,54 |
| MPAP, mmHg | 40,27±18,63 | 34,93±16,55 | 0,35 |
| E/A RV | 1,13±0,28 | 0,87±0,25 | 0,022 |
| Diameter PT, cm | 31,41±3,99 | 31,25±4,25 | 0,75 |
| Diameter RPA, cm | 25,79±3,37 | 26,75±5,50 | 0,92 |
| Diameter LPA, cm | 25,21±3,13 | 26,75±3,70 | 0,25 |

Echocardiographic examination was performed during hospitalization of patients on the device "Acuson X2000" (Siemens, Germany) using a sensor with an ultrasound frequency of 3.0 MHz, according to the standard protocol. Measured the following parameters: Left atrial diameter (LAD), Right atrial diameter (RAD), Left ventricular internal dimension at end –diastole (LVIDd), Left ventricular internal dimension at end –systole (LVIDs), Right ventricular dimension at end – diastole (RVDd), LV ejection fraction (LVEF) according to Simpson. Signs of RV overload were assessed, which were defined as RV diameter greater than 30 mm in the parasternal position or a ratio of RV to LV size greater than 1; and/or presence of systolic flattening of the interventricular septum (IVS); and / or the time of acceleration of blood flow (AT) in the PA trunk, less than 90 ms, or the pressure gradient across the tricuspid valve (TV), more than 30 mm Hg, in the absence of LV hypertrophy; and / or the presence of the sign "60/60" – the time of acceleration of blood flow in the PA trunk is less than 60 ms and the pressure gradient on the TV is less than 60, but more than 30 mm Hg; and / or the presence of McConnell's sign – normo- or hyperkinesia of the apical segment of the RV in the presence of hypo- or akinesia of the middle and basal segments of the RV, and also determined the mean pressure in the PA by the ratio of the time of acceleration (AT) of blood flow in the outflow tract of the RV to the time of expulsion of blood from the RV (ET) [26-29].

Ultrasound Doppler (USD) of the veins of the lower extremities was performed on the device "S20Pro" (SONOSCAPE, China) according to the standard protocol. The presence of thrombotic masses, their level and the nature of placement in the veins of the lower extremities were evaluated [30].

All patients were treated according to the recommendations of ESC 2019 [2]. High-risk and intermediate high-risk patients in the absence of absolute contraindications underwent thrombolysis – 126 high-risk patients. Anticoagulant therapy was prescribed to all patients during hospitalization: patients with thrombolysis began with parenteral anticoagulants. Patients who did not require thrombolytic therapy received parenteral anticoagulants with subsequent administration of dabigatran or apixaban or with warfarin dose adjustment. In the case of rivaroxaban, the drug was prescribed after thrombolysis and parenteral anticoagulants in high-risk patients or from the first day of hospitalization, if thrombolytic therapy was not performed.

In the analysis of the impact of the pandemic, patients were divided into two groups – 1 group (188 patients) before the pandemic, the second (106 patients) – during the pandemic (from March 2020 to March 2021). The divi-

sion of patients into groups was carried out in accordance with the information on the appearance of the first patient with COVID-19 in Ukraine. The uneven distribution of the number of patients reflects the true situation regarding the stay of patients with pulmonary embolism in the hospital during this period.

During the pandemic, our hospital received 82 fewer inpatients than in the same period a year earlier. However, it should be noted that the hospital did not accept patients with COVID-19 or with suspected COVID-19, so the actual number of such patients should be much higher.

Statistical processing of the obtained data was performed using Statistica and Microsoft Office Excel 2013. Categorical variables are given as the number of cases and the share, quantitative – in the form of mean ± standard deviation (M ± σ). In the normal distribution, quantitative characteristics were presented as mean ± standard deviation (M ± σ), and Student's t test was used to compare the mean of the two samples. Intergroup differences in qualitative traits were assessed using Pearson's X2 test. Uni- and multivariate log-regression analyzes were used to determine the predictors of the combined clinical endpoint of clinical and anamnestic indicators.

## RESULTS

According to the results of the comparative analysis shown in table I, the groups of patients did not differ significantly in age, sex, the main risk factors for VE. Regarding the revealed reliability of spinal cord injury, in the number of cases 2 in the first group and the absence in the second, to argue about the pattern is not logical.

There were no statistically significant differences between the groups in terms of the size of thrombosis (according to the results of computed angiography) and the results of risk stratification.

We analyzed the results of computed tomography in groups of patients (table II). No differences between the groups were found in the localization of thrombosis, its prevalence and the presence of signs of right ventricular lesions.

It is known that an important factor influencing both the hospital and long-term period after pulmonary embolism is the presence and severity of RV lesions and the presence of pulmonary arterial hypertension (PAH). Table III shows the results of a comparative analysis of echocardiography.

The results of the comparison show no significant difference between the sizes of left chambers of the heart, while it was found that the thickness of the left ventricular myocardium was significantly less in the second group, which may reflect the more frequent proportion of patients with hypertension in the first group.

Regarding the right ventricle (RV), there were significant differences between groups, with more pronounced changes in the first group. Patients in this group had a more significant increase in pulmonary artery pressure and a decrease in E/A RV, which may indicate impaired right ventricular relaxation.

Although polymerase chain reaction (PCR) test was performed to the patients in group 2 to rule out acute coronavirus infection, patients in this group included those who had previously suffered from COVID-19 infection and had relevant medical evidence to support this. In addition, some patients with a history of possible infection were tested for immunoglobulin M and G and tested negative. That is, group 2 was quite heterogeneous. There were patients with COVID-19, patients without COVID-19 confirmed by PCR and with immunoglobulin M and G levels, and patients who could theoretically have an infection but were not adequately screened. We performed a comparative analysis of the first two subgroups – with a history of COVID-19 and laboratory-excluded coronavirus. One subgroup included 30 patients with pulmonary embolism, in whom laboratory tests ruled out COVID -19, both acute and in the anamnesis, the second – included 19 patients who had a previous coronavirus infection. The results of the analysis are shown in table IV. As shown by the results of the subgroup of patients did not differ significantly in age, sex, traumatic and orthopedic risk factors for VTE, malignant neoplasms.

However, in patients with COVID-19 there were significantly less signs of history of superficial venous thrombosis of the lower extremities and signs of deep vein thrombosis (proximal and distal) during examination during hospital stay. In addition, patients with coronavirus infection were 3 times less likely to be a high risk of an unfavorable course of the disease in the hospital period, but right ventricular dysfunction (as assessed by E / A ratio) was more pronounced. The latter fact may be related not only to the development of pulmonary embolism, but also to changes in the heart in COVID- pneumonia [31].

Unfortunately, a total of 34 patients died among the examined patients (11.6%), despite the fact that mortality in the groups differed slightly (in 1 group – 13.3%, in the second – 8.5%), these differences were not significant (Table I).

A seemingly paradoxical fact about the reduction in the number of patients with pulmonary embolism during the pandemic suggested the possibility of an unfavorable course of the disease at the pre-hospital stage. We analyzed data from the Bureau of Forensic Science on cases of pulmonary embolism as a cause of death in periods comparable to clinical analysis. It is noteworthy that according to the results of the Kharkiv Regional Bureau of Forensic Medical Examination during the year before the pandemic with pulmonary embolism, the cause of death was 15 people, while in the pandemic – 32 people. Among those diagnosed with pulmonary embolism there were 30 women (before the pandemic – 9, during the pandemic – 21), men -17 (6

and 11, respectively). At the same time, men were younger – 55.4 ± 4.8 years, against 66.4 ± 4.2, both in total for 2 years and separately for periods. We have not been able to obtain detailed information on these patients who died suddenly from pulmonary embolism, mostly at home (41 people), so it is not possible to conduct an in-depth analysis.

## DISCUSSION

The results of our study, which included 294 patients with PE who were treated at the MNE "CCH No8" of KCC in the year before the pandemic and during the first year after the detection of coronavirus infection in Ukraine, show a decrease in the number of hospitalized patients by 43.6%. However, this may not indicate a decrease in the prevalence of pulmonary embolism with the onset of the pandemic, as some patients may have been afraid to go to the hospital for epidemiological reasons, some had COVID-19 and were treated in other hospitals, and some unfortunately, did not managed to go to the hospital. The decrease in the prevalence of VTE has been noted in several foreign publications, including registers, the authors of which also emphasize the careful interpretation of this fact and the possibility of lockdown on the frequency of patients seeking medical help [23, 32].

Comparative analysis of the clinical course of pulmonary embolism in groups of patients depending on the COVID 19 pandemic did not reveal significant differences in terms of computed pulmonary angiography and the results of risk stratification. Moreover, no significant difference in mortality was found. This does not coincide with the results of similar publications by other authors who claim a more severe course and worse prognosis in patients with pulmonary embolism during the pandemic [15, 33, 16, 34, 21, 17]. The difference may be explained by differences in patient structure – we included only patients who were hospitalized in the laboratory who ruled out acute coronavirus infection using laboratory tests, while other authors usually analyzed the general group of patients with pulmonary embolism or patients with acute coronavirus infection.

Many publications and several meta-analyzes have been devoted to the impact of the COVID 19 pandemic on the risk of thromboembolic complications. They can be divided into several groups: the study of the prevalence of venous thrombosis during the pandemic, the study of the disease during this period and venous thromboembolism as a complication of coronavirus infection [18, 32, 35-38].

Interesting results were obtained in one of the first meta-analyzes, which included original articles in English, published from January 1, 2020 to June 15, 2020 in PubMed / MEDLINE, Embase, Web of science and Cochrane. Significant objectively verified VTEs, such as pulmonary embolism and / or proximal deep vein thrombosis (DVT), have been evaluated. The study included 33 studies (n = 4009 patients) who had severe acute coronavirus infection and were hospitalized for this reason. The primary endpoint is the risk of developing these VTE, the secondary – separately the risk of proximal DVT and pulmonary embolism (G. Longchamp et al, Trombosis Journal 19, Art. 15,2021) [18].

The group of patients included in the analysis was quite heterogeneous in terms of thrombotic risk factors, and the incidence of VTE averaged 9% and 21% among patients hospitalized for intensive care unit. The incidence of proximal thrombosis of the lower extremity was 3% and 8%, and the incidence of pulmonary embolism was 8% and 17%, respectively. Proven and predicted risk factor for VTE was the lack of anticoagulants [18].

Other studies have found an even higher incidence of VTE among hospitalized patients with COVID — up to one-third of patients with COVID-19, predominantly pulmonary embolism. It has been shown that VTE is more common in patients with concomitant pathology and severe disease [34].

Our study found significant differences in the frequency of ultrasound examination of deep vein thrombosis of the lower extremities as a possible source of thrombosis in the subgroups comparing patients with pulmonary embolism with excluded and those who had had COVID19 during the pandemic. The "paradox" of the decrease in the proportion of patients with deep vein thrombosis of the lower extremities, among those who have suffered a coronavirus infection, in our opinion, may be due to the fact that there was damage to the endothelium of the pulmonary arteries, which can be observed for a long time. Also, the results of published studies suggest that COVID-19 may be not only thromboembolic impaired blood flow, but also immunothrombosis in situ, initiated by immunopathological response, often hereditary. There is currently uncertainty as to whether COVID19-related thrombotic events are due to routine VTE, immunothrombosis, or a combination thereof, both in the acute and post Covid periods [11].

It is known that SARS-CoV-2 has a predisposition to the respiratory tract, enhances cellular entry through the ACE2 receptor, which is expressed on the surface of epithelial cells of the respiratory tract. Pathological changes in COVID-19 include diffuse alveolar damage, pneumocyte type II activation, hyaline membrane formation, and fibrin deposition, leading to the development of microvascular abnormalities. Pulmonary microvascular abnormalities include intravascular fibrin

deposition, perivascular monocyte infiltration, angiogenesis, and microthrombus formation. The results of autopsy of patients with COVID-19 indicate systemic endothelial dysfunction [39, 11].

If we recall the classic Virchow's triad (chain of events of thrombosis), the impressions of coronavirus can be a classic illustrative material, where there are blood flow disorders and changes in vascular wall with inflammation, and disorders of coagulation and fibrinolysis, as well as platelet and neutrophil function.

An additional activator of thrombosis in COVID 19 is hypoxia, which occurs in moderate to severe COVID-19 and therefore may lead to worsening endothelial dysfunction and hypercoagulation. Activation of endothelial P-selectin and adhesion molecules (eg, intercellular adhesion molecule-1 (ICAM-1)) in hypoxia leads to platelet and leukocyte adhesion. Hypoxia promotes thrombosis by increasing the release of PAI-1 endothelium and inflammatory cytokines (eg, TNF, interleukin (IL) -2), while reducing thrombomodulin regulation. In addition, increased activity of prothrombotic factors may be initiated by immune disorders, activation and local adhesion of macrophages, stimulation of the release of proinflammatory cytokines, including IL-6 and TNF-α [11].

Elevated antiphospholipid antibody (APA) titers have been reported in patients with COVID-19, and it should be noted that the diagnosis of antiphospholipid syndrome in acute infection requires APA to be measured twice a week.

In our opinion, it is reasonable to assume that in some patients with coronavirus infection, PE may be the result of immunotrombosis in situ, as evidenced by significant differences in the incidence of lower extremity thrombosis between subgroups of patients during the pandemic (in a subgroup of patients who had an infection, signs of deep vein thrombosis of the lower extremities were less common).

The results of our study show that despite the lack of significant increase in hospital mortality from pulmonary embolism during the pandemic, the proportion of pulmonary embolism in the structure of overall mortality may increase as the number of pulmonary embolism increased according to forensic examination. A more complete answer to this question could be provided by the results of the national register, which unfortunately does not exist in Ukraine.

## CONCLUSIONS

1. In the comparative analysis it was found that in the clinical course of pulmonary embolism in groups of patients treated in the cardiology department of MNE "CCH #8" of KCC, before the pandemic, and during the pandemic COVID -19, but had no signs of acute coronavirus infection, there are no significant differences in age, sex and prevalence of circulatory disorders in the pulmonary arteries according to the results of computed tomography.
2. When comparing subgroups of patients, depending on the presence of a history of COVID-19, it was proved that pulmonary embolism in patients with coronavirus infection is significantly more often observed in the presence of diabetes mellitus and low superficial and proximal vein thrombosis of the lower extremities is less common than in patients with which, according to laboratory tests, there were no signs of coronavirus infection.
3. Subgroups of patients with pulmonary embolism, those who had had COVID-19 and those who had not had COVID-19 did not differ significantly according to the results of ultrasound examination of the heart, except for the presence of signs of right ventricular diastole disorder E/A in a subgroup of patients with a history of coronavirus infection (1 subgroup of patients $1.13 \pm 0.28$, in the second – $0.87 \pm 0.25$; $p = 0.022$).
4. We found no differences in mortality among patients with pulmonary embolism before and during the COVID-19 pandemic. However, this statement cannot be definitive, as pre-hospital mortality may have increased.

## REFERENCES


1. Kovalenko VM, Dolzhenko MM, Potashev SV. Nastanovy z klinichnoyi ekhokardiohrafiyi: posibnyk. NMAPO im. P.L. Shupyka MOZ Ukrayiny. [Guidelines for clinical echocardiography: manual. NMAPO named after P.L. Shupyka of the Ministry of Health of Ukraine]. NNTS «Instytut kardiolohiyi imeni M.D. Strazheska». K.: Naukova dumka. 2018, p.327. (in Ukrainian)
2. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society: The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology. European Heart Journal. 2020;41(4): 543-603. doi: 10.1093/eurheartj/ehz405].
3. Cohen AT, Agnelli G, Anderson FA et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality., VTE Impact Assessment Group in Europe (VITAE). Thrombosis and Haemostasis. 2007;98(4): 756-764. doi: 10.1160/TH07-03-0212.
4. Greer IA, Heit JA, Hutchinson JL et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. VTE Impact Assessment Group in Europe (VITAE). Thrombosis and Haemostasis. 2007; 98(4): 756-764. doi: 10.1160/TH07-03-0212.

5. Heit JA. Epidemiology of venous thromboembolism. Nature Reviews Cardiology. 2015;12(8): 464-474. doi: 10.1038/nrcardio.2015.8.
6. Patientregistret 1987–1996. Kvalitet och innehall. Stockholm: Epidemiologiskt Centrum, Socialstyrelsen. 1998, p.49.
7. Silverstein MD, Heit JA, Mohr DN et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Archives of Internal Medicine. 1998; 158(6):585-593. doi: 10.1001/archinte.158.6.585.
8. Bikdeli B, Madhavan MV, Jimenez D et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up JACC State-of-the-Art Review. Journals of the American College of Cardiology. 2020;75(23): 2950-2973. doi: 10.1016/j.jacc.2020.04.031.
9. Miro O, Jimenez S, Mebazaa A et al. Pulmonary embolismin patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome. European Heart Journal. 2021; 42: 3127–3142. doi:10.1093/eurheartj/ehab314.
10. Polo Friz H, Gelfi E, Orenti A et al. Acute pulmonary embolism in patients presenting pulmonary deterioration after hospitalisation for non-critical COVID-19. Internal Medicine Journal. 2021;51:1236–1242. doi:10.1111/imj.15307.
11. Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. Thorax 2021;76:412–420. doi:10.1136/thoraxjnl-2020-216243.
12. Tseluyko VY, Yakovleva LM, Sukhova SM et al. Kliniko-anamnestychna kharakterystyka ta faktory ryzyku u khvorykh na hostru tromboemboliyu lehenevoyi arteriyi sered meshkantsiv m. Kharkova. [Clinical and anamnestic characteristics and risk factors in patients with acute pulmonary embolism among residents of Kharkiv]. Medytsyna nevidkladnykh staniv. 2021; 17(3): 58-63. (in Ukrainian)
13. Donzé J, Le Gal G, Fine MJ et al. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. Journal of Thrombosis and Haemostasis. 2008; 100(5): 943-948. doi: 10.1160/TH08-05-0285.
14. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Advances. 2020; 4(19): 4693-4738. doi: 10.1182/bloodadvances.2020001830.
15. Helms J, Tacquard C, Severac F et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020; 46: 1089–98.
16. Li T, Cheng GS, Pipavath SNJ et al. The novel coronavirus disease (COVID-19) complicated by pulmonary embolism and acute respiratory distress syndrome. J Med Virol. 2020; 92: 2205–8.
17. Mumoli N, Conte G, Cei M et al. In-hospital fatality and venous thromboembolism during the first and second COVID-19 waves at a center opting for standard-dose thromboprophylaxis. Thrombosis Research. 2021. doi: 10.1016/j.thromres.2021.04.026.
18. Proximal deep vein thrombosis and pulmonary embolism in COVID-19 patients: a systematic review and meta-analysis. Thrombosis Journal. 2021; 15 (3). doi: 10.1186/s12959-021-00266-x.
19. Rodionov RN, Westendorf JB, Bode Böger SM et al. Homoarginine and methylarginines independently predict long term outcome in patients presenting with suspicion of venous thromboembolism. Scientific Reports 11. 2021. doi:10.1038/s41598-021-88986-y.
20. Yunqiang Nie , Li Sun , Wei Long  Clinical and anamnestic characteristics and risk factors in patients with acute pulmonary embolism among residents of Kharkiv. Clinical importance of the distribution of pulmonary artery embolism in acute pulmonary embolism. Journal of International Medical Research. 2021;49(4):1–9. doi: 10.1177/03000605211004769.
21. Malas MB, Naazie IN, Elsayed N et al. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. EClinicalMedicine. 2020; 29: 100639.
22. Ren B, Yan F, Deng Z et al. Extremely high incidence of lower extremity deep venous thrombosis in 48 patients with severe COVID-19 in Wuhan. Circulation. 2020;142(2):181–3.
23. Rieder M, Goller I, Jeserich M et al. Rate of venous thromboembolism in a prospective all-comers cohort with COVID-19. J Thromb Thrombolysis. 2020; 50: 558–66.
24. Stein PD, Matta F, Hughes MJ. In Hospital Mortality with Deep Venous Thrombosis. The American Journal of Medicine. 2016; 130(5): 596-600. doi: 10.1016/j.amjmed.2016.10.030iii].
25. Hofer M. CT Teaching Manual: A Systematic Approach to CT Reading, 4th Edition. MEDIDAK Publishing GmbH. 2013, p.367.
26. Kovalenka VM, Kornats'koho VM. Khvoroby systemy krovoobihu yak medyko-sotsial'na i suspil'no-politychna problema: analitychno-statystychnyy posibnyk. [Diseases of the circulatory system as a medical-social and socio-political problem: analytical and statistical guide] NNTS «Instytut kardiolohiyi imeni M.D. Strazheska». K.: Kolomitsyn V.YU. 2014, p.119. (in Ukrainian)
27. Kitabatake A, Inoue M, Asao M et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation. 1983; 68(2):302-309.
28. Lang R, Goldstein SA, Kronzon I et al. ASE's Comprehensive Echocardiography. Elsevier Health Sciences. 2015, p.941.
29. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal Cardiovascular Imaging. 2015; 16(3): 233-271. doi: 10.1093/ehjci/jev014.
30. Konstantinides S, Meyer G, Becattini C et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Heart Journal. 2019;41(4):543-603.
31. Emrah Acar MD, Alev Kilicgedik MD, Servet Izci MD et al. Time interval between E and E' waves can predict complicated clinical course in patients with acute pulmonary embolism. J Clin Ultrasound. 2021;49(6):580-585. doi: 10.1002/jcu.22995.

32. Stefano Barco MD, Luca Valerio MD, Andrea Gallo MD et al. Global reporting of pulmonary embolism–related deaths in the World Health Organization mortality database: Vital registration data from 123 countries. Res Pract Thromb Haemost. 2021;5(5). doi: 10.1002/rth2.12520.
33. Klok FA, Kruip MJHA, van der Meer NJM et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145–7.
34. Llitjos J-F, Leclerc M, Chochois C et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. The Journal of Thrombosis and Haemostasis. 2020;18(7): 1743-1746. doi: 10.1111/jth.14869.
35. Franco-Moreno A, Herrera-Morueco M, Mestre-Gomez B et al. Incidence of deep venous thrombosis in patients with COVID-19 and pulmonary embolism: compression ultrasound COVID study. J Ultrasound Med. 2021; 40: 1411–6.
36. Kho J, Ioannou A, Van den Abbeele K et al. Pulmonary embolism in COVID-19: clinical characteristics and cardiac implications. Am J Emerg Med. 2020; 38: 2142–6.
37. Thomas W, Varley J, Johnston A et al. Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. Thromb Res. 2020; 191: 76–7.
38. Malas MB, Naazie1 IN, Elsayed N et al. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinical Medicine. 2020, p.29-30.
39. Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417–8.

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ORIGINAL ARTICLE

# EVALUATION THE PREVALENCE OF MULTIDRUG RESISTANCE BACTERIA AMONG IRAQI PATIENTS AND ITS ASSOCIATION WITH PATIENTS' PREDICTIVE FACTORS: A CROSS-SECTIONAL STUDY

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## ABSTRACT

**The aim**: The study aimed to evaluate the prevalence of multidrug resistance bacteria (MDR),, it's types and explore the patient's predictive factors associated with it.
**Materials and methods**: The study was a cross-sectional observational study conducted in a microbiology lab in AL-Zahraa Teaching Hospital and Alsader Medical City, in Najaf Province, Iraq. The participants included patients presented with different kinds of infections and caused by organisms isolated from different sources. The patients had positive growth media were 304 out of total 475 patients.
**Results**: The data extraction sheet included the laboratory culture and sensitivity report and patient sociodemographic factors and risk factors. The study displayed an extremely high prevalence of MDR bacteria 88% and the prevalence of extensive drug resistance (XDR) was 23%, whereas Pan-drug resistance (PDR) prevalence was 2%. Specifically, Methicillin resistance *Staphylococcus Aureus* (MRSA) was detected in 73% of the total patients infected with *Staph*. *Bacteria*. The prevalence of Extended spectrum beta-lactamases (ESBLs) was reached to 56% among the patients infected with *Enterobacteria*, while carbapenem resistance (CR) was recorded in 25% of the patients infected with different kinds of bacteria. Only education level was significantly associated with the prevalence of MDR. Patients with (college/post-graduate) education were associated with a low incidence of MDR.
**Conclusions:** A very high prevalence of multidrug resistance bacteria was noted in patients with a bacterial infection. Among all patients' characters, only higher education was associated with lower incidence.

**KEY WORDS:** prevalence, antimicrobial resistance, multidrug resistance, predictive factors, education

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## INTRODUCTION

Antimicrobial resistance (AMR) is a potentially disastrous problem that is mounting globally. The surveillance studies are vital to control the distribution of AMR by creating a clue for actions nationally and globally. Multidrug resistance bacteria (MDR) incidence has been studied in a lesser extent in Iraq. Antimicrobial resistance is an international and communal health problem and constantly evolving phenomenon that menace infection and disease control [1]. The Anti-

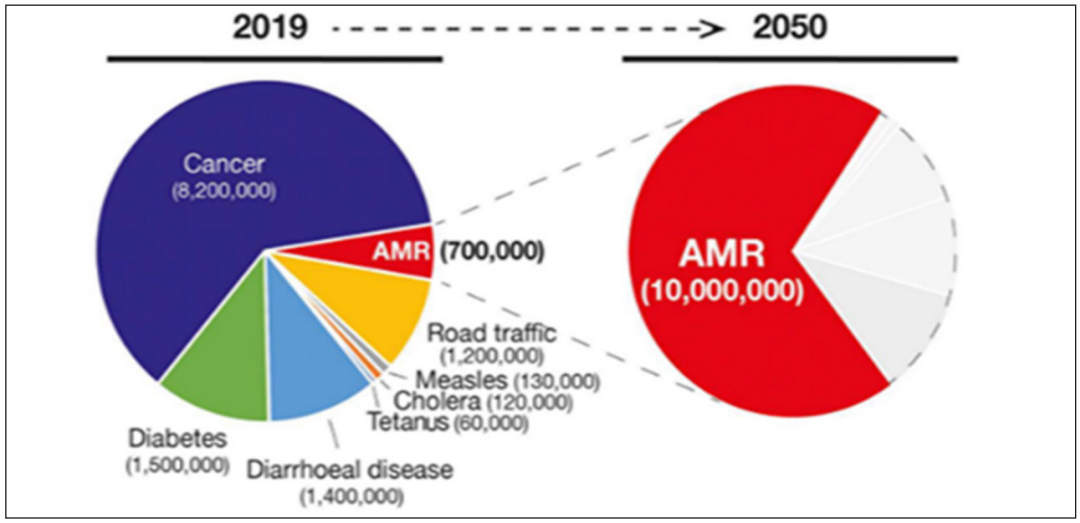


**Fig. 1.** Number of estimated deaths annually in 2019 and the prognosis of deaths in 2050 owing to AMR [5].

microbial resistance occurred when the organisms (viruses or bacteria) change with time, and no longer react to medicines that lead to increase the danger of disease spreading, severe infections and death [2], while antibiotic resistance defined as the loss of drug efficacy to suppress the bacterial growth. Thus, these bacteria become resistant and still proliferated despite the presence of antibiotics [3]. Antimicrobial resistance can affect all people in several countries. Annually, the treatable infections related deaths were 5.7 million patients, typically in countries of low- and middle-income (LMICs), whereas the well come Trust and the British Government stated in its latter report that the resistant infections related deaths are 700.000 and will reach to 10 million people in the year of 2050 [4] (Fig. 1).

### PRINCIPAL FORMS OF ANTIMICROBIAL RESISTANCE

Speaking about bacterial resistance, the following types are distinguished: natural resistance, cross resistance, acquired resistance and multidrug resistance (MDR) [6]. Different definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pan drug-resistant (PDR) bacteria are being used literally to characterize the different patterns of resistance found. To create a standardized international terminology to describe acquired resistance profiles in *Enterococcus spp*., *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *S. aureus*, *A. baumannii* species and *P. aeruginosa*, the group of international experts came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC). The ECDC define MDR as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. XDR is described as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., the isolates of bacteria are still sensitive to only one or two classes. PDR was described as all agents across all antimicrobial categories were not susceptible to this bacteria and different antimicrobial categories included cephalosporins, fluroquinolones, aminoglycosides, glycopeptides and other categories were made with the intent of placing antimicrobial agents into therapeutically related groups and each category is considered similarly relevant [7]. Previously the species of AMR bacteria were confined to the hospital environment, but now they can be found everywhere [8]. The human and animal health are presently affecting by the serious risk of AMR with longer hospital admissions, impairments, higher mortality and excessive costs of treatment failures. For instance, antimicrobial resistance in Europe, is responsible takes for over nine billion euros per annum [9], also antimicrobial resistance jeopardizes the treatment of a variety of common illnesses as well as regular surgical operations, cancer treatment, and organ transplants [10]. The main causes behind the progress of AMR problem were human behavioral factors, such as excessive/misuse of antibiotics, wide commercial its using, such as personal care industry and agricultural employment of antimicrobials and microbial causes [11-12]. The sprouting problem of AMR was recognized since 2001 by World Health Organization (WHO) which called for addressing the problem by joining the efforts [13], also in 2014 WHO responded to the call of the World Health Assembly (WHA) for progress of an action plan against AMR and the result was establishment of global antimicrobial resistance surveillance system (GLASS) in the next year [14]. AMR surveillance conducted to (a) control the disease burden, (b) follow the sequential and geographic and inclinations for recognition of eruption, (c) creating an evidence for the empirical treatment by determination of congregation and spreading and (d) assess the value of antimicrobial stewardship strategies in limiting the infections [15]. Some Arab nations, like Iraq, suffer from incomplete monitoring programs and insufficient infection prevention and control strategies [16]. It is difficult to compare Iraq to the rest of the globe because of this issue [17].

## THE AIM

Thus, the current study's objectives included assessing the types of multidrug-resistant bacteria (MDR), their prevalence, and the patient-related predictors of MDR.

## MATERIALS AND METHODS

### STUDY DESIGN AND SETTING

A cross-sectional observational study were conducted on patients presented to microbiological laboratory of AL-Alsader Medical City and AL-Zahraa Teaching Hospital, Najaf governate/ Iraq during the period of October 2021 to February 2022.

### STUDY POPULATION

The participants of research were patients presented with different kinds of infections and requested for culture/sensitivity test for organisms isolated from different sources such as blood, urine, stool and other sources. To calculate the number of samples required to estimate the prevalence of MDR in AL- Najaf community we used Daniel equation. We assumed the confidence

**Table I.** Patient information sheet.

| | | |
|---|---|---|
| 1 | **Patient code** | |
| 2 | **Age** | |
| 3 | Gender | ☐ Male ☐ Female |
| 4 | Area of residence | ☐ Rural ☐ Urban |
| 5 | **Mobile number** | |
| 6 | Education level | Without formal education<br>Primary or secondary education<br>College/postgraduation education |
| 7 | Is there any health care provider among your family members? | ☐ Yes ☐ No |
| 8 | Monthly Income | ☐ Low≤0.5 million IDs<br>☐ Moderate (0.5-1.5 million IDs)<br>☐ High ≥ 1.5 million IDs |
| 9 | Are you a smoker? | ☐ Yes ☐ No |
| 10 | Do you have any Comorbidities? You can choose more than one. | DM<br>Hypertension<br>Asthma or COPD<br>Chronic kidney disease<br>Malignancies<br>Any Chronic illness<br>No comorbidities |
| 11 | Had you been admitted to hospital in last three months? | ☐ Yes ☐ No |
| 12 | Are you using medical devices such as urinary catheters, or gastrointestinal tubes etc.? | ☐ Yes ☐ No |
| 13 | Have you used antibiotics in the last three months? | ☐ Yes ☐ No |
| 14 | Do you use immunosuppressant medication or corticosteroids? | ☐ Yes ☐ No |
| 15 | Have you ever been infected and/or hospitalized with COVID-19? | ☐ Yes ☐ No |
| 16 | Have you received influenza or COVID-19 vaccine? | ☐ Yes ☐ No |

interval (CI) was 95% with precision percent ±5% so the sample size required was 385 samples. We aimed to include additional more than 20% of patients calculated sample considering possibility of incomplete data of some participants and the probability of no growth bacteria therefore the actual sample was 475 and out of them only 304 shown growth bacterial culture. These 304 participants are still sufficiently good to calculate provenance of MDR bacteria considering the confidence interval (CI) was 90% with precision percent ±5% so the sample size required was 267 samples.

## TOOLS

There were two parts for data collection in each patient. The first part was patient information sheet included patient sociodemographic factors and risk factors (Table I), and the second part was the laboratory culture and sensitivity report. The determination of bacterial pathogen's susceptibility to antimicrobial agents and identifying the potential drug resistance done in the clinical microbiology laboratories by using the classic phenotypic AST method and automatic instrument system like the Vitec 2 compact system.

## INCLUSION AND EXCLUSION CRITERIA

Prior to interviews, patients gave their verbal consent after being fully informed about the proposed study and expressing their willingness and ability to participate. The individuals omitted from our study were either foreigners (who do not speak Arabic), not first-degree relatives to the patient, lacked sufficient knowledge about the patients, or declined to take part in the interview

## ETHICAL CONSIDERATION

This study was approved by the Ethics and Scientific Committee of Faculty of Pharmacy/the University of Kufa/college of pharmacy with reference number (469), as well as by the Scientific Committee of Researches

**Table II.** The characteristics of the participating patients

| Character | Subcategories | N | [%] |
|---|---|---|---|
| Age categories | Adult | 223 | 46.9 |
| | Adolescent | 29 | 6.1 |
| | Child | 148 | 31.2 |
| | Neonate | 75 | 15.8 |
| | Total | 475 | 100.0 |
| Gender | Female | 285 | 60 |
| | Male | 190 | 40 |
| | Total | 475 | 100.0 |
| Residence area | Rural | 90 | 18.9 |
| | Urban | 385 | 81.1 |
| | Total | 475 | 100.0 |
| Education level* | Without formal education | 40 | 15.9 |
| | Primary or secondary education | 163 | 64.7 |
| | College/postgraduation education | 49 | 19.4 |
| | Total | 252 | 100.0 |
| Monthly income | Low | 267 | 56.2 |
| | Moderate | 185 | 38.9 |
| | High | 23 | 4.8 |
| Smoking status | No | 203 | 80.6 |
| | Yes | 49 | 19.4 |
| | Total | 252 | 100.0 |
| Health care provider among family | No | 394 | 82.9 |
| | Yes | 81 | 17.1 |
| | Total | 475 | 100.0 |
| Participants provided information | child parents | 223 | 46.9 |
| | Patients | 252 | 53.1 |
| | Total | 475 | 100.0 |

*223 = not included in the education classification since they researcher interviewed parent(s) of children ≤12 years old.

of Al-Najaf Health Department with approval number (46202). Our study registered at Clinical Trials.gov with the registration number (NCT05100407).

### STATISTICAL ANALYSIS

The results were analyzed by using Statistical Package for Social Sciences (SPSS) version 25. The descriptive analyses expressed by (means, frequencies, standard deviation and percentages) were conducted for all items of study. The association between categorical variables and MDR prevalence was analyzed by Chi-Square test.

## RESULTS

### THE PARTICIPANT CHARACTERISTICS

The study included 475 patients. The patients with positive growth media were 304 only. The majority (60%) were female. Their age ranged from few days to 72 years with an average of 18.2 (± 17.2) years. The vast majority of patients (81.1%) lived in urban areas. The majority of patients (64.4%) had primary or secondary school degrees. More than half (56.2%) had low income and only 4.8% with high income (Table II).

### PATIENTS RISK FACTORS

More than one-quarter (27.4%) had comorbidities. The majority (86.1%) used antibiotics in the last months and 43.2% were admitted to hospitals in the last three months. Some of them (24%) were infected with COVID-19 and only 13.7% have received COVID-19/flu vaccines. Also, only 11.8% of patients have using medical devices and another 11.8% of patients using immunosuppressant (Table III).

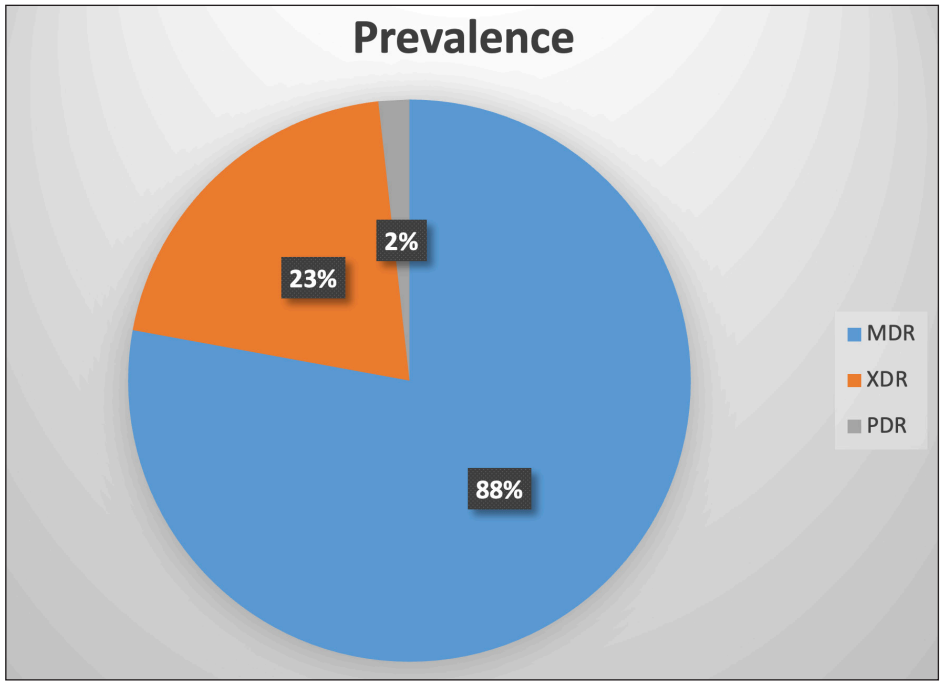


**Fig. 2.** Prevalence of multidrug resistance bacteria.

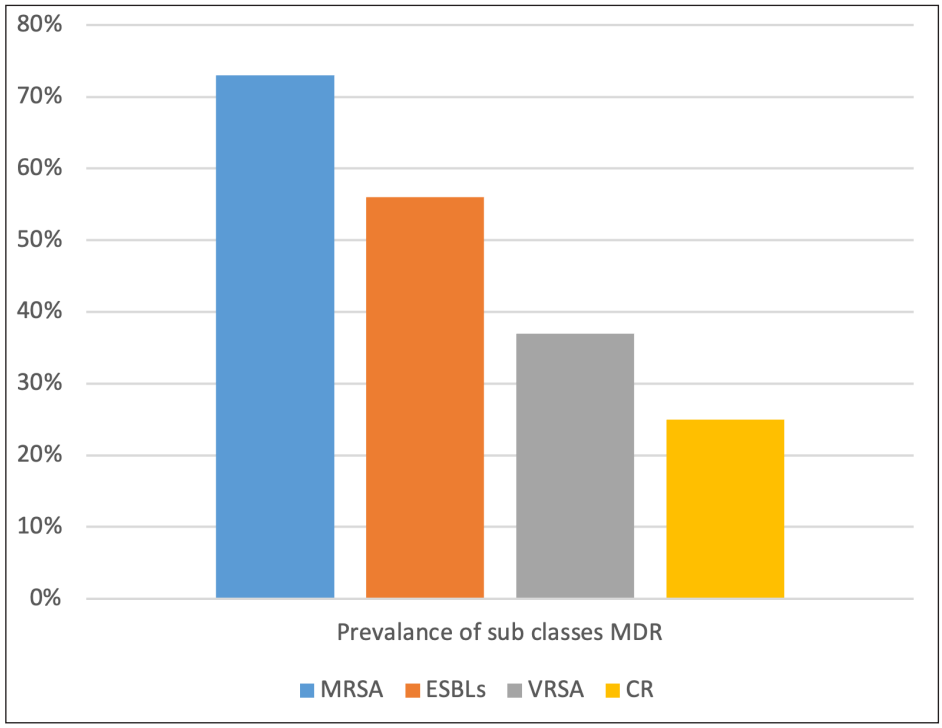


**Fig.3.** Prevalence of different type of multidrug resistance bacteria.

## PREVALENCE OF MULTI DRUG RESISTANCE BACTERIA (MDR), EXTENDED DRUG RESISTANCE BACTERIA (XDR) AND PAN DRUG RESISTANCE BACTERIA (PDR)

The study showed very high prevalence of MDR 88% where 231 patients infected with bacteria resistance to three and more of therapeutically relevant antimicrobial category out of total 263 patients eligible for MDR detection. The prevalence of XDR reached to 23% where 53 of total patients infected with bacteria susceptible only to one or two of therapeutically relevant antimicrobial category out of total 229 patients eligible for XDR detection. Whereas PDR prevalence was 2% where 5 patients infected with bacteria resistance to all therapeutically relevant antimicrobial category out of total 295 patients eligible for PDR detection (Fig. 2).

## PREVALENCE OF DIFFERENT SUBCLASS OF MULTI DRUG RESISTANCE BACTERIA

In this study 73% of the total 33 patients infested with *S. aureus* detected with MRSA. While VRSA identified

**Table III.** Patients risk factors

| Risk Factors | Subcategories | N | [%] |
|---|---|---|---|
| Having comorbidities | Yes | 130 | 27.4* |
| Having hypertension | Yes | 40 | 8.5 |
| Having diabetes | Yes | 25 | 5.3 |
| Having CKD | Yes | 23 | 4.8 |
| Having asthma/COPD | Yes | 19 | 4.0 |
| Having cancer | Yes | 7 | 1.5 |
| Having other co-morbidities | Yes | 54 | 11.4 |
| Been admitted to hospital in last three months | Yes | 205 | 43.2 |
| Using medical devices such as urinary catheters, or gastrointestinal | Yes | 56 | 11.8 |
| Using antibiotics in the last three months | Yes | 409 | 86.1 |
| Using immunosuppressant medication or corticosteroids | Yes | 56 | 11.8 |
| Been infected or hospitalized with COVID-19 | Yes | 118 | 24.8 |
| Received influenza or COVID-19 vaccine(s) | Yes | 65 | 13.7 |

*Some patients had multiple comorbidities

in total 27 eligible patients infested with *S. aureus* with prevalence 37%. The prevalence of ESBLs reached to 56% among total 190 patients infected with enterobacteria mainly *E. coli* and *Klebsiella*. Regarding carbapenem resistance (CR) were recorded in 25% of total 277 patients with different kinds of bacteria (Fig. 3).

### THE ASSOCIATION BETWEEN THE PREVALENCE OF MULTIDRUG RESISTANCE BACTERIA AND THE PATIENTS' CHARACTERISTICS

According to Chi-square analysis, patient education has significant relationship with the incidence of multidrug resistance (MDR) bacteria. Patients with primary or secondary school degrees have higher rates of MDR incidence compared with those with higher (college/post-graduate) education. However, no other patient characteristics or risk factors have significant influence on the incidence of MDR bacteria (Table IV).

## DISCUSSION

### THE PREVALENCE OF MDR, XDR PDR

This study showed very high prevalence of MDR – 88% and the prevalence of XDR reach to 23%, whereas PDR prevalence is 2%. The results were compatible with report of MSF organization in Iraq which mentioned that 90% of microbiologically confirmed patients treated in Mosul were had MDR infection [18], also MDR prevalence in previous study conducted in Babel, Iraq was 88.09% of the isolates while XDR prevalence was 11.9% [19]. On the other hand, a previous Saudi study stated that the MDR incidence was 57.3% and 3.5% was the prevalence of XDR and no PDR cultures was detected [20]. Another study conducted in Tehran-Iran mentioned that 54.5% of P. aeruginosa isolates was recognized as MDR and 33% was the prevalence of XDR and there was no PDR among the clinical isolates [21], while study conducted in Pakistan estimated that 81% of E. coli isolates were MDR and XDR were 8.7% in alignment with our study [22].

The overexcited use of antibiotics recently without culture/sensitivity testing, is the chief imperative reason behind frighteningly high MDR and XDR prevalence which encouraging the development of MDR and lead to spreading of resistant bacteria in the medical treatment [19]. The clinical and financial burden of MDR, XDR and PDR to patients really challenging.

The leader of Joint Commission Resources Practice Infection Prevention and Control Services, Barbara Soule, has told, "Patients who are infected with MDR infections frequently have an increased risk of mortality and prolonged illness. Also, the cost of care for these patients can be more than the double as compared with those with no MDR infections" [23]. For instance, XDR-Gram Negative bacteria are accompanying with worse medical consequence and lead to prolonged length of hospital stay (LOS). Additionally, MDR colonization, which is thought to be a risk factor for the same MDR infection in specific patients, might have a catastrophic clinical outcome and, as a result, lengthen the hospital stay [24]. Also, unfortunately these infections had very limited treatment options. For some types of XDR and PDR, only one or two antibiotics can be effective and accompanying with toxic side effects [25]. The other problem is that the bacteria are developing resistance at a quicker pace than the development of new drug [26].

**Table IV.** The relationships between multi-drug resistance bacteria and patient characteristics.

| Variables | | | MDR | | Total | P-value |
|---|---|---|---|---|---|---|
| | | | No | Yes | | |
| Age category | Adult | Count | 18 | 135 | 153 | .762 |
| | | % within | 11.8% | 88.2% | 100.0% | |
| | Adolescent | Count | 1 | 15 | 16 | |
| | | % within | 6.3% | 93.8% | 100.0% | |
| | children | Count | 9 | 63 | 72 | |
| | | % within | 12.5% | 87.5% | 100.0% | |
| | Neonate | Count | 4 | 18 | 22 | |
| | | % within | 18.2% | 81.8% | 100.0% | |
| Gender | female | Count | 20 | 136 | 156 | .566 |
| | | % within | 12.8% | 87.2% | 100.0% | |
| | Male | Count | 11 | 94 | 105 | |
| | | % within | 10.5% | 89.5% | 100.0% | |
| Area of residence | Rural | Count | 7 | 31 | 38 | .202 |
| | | % Within | 18.4% | 81.6% | 100.0% | |
| | Urban | Count | 25 | 200 | 225 | |
| | | % within | 11.1% | 88.9% | 100.0% | |
| Education | None | Count | 4 | 25 | 29 | .010* |
| | | % within | 13.8% | 86.2% | 100.0% | |
| | Primary/secondary | Count | 6 | 100 | 106 | |
| | | % within | 5.7% | 94.3% | 100.0% | |
| | College/post-graduate | Count | 9 | 25 | 34 | |
| | | % within | 26.5% | 73.5% | 100.0% | |
| Monthly income | Low | Count | 19 | 126 | 145 | .752 |
| | | % Within | 13.1% | 86.9% | 100.0% | |
| | Middle | Count | 12 | 91 | 103 | |
| | | % within | 11.7% | 88.3% | 100.0% | |
| | High | Count | 1 | 14 | 15 | |
| | | % within | 6.7% | 93.3% | 100.0% | |
| Smoker | No | Count | 16 | 118 | 134 | .714 |
| | | % within | 11.9% | 88.1% | 100.0% | |
| | Yes | Count | 3 | 32 | 35 | |
| | | % within | 8.6% | 91.4% | 100.0% | |
| Is there any health care provider among your family members? | No | Count | 23 | 188 | 211 | .236 |
| | | % within | 10.9% | 89.1% | 100.0% | |
| | Yes | Count | 9 | 43 | 52 | |
| | | % within | 17.3% | 82.7% | 100.0% | |
| Had you been admitted to hospital in last three months? | No | Count | 19 | 149 | 168 | .571 |
| | | % within | 11.3% | 88.7% | 100.0% | |
| | Yes | Count | 13 | 82 | 95 | |
| | | % within | 13.7% | 86.3% | 100.0% | |
| Are you using medical devices such as urinary catheters, or gastrointestinal tubes? | No | Count | 26 | 211 | 237 | .073 |
| | | % within | 11.0% | 89.0% | 100.0% | |
| | Yes | Count | 6 | 20 | 26 | |
| | | % within | 23.1% | 76.9% | 100.0% | |
| Have you used antibiotics in the last three months? | No | Count | 4 | 29 | 33 | .993 |
| | | % within | 12.1% | 87.9% | 100.0% | |
| | Yes | Count | 28 | 202 | 230 | |
| | | % Within | 12.2% | 87.8% | 100.0% | |
| Do you use immunosuppressant medication or corticosteroids? | No | Count | 29 | 208 | 237 | .918 |
| | | % within | 12.2% | 87.8% | 100.0% | |
| | Yes | Count | 3 | 23 | 26 | |
| | | % within | 11.5% | 88.5% | 100.0% | |
| Have you ever been infected and/or hospitalized with COVID-19? | No | Count | 27 | 161 | 188 | .085 |
| | | % within | 14.4% | 85.6% | 100.0% | |
| | Yes | Count | 5 | 70 | 75 | |
| | | % within | 6.7% | 93.3% | 100.0% | |
| Have you received influenza or COVID-19 vaccine? | No | Count | 26 | 193 | 219 | 0.744 |
| | | % within | 11.9% | 88.1% | 100.0% | |
| | Yes | Count | 6 | 38 | 44 | |
| | | % within | 13.6% | 86.4% | 100.0% | |

*Significant according to Chi-square analysis (P-value<0.05)

## PREVALENCE OF DIFFERENT SUBCLASS OF MULTI DRUG RESISTANCE BACTERIA

In this study, MRSA detected in 73% of the total patients infected with S. aureus, while a study from Baghdad-Iraq conducted in Ibn Sina hospital found that the prevalence of MRSA isolates was around 46.1% which detected an increasing in the trend of MRSA in comparison with our study [27]. Another Iraqi study held in Duhok city stated that the prevalence of MRSA and its virulence factors were higher in Iraqi community than in Syrian refugees [28]. A review article in KSA estimated that the overall prevalence of MRSA during 10 years was 35.6% [29]. As well an English study conducted for a five year period mentioned that the most common organism of surgical site infections was S. aureus, 64% out of them were MRSA, whereas MRSA percentage was decreased to 32% which reflecting the role of government in England who having made the reportage of MRSA mandatory for all hospitals, subsequently made the target of halving their MRSA rates [30], whereas the prevalence of ESBLs reached to 56% among total patients infected with enterobacteria mainly *E. coli* and *Klebsiella* and the result was in coincidence with Iranian study which found that prevalence of ESBL isolates were 55.4% [31]. Also 2 different Iraqi studies mentioned that percentage of ESBL in *K. pneumonia* and *E. coli* isolates were 36.7% and 31% respectively [32-33]. Regarding carbapenem` resistance (CR), the current study recorded (CR) in 25% of total 277 patients with different kinds of bacteria. In the same range, a systematic review found that 23.9% of Enterobacteriaceae isolates in KSA were CR, while in Iraq 22% of K. pneumonia isolates recovered from hospitals in AL-Anbar governed were CR [34]. Carbapenem resistance associated with high case-fatality rates and limited antibiotics choices since the carbapenem antibiotics considered as last resort so increase the CR rate led to public health challenge [35].

## ASSOCIATION OF MDR WITH PATIENTS' PREDICTIVE FACTORS

There is no association between MDR and patients' predictive factors except for education level and MDR. A cross sectional survey from Singapore found no association between ESBL-MDR colonization and education level in contrast to our result, but similar to our result in term of previous antibiotics use and history of chronic diseases [36]. On the other hand, an Iranian study stated that the male with history of chronic diseases, past antibiotics use, previous hospital admission or catheter use were more associated with proliferation of ESBL isolates [31]. The possible explanation for non-association of most patients' risk factors with MDR or XDR is the ongoing over/misuse of antibiotics triggered the proliferation of MDR bacteria and associated capability of these organisms to spread from one person to another reflected by extremely high prevalence of MDR in this study which is further exacerbated by lack of awareness, weak infrastructure such as poor sanitation and debilitating health care system in the developing countries creating endemic prevalence pattern of MDR bacteria and can spread everywhere [24].

# CONCLUSIONS

A very high prevalence of multidrug resistance bacteria was noted in patients with a bacterial infection. Among all patients' characters, only higher education was associated with lower incidence.

## REFERENCES


1. Colomb-Cotinat M, Lacoste J, Brun-Buisson C et al. Estimating the morbidity and mortality associated with infections due to multidrug-resistant bacteria (MDRB). Antimicrob Resist Infect Control. 2016;5:56. doi: 10.1186/s13756-016-0154-z.
2. World Health Orization. Antimicrobial resistance, https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. 2021 [Access: March 2022].
3. Bin ZS, Hussain MA, Nye R et al. A Review on Antibiotic Resistance: Alarm Bells are Ringing. Cureus. 2017;9(6):e1403. doi: 10.7759/cureus.1403.
4. Wall S. Prevention of antibiotic resistance an epidemiological scoping review to identify research categories and knowledge gaps. Glob Health Action. 2019;12(1):1756191. doi: 10.1080/16549716.2020.1756191.
5. Rosini R, Nicchi S, Pizza M et al. Vaccines Against Antimicrobial Resistance. Front Immunol. 2020;11:1048.
6. Hasan TH, Al-harmoosh RA. Mechanisms of Antibiotics Resistance in Bacteria. Syst Rev Pharm. 2020;11(6):817-823.
7. Magiorakos AP, Srinivasan A, Carey RB et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-281.
8. Vivas R, Barbosa AAT, Dolabela SS et al. Multidrug-Resistant Bacteria and Alternative Methods to Control Them: An Overview. Microb Drug Resist. 2019;25(6):890-908.
9. Dadgostar P. Antimicrobial resistance: implications and costs. Infect Drug Resist. 2019;12:3903-3910.
10. Dong H, Zhen X, Lundborg CS et al. The Clinical and Economic Impact of Antibiotic Resistance in China : A Systematic Review. MDPI. 2019; 8(3):115. doi: 10.3390/antibiotics8030115.

11. Mogasale VV, Saldanha P, Pai V et al. A descriptive analysis of antimicrobial resistance patterns of WHO priority pathogens isolated in children from a tertiary care hospital in India. Sci Rep. 2021;11(1):1-7. doi: 10.1038/s41598-021-84293-8.
12. Rezasoltani S, Yadegar A, Hatami B et al. Antimicrobial Resistance as a Hidden Menace Lurking Behind the COVID-19 Outbreak: The Global Impacts of Too Much Hygine on AMR. Front Microbiol. 2019;11:590683. doi: 10.3389/fmicb.2020.590683.
13. Truppa C, Abo-Shehada MN. Antimicrobial resistance among GLASS pathogens in conflict and non-conflict affected settings in the Middle East: a systematic review. BMC Infect Dis. 2020;20(1):1-26.
14. Sulis G, Sayood S, Gandra S. Antimicrobial resistance in low- and middle-income countries: current status and future directions. Expert Rev Anti Infect Ther. 2022;20(2):147-160. Doi: 10.1080/14787210.2021.1951705.
15. Goddard L, Wozniak TM. Antimicrobial Resistance Surveillance to Support Decision- Making in a High-Prevalence Region: An Evaluation. Front. Trop. Dis. 2021;2:1-10. doi: 10.3389/fitd.2021.772491.
16. Rizk NA, Moghnieh R, Haddad N et al. Challenges to antimicrobial stewardship in the countries of the arab league: Concerns of worsening resistance during the COVID-19 pandemic and proposed solutions. Antibiotics (Basel). 2021;10(11):1320. doi: 10.3390/antibiotics10111320.
17. Devi S. AMR in the Middle East: a perfect storm. Lancet. 2019;394(10206):1311-1312. doi: 10.1016/s0140-6736(19)32306-2.
18. The invisible burden of antibiotic resistance in Mosul, Iraq, MSF. 2019, https://www.msf.org/invisible-burden-antibiotic-resistance-mosul-iraq [Access: March 2022].
19. Al-Hasnawy HH, Judi MR, Hamza, Jasim H. The Dissemination of Multidrug Resistance (MDR) and Extensively Drug Resistant (XDR) among Uropathogenic E. coli (UPEC) Isolates from Urinary Tract Infection Patients in Babylon Province, Iraq. Baghdad Sci J. 2019;16(4(Suppl.)): 0986. https://bsj.uobaghdad.edu.iq/index.php/BSJ/article/view/4597 [Access: March 2022].
20. Alkofide H, Alhammad AM, Alruwaili A et al. Multidrug-Resistant and Extensively Drug- Resistant Enterobacteriaceae : Prevalence , Treatments, and Outcomes – A Retrospective Cohort Study. Infect Drug Resist. 2020;13:4653-4662.
21. Saderi H, Owlia P. Detection of multidrug resistant (MDR) and extremely drug resistant (XDR) pseudomonas aeruginosa isolated from patients in Tehran, Iran. Iran J Pathol. 2015;10(4):265-271.
22. Sabir S, Anjum AA, Ijaz T et al. Isolation and antibiotic susceptibility of E. coli from urinary tract infections in a tertiary care hospital. Pakistan J Med Sci. 2014;30(2):389-392.
23. Basak S, Singh P, Rajurkar M. Multidrug Resistant and Extensively Drug Resistant Bacteria : A Study. J Pathog. 2016;2016:4065603. doi: 10.1155/2016/4065603.
24. Mutters NT, Günther F, Sander A et al. Influx of multidrug-resistant organisms by country-to-country transfer of patients. BMC Infect Dis. 2015;15(1):4-9. doi: 10.1186/s12879-015-1173-8.
25. Peterson LR. Bad Bugs, No Drugs: No ESCAPE Revisited. Clin Infect Dis. 2009;49(6):992-993. doi: 10.1086/605539.
26. Basak S, Rajurkar MN. Newer β-lactamases and E. coli – a cause of concern. Trends Infect. Dis, 2014,3:47-72.
27. Co EM, Keen EF 3rd, Aldous WK. Prevalence of methicillin-resistant Staphylococcus aureus in a combat support hospital in Iraq. Mil Med. 2011;176(1):89-93. doi: 10.7205/milmed-d-09-00126.
28. Hussein N, Salih RS, Rasheed NA. Prevalence of Methicillin-Resistant Staphylococcus aureus in Hospitals and Community in Duhok , Kurdistan Region of Iraq. Int J Infect. 2019;6(2):e89636. doi: 10.5812/iji.89636.
29. Yousef SA Al, Taha EM. Methicillin-Resistant Staphylococcus aureus in Saudi Arabia: Genotypes Distribution Review. Saudi J Med Med Sci. 2016;4(1):2-8. doi: 10.4103/1658-631x.170880.
30. Johnson AP. Methicillin-resistant Staphylococcus aureus: the European landscape. J Antimicrob Chemother. 2011; 66(Suppl 4):iv43-iv48. doi: 10.1093/jac/dkr076.
31. Yousefipour M, Rasoulinejad M, Hadadi A et al. Bacteria Producing Extended Spectrum β-lactamases (ESBLs) in Hospitalized Patients : Prevalence, Antimicrobial Resistance Pattern and its Main Determinants. Iran J Pathol. 2019; 14(1): 61-67. doi: 10.30699/ijp.14.1.61.
32. Al-azawi IHS. Detection of Extended Spectrum Beta Lactamase (ESBL) in Klebseilla pneumoniae Isolated from Urinary Tract Infections. AL-Qadisiya Med J. 2014;10(18):168-173.
33. Aka ST, Haji SH. Evaluation of multi drug resistance among extended spectrum β-lactamase-producing Escherichia coli causing urinary tract infection in Erbil City. Zanco J Med Sci. 2015;19(2):998–1004. doi: 10.15218/zjms.2015.0023.
34. Sleiman A, Abou AG, Banna H et al. Prevalence and molecular epidemiology of carbapenem-resistant Gram-negative bacilli and their resistance determinants in the Eastern Mediterranean Region over the last decade. J Glob Antimicrob Resist. 2021;25:209-221. doi: 10.1016/j.jgar.2021.02.033.
35. Jean S, Harnod D, Hsueh P. Global Threat of Carbapenem- Resistant Gram-Negative Bacteria. 2022;12(March):1-19. doi: 10.3389/fcimb.2022.823684.
36. Mo Y, Seah I, Lye PSP et al. Relating knowledge, attitude and practice of antibiotic use to extended-spectrum beta-lactamase-producing Enterobacteriaceae carriage: Results of a cross-sectional community survey. BMJ Open. 2019;9(3):e023859. doi: 10.1136/bmjopen-2018-023859.

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ORIGINAL ARTICLE

# TRANSFORMATION CHANGES OF PUBLIC HEALTHCARE WITHIN EPIDEMIOLOGICAL RISK MANAGEMENT LEVEL

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## ABSTRACT

**The aim:** Establishing priority areas for the development of the public health system in conditions of high risks of epidemic threats

**Materials and methods:** Systemic analysis of approach methods to the public health transformation, regarding epidemiological risks management, as well as bibliosemantic, analytical, epidemiological, sociological and experimental research meth

**Results:** The article proves effectiveness of the public health transformation by reviewing world and European experience of the centers of disease control and prevention, sociological and expert studies of preventing and management of real epidemic threats, as well as introduction of the infection control preventive measures

**Conclusions:** The epidemiological welfare of any country is based on systemic monitoring within the modern centralized data arrays; analysis of the infectious and non-infectious morbidity; prediction, detection and quick management of emergencies; assessment of the measure effectiveness; staffing reference-laboratories with high-qualified personnel, facilities and using modern study methods; training public health specialists, who will enhance public health transformation processes within the preventive functions

**KEY WORDS:** public health, epidemiological risks, transformation changes, centers of control and disease prevention

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## INTRODUCTION

The new challenges, represented with the world emergency that affected the society, science and medical practice, were caused by the pandemics of acute respiratory disease COVID19, which set new tasks for the healthcare epidemiological risks management [1]. High virulence and mutagenic activity of the SARS-Cov-2 as well as absent human immune response led to significant infection spread among various age groups, including children [2]. The quick COVID19 spread and its high mortality stipulated for the population healthcare priority in all healthcare policy directions, and the healthcare preventive potential should be expanded by introducing new reforms nowadays.

The epidemiological supervision has obtained a new significance due to increase in number of factors which affect the human health. The overall population health is affected by combination of specific life factors, which determine possibilities of the body pathological processes development and intensification. The situation was clearly outlined during the COVID19 epidemics: chronic patients more often contracted the disease, followed by complicated disease course and lethal outcomes.

Strict control over sanitary laws execution in infectious diseases prevention requires shift of epidemiological supervision role in the healthcare towards its prominent significance, with distinct coordination and operative reaction onto epidemiological threats [3]. Providing epidemiological welfare and population health priority in the country as a basis for national security and economic development is an issue of primary importance nowadays.

## THE AIM

The aim of the article was to detection of the healthcare development priority directions under high epidemiological risks.

## MATERIALS AND METHODS

The studies of 2021-2023 were dedicated to establishment of the healthcare advocacy component regarding national needs as well as the European and international experience. The study used the biblio-semantic, analytical, epidemiological, sociological and experimental methods, according to the author's program (approved

by the ethical commission of P.L. Shupik NMAPE on 11.01.2021, protocol № 1; scientific boards of P.L. Shupik NMAPE on 27.01.2021 , protocol № 1). The program was aimed at defining the approach methods to shaping the advocacy and social mobilization competences in the healthcare specialists as well as detecting the intra-sectoral and intra-department activity mechanisms within the healthcare preventive branch. The systemic analysis method was used for defining approach methods to the healthcare transformation, the biblio-semantic – for analysis of the healthcare system world development experience, sociological – for defining functions of the disease control and prevention centers within the healthcare; expert assessment method – for assessment of changes in the healthcare functions during transformation. Using the epidemiological studies, the authors defined basic factors of the professional pathologies, including those among the medical staff, in various branches of production. The statistical method was used for the study data treatment, in order to calculate the mean average and error, with the software OpenEpi, package R, Excel with unlimited non-commercial license [4, 5].

The sociological and expert study sample includes 76 specialists of State Institution "Center of disease control and prevention" in 5 regions of Ukraine.

## RESULTS

The current healthcare conditions stipulate for the timely foundation of regional centers of Disease Control and Prevention (CDCP), with composed plan of communication actions between various sectors and departments regarding the prevention and quick responding onto challenges, due to cooperation with the departments and structures of various ministries (education, environmental protection, State Consumer's Service, State Service of Emergencies, State Labour Service, etc.) [6, 7].

The Ministry of Health of Ukraine Center of Public Health is a main expert establishment which provides coordination and academic supervision of epidemic service in the regional CDCP. An important component of the epidemiological care is indication and identification of the infectious diseases causative agents, studying the cause-effect disease factors, timely detection, prevention and management of risks in the healthcare. The significant Healthcare function is provided by development of the modern information asset for monitoring of the environment data and their quality, human life activity condition, analysis of information aimed at detection of health risks and assessment of epidemiological welfare; producing evidence-based programs of prevention and education as well as composing standard documents.

The cause of disrupted epidemiological welfare in Healthcare of Ukraine nowadays is a group of biological factors (63.64 ± 5.48 %, $P<0.05$). Our country has recently applied the methods of prevention and management of COVID-19 disease (Table I). The CDCPs function, following the best world practices, which is an important point in strengthening the healthcare preventive strategy. Implementation of the international sanitary regulations, experience of prevention and control over the non-infectious and infectious diseases by information exchange will reduce expenses for reforms.

The practice activity of the CDCPs is occupied with the infections control as follows ( See table II).

The intersectoral and interdepartment relations are important for the timely management of the infection prevention in the country (See table III).

In order to solve the tasks of preventive medicine under the biohazard emergency conditions, the CDCP specialists showed appropriate medical competences in 54.55 ± 5.67 % of cases. A systemic epidemiological health and welfare supervision represents the basic function: diagnostics of infection and identifying the causative agent (70.13 ± 5.22 % of practically applied cases). The preventive measures depend on the analysis of obtained information about infections: control of immunizations among various population groups is impossible without reliable data on the state level, so the information fund of the departments must be generalized and concentrated in the Center of Public Health. This idea was supported by 71.43 ± 5.15 % experts. Noteworthy, the anti-epidemic services of the CDCP represent 75.32 ± 4.91 % of all their services.

The quality of medical service refers to the main factors affecting the population health (77.92 ± 4.73 % of expert opinions). Laboratory studies were included to the population health characteristics in 67.53 ± 5.34 % of cases.

As for promotion within the healthcare, the experts most often emphasized healthy lifestyle (77.92 ± 4.73%) and healthy life environment (75.32 ± 4.91 %), medical education (84.43 ± 4.13 %) as well as informing population about the health risks (71.43 ± 5.15 %).

The Public Health is related to the social and economic programs of country development, demographic structure, morbidity character and existing management system [8-10].

## DISCUSSION

The review of the scientific sources regarding the foundation and development of the Public Health system in various countries defines a basic leading force which caused further progress and perfection in the popula-

**Table I.** Measures of CDCP aimed at prevention and management of the epidemiological welfare risks

| Measures | Frequency , % ($P \pm m_p$) |
|---|---|
| Preventing the risk | 70.13 ± 5.21 |
| Holding laboratory studies and identifying the causative agent | 80.52 ± 2.57 |
| Prevention of infection spread | 74.03 ± 4.99 |
| Health education | 73.73 ± 5.07 |
| Assessment of the risk eradication | 54.55 ± 8.67 |

**Table II.** Infectious control within the CDCP

| Infectious control types | Frequency, % ($P \pm m_p$) |
|---|---|
| Management | 68.83 ± 5.18 |
| Prevention | 79.22 ± 7.62 |
| Anti-epidemic | 75.32 ± 4.91 |
| Epidemiological analysis | 83.17 ± 4.26 |

**Table III.** Intrasectoral relations in the CDCP

| Department | Frequency, % ($P \pm m_p$) |
|---|---|
| Healthcare | 93.5 ± 2.80 |
| State Labour Service | 64.94 ± 5.44 |
| State Consumer Service | 72.73 ± 5.08 |
| Veterinary medicine | 41.56 ± 5.62 |
| Education | 53.25 ± 5.69 |
| Executive power | 88.31 ± 3.66 |

tion healthcare, aimed at reducing people health risks and protecting state biosafety parameters [11, 12].

In the USA the CDC was founded on 1.07.1946 [13]. Fortification of national safety in healthcare and its protection from infectious diseases, as well as the communities support compose the main factors of the centers activity. The CDC functions include: registering the morbidity, statistical and epidemiological analysis, predicting the environmental conditions, introducing the infectious diseases treatment and prevention methods, training staff(including the non-USA residents), and conducting the studies. The USA CDC is responsible for the permanent epidemiological control in the country and the world. If morbidity level in the USA increases, or any similar threat is traced, an "emergency" group is formed, which, after the thorough analysis, proposes the subsequent actions, including the studies. The CDC specialists are immediately sent to any region of the world where the new dangerous epidemics arise.

The public progress globalization contributes to the infectious diseases spread, as they present appropriate problems for the healthcare in the whole. Common challenges for most countries for their management need the motivated transformation of the Public Health. Modern conditions require intensification of state services in healthcare, concentrated on prevention and preventive control, presenting functional opportunities of the healthcare and its institutions as well as the primary establishments. The participation of the communities and population in poly-institutional coordination mechanisms of the health-related social mobilization, combined with training specialists of preventive medicine would be supportive for its implementation [14].

In European countries the inter-branch programs favoring health are implemented, which includes disease prevention, increasing longevity and improving the health by coordinated efforts of the society, organizations, public communities and certain people [11, 12, 14-17]. The European Center on Disease Prevention and Control is an independent organ of the European Union, the mission of which is fortifying the European defense against infections. It was founded in 2005 and is situated in Stockholm(Sweden). Its foundation was triggered by the atypical pneumonia outbreak.

The economic EU integration and open borders as well as increase in cooperation in public health protection became important directions of the center activity. The Center functions as a matrix structure: with the main scientist office, supervision and support of response operations, potential of the healthcare and relations protection, management of resources and coordination, and the information and communication

technologies. The main scientist office deals with 8 programs on diseases, microbiology coordination and the Coordination Council scientific board. Its network includes 28 countries – the EU members and 3 countries: Iceland, Liechtenstein and Norway. The center's staff is represented with 300 people, its year budget makes up more than 50mln euro.

In conclusion, it is necessary to state that the COVID 19 pandemics in Ukraine defines gaps in quick coordination and operative responding. This is why foundation of the CDCP system in Ukraine will favor development of the epidemiological control system in regions.

## CONCLUSIONS

1. Providing the epidemiological welfare of the country is based on a systemic monitoring and analysis of the infectious and non-infectious morbidity of the population, environmental factors, defining the health risks factors, predicting and preventing, timely detection and quick management of emergencies, as well as assessment of the conducted activities effectiveness.
2. The intersectoral and interdepartment coordination on issues of the population health protection, foundation of modern strong informational technical system with common centralized health information asset and the statistical analysis information system will help to solve the health policy issue.
3. The main task of the infectious control nowadays if staffing of the reference-laboratories with high-qualified personnel, facilities and modern study methods, accepted internationally.
4. Modern training of the preventive medical personnel and epidemiologists is an urgent issue, as it will provide the preventive healthcare branch with the specialists.
5. Composing the real practice programs of the sanitation education, aimed at improving the population medical awareness, will intensify transformation of the public healthcare within the preventive mission.

## REFERENCES


1. Law of Ukraine of March 17, 2020 № 530-IX «On Amendments to Certain Legislative Acts of Ukraine Aimed at Preventing the Occurrence and Spread of Coronavirus COVID-19». 2021. https://zakon.rada.gov.ua/laws/show/530-20#Text [date access 05.12.2022]
2. Shyrobokov VP. Coronavirus and other emergent infections. Ukrainian Medical Journal. 2020; № 2 (136): 31-33.
3. Order of the Ministry of Health of Ukraine 30.07.2020 № 1726. Registered in the Ministry of Justice of Ukraine 30.12.2020 for № 1332/35615 «On approval of the Procedure for accounting, reporting and epidemiological surveillance (surveillance) of infectious diseases and the List of infectious diseases, subject to registration». 2020. https://zakon.rada.gov.ua/laws/show/z1332-20#Text [date access 05.12.2022]
4. Antomonov MIu. Mathematical processing and analysis of medical and biological data. Kyiv «Malyi druk». 2006, p.558.
5. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06 [date access 05.12.2022]
6. Resolution of the Cabinet of Ministers of Ukraine of February 17, 2021 № 106 «On Amendments to the Resolution of the Cabinet of Ministers of Ukraine of November 27, 2019 № 1121». 2021. https://zakon.rada.gov.ua/laws/show/106-2021-п#Text. [date access 05.12.2022]
7. Resolution of the Cabinet of Ministers of Ukraine of November 27, 2019 № 1121 «On approval of the Procedure for the use of funds provided in the state budget for the implementation of the program» Public Health and measures to combat epidemics». 2019. https://zakon.rada.gov.ua/laws/show/1121-2019-п#Text [date access 05.12.2022]
8. Khomenko IM., Ivakhno OP, Pershehuba YaV, Piven NV. Prospects for the training of medical personnel in the public health system. Medychni perspektyvy. 2021;26(2):141-146. doi: 10.26641/2307-0404.2021.2.234655.
9. Khomenko IM, Ivakhno OP, Pershehuba YV et al. Management of institutional and preventive activities in the public health system of Ukraine. Wiad Lek. 2021;74(5):1237-1240.
10. Gulchii OP, Khomenko IM, Zakharova NM et al. Methodological approaches to upgrading public health professionals training competency-based model in Ukraine. Wiadomosci Lekarskie. 2018;71(7):1336-1341.
11. Dzau VJ, McClellan MB, McGinnis JM. et al. Vital Directions for Health and Health Care: Priorities for 2021. Health AFF (Millwood). 2021; 40(2):197-20. doi: 10.1377/hlthaff.2020.02204.
12. Hruzieva TS, Melnyk VV. Public Health Control Organization in the United States and the European Region. Ukraine. The health of the nation. 2015; 2:96-103.
13. Eckelman MJ, Sherman J. Environmental Impacts of the U.S. Health Care System and Effects on Public Health. PLoS One. 2016;11(6): e0157014. doi: 10.1371/journal.pone.015701.
14. Ebi KL. Environmental health research needed to inform strategies, policies, and measures to manage the risks of anthropogenic clange. Environ Health. 2021;20:109. doi:10.1186/s12940-021-00792-1.
15. Zimmerman FJ. Population Health Science: Fulfilling the Mission of Public Health. Milbank Q. 2021; 99 (1):9-23. doi:10.1111/1468-0009.12493.

16. Batra Sonal MD, Orban Julie MPH, Guterbock TM et al. Social Mission Metrics: Developing a Survey to Guide Health Professions Schools, Academic Medicine: December. 2020; 95(12): 1811 – 1816. doi:10.1097/ACM.0000000000003324.
17. Kochler K, Latshaw M, Matte T et al. Building Healthy Community Environments: A Public Health Approach. Public Health Reports. 2018; 133(1):35S-43S. doi: 10.1177/0033354918798809.

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ORIGINAL ARTICLE

# STUDYING ANXIETY AS A PREDICTOR IN STUDENTS TO PREDICT THE DEVELOPMENT OF BURNOUT

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## ABSTRACT

**The aim:** Research of a subjectively significant personal social-psychological and individual-psychological characteristic – anxiety in students, which can be a predictor of the occurrence of EBS. To identify the scale and prevalence of the specified predictor in the student environment.

**Materials and methods:** A survey was conducted among 556 respondents. The survey was conducted according to the Spielberg-Hanin Anxiety Scale, which is available online with automatic scoring and retrieval of results. The test involves determining the levels of situational (reactive) and personal anxiety. To achieve the goal of the research, a set of methods was used: a systematic approach, a sociological method, and a medical-statistical method. The data are provided in the form of relative values with errors.

**Results:** Almost half of the students who participated in the study feel the influence of the anxiety factor, which increases the likelihood of emotional burnout. The "tension" phase – nervous (anxious tension) is a harbinger and "trigger" mechanism in the formation of emotional burnout. According to the results of the study, up to 50% of respondents are in the first phase of emotional burnout or have already passed it. This determines the need for preventive work with students, among whom the survey was conducted, to prevent the occurrence of emotional and, subsequently, professional burnout. The low level of anxiety, which was 8.49% ± 1.18% among respondents, needs further study, as it may indicate the suppression of experiences by consciousness and hidden anxiety, which is an even more provoking factor for emotional burnout than a high level of anxiety.

**Conclusions:** Empirical research has established a significant prevalence among students of a high and medium level of personal characteristic – anxiety, which has signs of a negative internal factor and can be a predictor of the development of EBS.

**KEY WORDS:** stress, emotional burnout syndrome (EBS), anxiety, predictor, personal characteristic, individual factor

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## INTRODUCTION

Burnout is considered a form of professional stress. [1-4] According to the International Classification of Diseases (ICD-X) (ICD-10), the syndrome of emotional burnout is assigned to the rubric Z73 – "Stress associated with difficulties in maintaining a normal lifestyle." The World Health Organization defines occupational stress as a "disease of the 21st century" because it is present in any profession, and its spread has reached epidemic proportions, affecting workers of various professions and fields of activity.

This medical problem has devastating consequences for society, professional and family relationships. It is based on mental and behavioral changes. Emotional burnout syndrome (EBS) is found in more than 40% of public sector workers in the US and Canada, 51% of nurses and paramedics, 54% of doctors, and 57% of teachers. [2].

According to statistics for 2019, about 210 million people in the world suffer from burnout syndrome, which is approximately 5-7% of the entire population. According to the results of a July 2020 survey conducted by FlexJobs and Mental Health America (MHA), 75% of workers have experienced burnout, and 40% of respondents believe that this is a direct result of the coronavirus pandemic.

Today it is known that the development of EBS is dependent on the activity (study or work) of a person, which leads to despair. As a rule, there is a dissonance between personal contribution to work and the received or expected reward.

Most often, EBS develops in people who, by their profession, communicate a lot. This category includes doctors, nurses, teachers, social workers, and many other professions. It is known that the percentage

of EBS among doctors and, unfortunately, students, in particular doctors, can reach up to 50% [5, 6]. The existence of the problem of EBS among students is confirmed by many domestic and foreign scientists [6-10]. Moreover, the percentage of EBS in this category can reach 45-52.8% [5, 6]. Factors that negatively affect the development of emotional burnout in the student environment are social insecurity, dissatisfaction with the learning process, the presence of social comparison, unfairness in evaluation, the unfulfillment of expected dreams regarding education and the future profession, difficulty in communication, and the presence of competition. All this leads to a decrease in motivation in learning with certain consequences. At the same time, it is known that motivational factors are leading to the successful adaptation of students to study, and also that high motivation to study is a safeguard against emotional burnout. This motivation can be reduced when applicants submit documents for admission to different universities at the same time, which sometimes leads to a random choice of a future profession, and not according to their desire. In this case, there is no consistency of the individual typological features of the personality with the choice of the future [8].

Scientists have discovered the dependence of emotional burnout (EB) in students on the peculiarities of the motivational, semantic and communicative spheres. Thus, in individuals who are afraid of failure and have no hope of success in their activities, EB is formed faster. This is especially noticeable during the formation of the resistivity phase. There is a direct correlation between «motivation to prevent failure» with the development of «exhaustion». «Communicative motive» is considered to be the most important factor in the formation of burnout [6]. The conclusion of the past, dissatisfaction with the present, and one's achievements in persons with EB concentrate attention on negative experiences and vice versa, satisfaction with one's life reduces the risk and difficulty of developing emotional burnout [8].

To date, the study of EBS does not have results in the form of a single system of psychological determinants of this phenomenon. Factors causing EB are grouped according to signs of professional activity and individual characteristics. Individual factors include age, gender, education, marital status, work experience, and personal characteristics (endurance, locus of control, resistance style, self-esteem, anxiety, neuroticism, and extraversion). Sometimes a third group of factors is singled out, where meaningful aspects of activity are considered independent. These can be – working conditions, work overload, duration of the working day, the content of work, the number of patients or students and, conversely, the difficult relationship between the student and the teacher, the complexity of their problems, the depth of contact with patients, students, teachers, participation in decision-making, feedback connection [11]. If some foreign researchers consider the presence of organizational problems to be the main prerequisite of EB, other researchers prefer personal characteristics – low self-esteem, high neuroticism, anxiety, and externality [12]. According to some scientists, nervous (anxious) tension is a harbinger, and at the same time acts as a "starting" mechanism in the formation of EB. The dynamic nature of the tension is indicated by the constancy, which is exhausting and the strengthening of psychologically traumatizing factors. Considering that the first "phase" or "stage" of EB is very anxious stress-anxiety, it can be assumed that high anxiety is not just an influencing factor, but its presence indicates the initial phase of EB in a person. This is confirmed by the authors of the dynamic model.

The occurrence of burnout depending on personal characteristics should be considered from the standpoint of their complex impact on the individual. The five-factor personality model proposed by P. Costa and R. McCrae is most often used in research on this issue. Personal factors affecting the appearance of emotional burnout include anxiety, emotional reactivity, and negative affect [13]. Scientists point to a positive relationship between burnout and aggressiveness and a negative relationship between burnout and a sense of group cohesion. This negative relationship between burnout and social support can be seen in helping professions. Stressful situations provoke the activation of anxiety symptoms in a person. There is a direct dependence of this activation on the number of stressful situations. That is why psychologists, psychiatrists, sociologists, and medical workers point to the necessity and urgency of researching the phenomenon of anxiety [12].

Anxiety is defined as a person's experience of a state of emotional discomfort caused by the expectation of an unfavorable development of events or a premonition of possible danger. [8].

Given that anxiety is a basic component in intra-individual personality development, it has a strong influence on professional and academic success. It is necessary to distinguish when anxiety is a natural feeling in front of any incomprehensible circumstances (unknownness, threat, danger) and when anxiety is inadequate, mostly an intense reaction to some life circumstances or interpersonal manifestations. Scientists interpret the causes and manifestations of anxiety in different ways. Thus, L. Burlachuk says that anxiety is a person's tendency to experience and worry, and the main thing is that such a person has a low threshold for

anxiety. R. Nemov considers anxiety to be a personal trait, which is characterized by an increase in the level of anxiety, anxiety, and fear in various non-standard conditions and situations. V. Davydov also considers anxiety as an individual property, quality, and feature. He considers anxiety to be a manifestation of worry, experiencing both negative thoughts and feelings and fear. The scientist points out that such an experience can also be characteristic of situations where there is no threat or danger. Summing up the opinion of scientists, R. May claimed that the constructs of personality anxiety are: a psychological property; an individual feature of an individual; the individual's tendency to experience anxiety; a state of high tension and anxiety. Z. Freud distinguished between the concepts of «fear» and «anxiety». He considered anxiety a reaction to an unknown (sometimes groundless) danger and fear a reaction to a real danger. V. Merlin focused the attention of scientists on the emotionality of anxiety and believed that it would manifest itself in various threatening situations. And his colleague, the American psychologist K. Izard, considers anxiety to be a combination of negative emotions, for example, anger, sadness, and fear [14]. According to Ch. Spielberger, anxiety is an emotional state or reaction, where there is intensity, variability, perceived unpleasant experiences, fears, and activation of the autonomic nervous system [15].

Anxiety as a dominant symptom of neurotic disorders can take different forms. Anxiety that manifests itself in various phobias is called phobic. It is characterized by isolation and has a strong intensity of manifestation. There is a desire to avoid stimuli that carry a threat and danger. Panic anxiety is also called paroxysmal – it manifests itself as a momentary reaction, usually in the form of episodes, more often in a person who has panic disorders. Generalized anxiety is manifested in general anxiety disorder of the personality. As a rule, these manifestations are intense and obsessive. Somatophoric personality disorders are characterized by anxiety, which is manifested in a person's complaints about somatic disorders, but this is not confirmed by a medical examination. Reaction to unexpected situations, post-traumatic stress disorders, as well as disorders that are associated with maladjustment is considered anxiety that occurs as a response to a stressful situation.

Secondary anxiety is distinguished, which has symptoms of mental and somatic disorders and can be a reaction to the use of psychoactive and psychotropic substances [12].

The state of anxiety, as a rule, is accompanied by tension, nervousness, and various fears, especially the fear of failure and unmotivated restlessness. Psychologists consider anxiety to be a leading component in the personality structure. Elizabeth Römer and Thomas Borkovcs point out that disturbing thoughts in the brain of an individual tend to move continuously: one disturbing thought is replaced by the next and so on in a circle [16].

## THE AIM

Study of a subjectively significant personal social-psychological and individual-psychological characteristic – anxiety in students, which can be a predictor in the occurrence of EBS. To identify the scale and prevalence of the specified predictor in the student environment.

## MATERIALS AND METHODS

The scientific research was carried out based on the O.O. Bogomolets National Medical University and T.G. Shevchenko Kyiv National University. A survey was conducted among students using the anonymous questionnaire method. The scope of the study was 610 respondents. At the same time, the results of the questionnaires of 54 respondents were not taken into account due to insincerity in the answers. Insincerity in answers was determined by the scale of lies according to the Eysenck method (EPI, option B).

The primary material was 556 questionnaires of sociological research based on the version of the standardized questionnaire for the analysis of indicators of personal anxiety according to the Spielberg-Hanin method of RPAS (reactive and personal anxiety scale). This questionnaire consists of 20 statements that refer to anxiety as a state (state of anxiety, reactive or situational anxiety) and 20 statements to define anxiety as a disposition, a personality trait (trait anxiety). The Spielberger-Hanin scale of reactive and personal anxiety is the only method that allows differential measurement of anxiety both as a personality trait and as a state.

228 surveyed students study at O. O. Bogomolets National Medical University and 328 – at T. G. Shevchenko Kyiv National University, which is 41.01% and 58.99%, respectively, of all surveyed respondents.

To achieve the goal of the research, a complex of research methods was used, the main of which was the systematic approach. The sociological method was used for the analysis of documents and questionnaire survey with notification of the purpose and task of the study, with the mandatory obtaining of prior oral voluntary consent to participate in anonymous questionnaires. The medical-statistical method was used at several stages of the research: at the first stage, the purpose of the research was formulated, the research plan and program were drawn up, the object and the observation

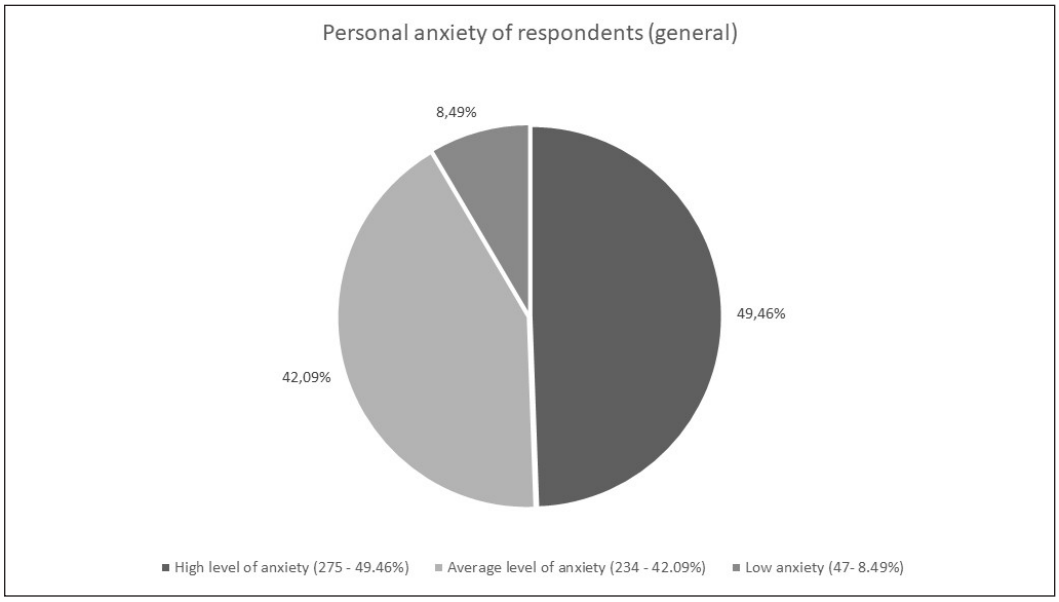


**Fig. 1.** Personal anxiety of respondents (general)

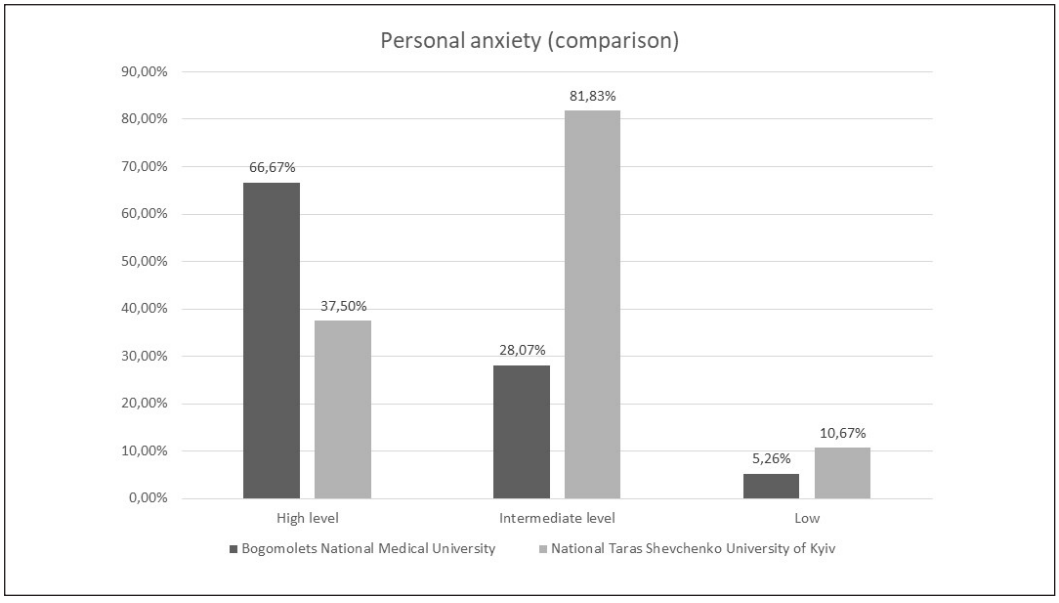


**Fig. 2.** Personal anxiety (comparison)

unit were determined; at the second stage, the information collection was carried out; at the third stage – the grouping of the received data according to the relevant characteristics according to the research program and compilation of statistical data; at the fourth stage, the analysis of the obtained results was performed.

The data are provided in the form of relative values with errors [1].

## RESULTS

Why do young people who are students lose interest in learning? Why is the motivation to study a profession that should become the basis of a lifetime, the foundation of well-being becomes less than in some other circumstances? Explanations can be different. Psychologists, most often, explain this by the development of burnout and indicate that anyone can suffer from this disease.

To study this phenomenon, and its possible development and distribution among students, we conducted a study of personal characteristics, in particular anxiety, which can be a predictor in the genesis of burnout.

The research took into account the results of a survey of 556 people, of which 228 people study at the O. O. Bogomolets National Medical University and 328 at the T. G. Shevchenko Kyiv National University, which is 41.01% and 58.99% accordance. The data are presented in Table I.

According to the results of the study, when analyzing indicators of personal anxiety according to the Spielberg-Hanin method, it was found that the factor is present in all 556 studied students, 47 of them have a low level of personal anxiety (PA), which is 8.49% ± 1.18%, 234 people have an average the level of PA,

**Table I.** Number of respondents in higher educational institutions

| № | Respondents | Quantity | Quantity |
|---|---|---|---|
| 1. | Bogomolets National Medical University | 228 | 41,01% |
| 2. | National Taras Shevchenko University of Kyiv | 328 | 58,99% |
| 3. | Total number | 556 | 100,00% |
| 4. | Interviewed by the whole method of guestioning | 610 | |
| 5. | Unanswers | 54 | |

**Table II.** Indicators of personal anxiety

| Personal anxiety | High level | | Intermediate level | | Lov | |
|---|---|---|---|---|---|---|
| | Quantity | % | Quantity | % | Quantity | % |
| Bogomolets National Medical University | 152 | 66,67% ±3,12% | 64 | 28,07% ±2,98% | 12 | 5,26% ±1,48% |
| National Taras Shevchenko University of Kyiv | 123 | 37,5% ±2,67% | 170 | 51,83% ±2,76% | 35 | 10,67% ±1,7% |
| Total number | 275 | 49,46% ±2.12% | 234 | 42,09% ±2.09% | 47 | 8,49% ±1.18% |

**Table III.** Indicators (intensive and extensive)

| Students | Intensive indicator (number of cases per 100 students) | Extensive indicator, % |
|---|---|---|
| Bogomolets National Medical University | 66.667 | 47.649 |
| KNU them. T.G. Shevchenko | 17.105 | 12.226 |
| Total | 56.140 | 40.125 |

which is 42.09% ± 2.09%, and 275 students who have a high level of PA, which is 49.46% ± 2.12%.

The data are presented in Table II.

It was found that almost half of the respondents feel a significant influence of the factor that increases the probability of emotional burnout in the mentioned students. This can be seen in the presented diagram (Fig. 1).

A comprehensive study of the phenomenon of anxiety gives reason to assert its significant typological variability, therefore, when analyzing the obtained result, it should be remembered that the low level of PA, which was 8.49% ± 1.18% of the respondents, in some cases may indicate the displacement of experiences by consciousness and latent anxiety, which is an even more provoking factor for emotional burnout than high levels of anxiety. At the same time, according to a comparative analysis of the content of anxious experiences with different intensities of anxious states young people with a reduced level of anxiety are noted to have a preserved positive self-image and the preservation of their own «I» in the social environment.

When examining the dependence of the predictor development in respondents on external factors and comparing the obtained indicators of PA among students studying at different universities, it was established that the indicators of the prevalence of PA differ significantly. Thus, among the students of the T. G. Shevchenko Kyiv National University, a high level of PA was present in 123 people, which is 37.5%, against 152 students – 66.67% at the O.O. Bogomolets National Medical University, the average level of PA was found in 170 students – 51.83% of T. G. Shevchenko Kyiv National University against 64 students – 28.07% of O. O. Bogomolets National Medical University, and a low level of PA was found in 35 students – 10 .67% of T.G. Shevchenko Kyiv National University. At the same time, among the students of the O.O. Bogomolets National Medical University, 12 people with a low level of PA were found, which amounted to 5.26%. The data are presented in diagrams (Fig. 3 and Fig. 4).

Having analyzed indicators of the level of PA among students of two universities, we found that the share of high anxiety levels among medical students is 1.8 times higher (by 29.17%) than among students of T. G. Shevchenko KNU. Also, in the medical university, there is 2.03 times (by 5.41%) smaller share of low level of PA.

An intensive indicator was calculated to characterize the frequency, level, and spread of anxiety among students.

To study specific gravity, structure, and distribution, an extensive indicator of personal characteristics was calculated.

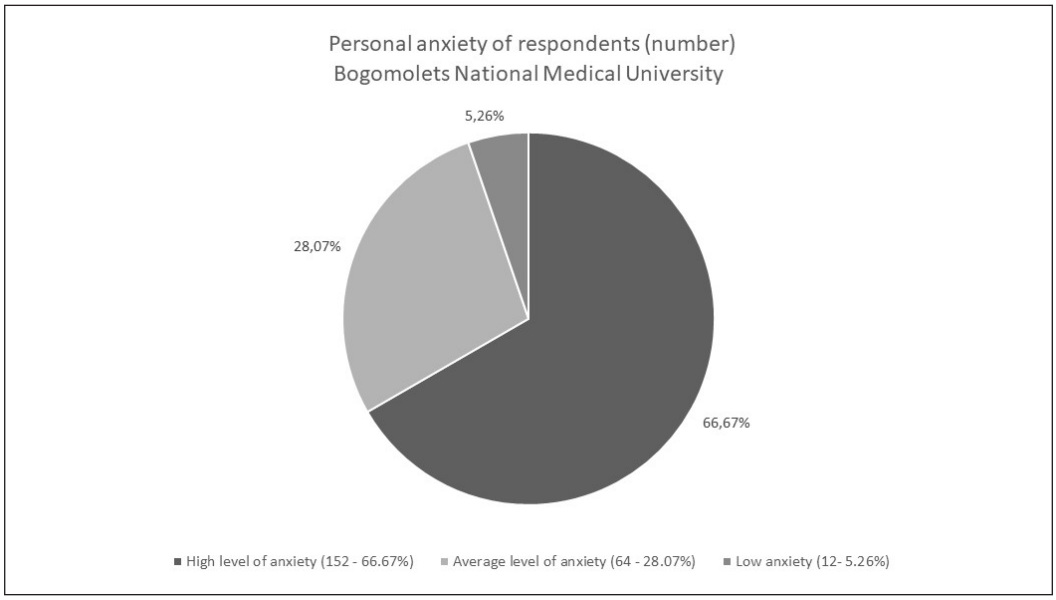


**Fig. 3.** Personal anxiety of respondents (number), National Taras Shevchenko University of Kyiv

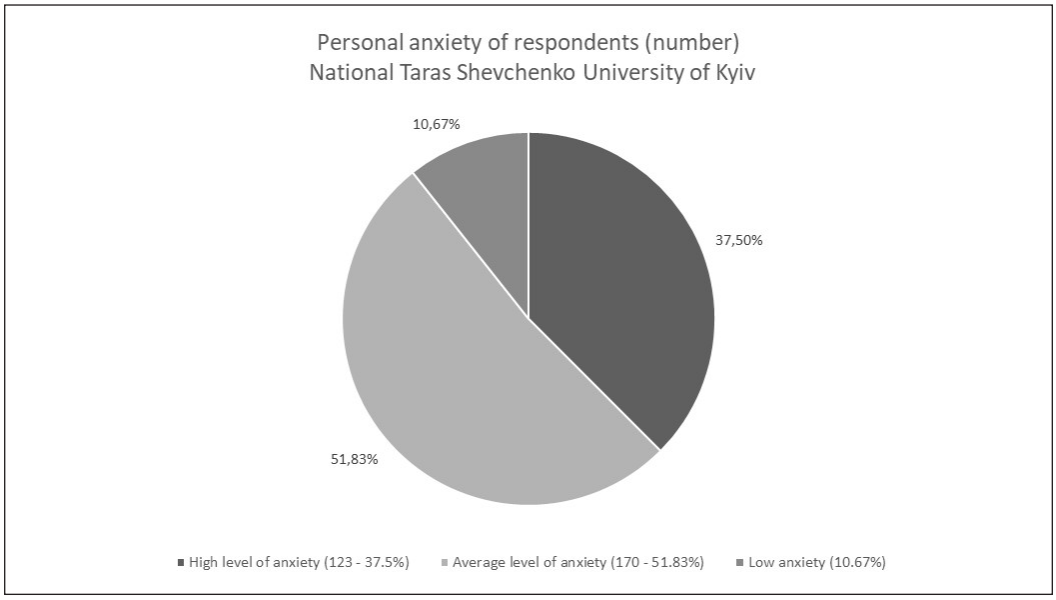


**Fig. 4.** Personal anxiety of respondents (number), Bogomolets National Medical University

According to the calculation data, it can be seen that among the students of O. O. Bogomolets NMU, personal anxiety occurs more often than among students of T. G. Shevchenko KNU.

## DISCUSSION

According to V.V. Boyko [17], the emotional burnout syndrome includes three phases: stress, resistance, and exhaustion. Each phase includes 4 symptoms. The "tension" phase – nervous (anxious tension) is a harbinger and "trigger" mechanism in the formation of emotional burnout. So, according to the obtained data, we can assume that half of the respondents are in the first phase of emotional burnout or have already passed it. This determines the need for preventive and explanatory work with students, among whom a survey was conducted to prevent the occurrence of emotional and, subsequently, professional burnout.

The obtained results proved that the influence of the internal factor – personal anxiety on personality among students is quite widespread. A higher prevalence and intensity of PA manifestation among medical students than among students of T. G. Shevchenko KNU. Therefore, it is possible to assume the opinion that medical students are more prone to emotional burnout under the influence of the mentioned factor.

Studying the phenomenon of anxiety among students, we considered it as subjective discomfort of the individual, which harms the interaction of the individual with others and the attitude towards oneself. This was due to the research of Y. Zajcev and A. Hvan [18], who emphasize the importance of considering anxiety in the context of the analysis of neoplasms and age crises, and

A. Gormin, who believes that an individual at a young age tends to partially return to an already experienced crisis and, in some cases, experiences it again [1], which, in our opinion, has a destabilizing character for the psychological health of the individual and can act as a predictor for the development of emotional burnout.

## CONCLUSIONS

Our empirical research proves the presence and significant prevalence of the factor – anxiety, which has negative signs on the student environment. According to scientific data, the mentioned negative factor, especially at a high and medium level, can be a predictor of EBS among students.

Manifestations of emotional burnout syndrome in students include decreased motivation to study, dissatisfaction with the learning process, conflicts with colleagues and teachers, chronic fatigue, exhaustion, nervousness, unreasonable excitement, boredom, longing, irritability, and distancing from colleagues and relatives. The mentioned symptoms in patients do not appear at the same time and do not appear with the same force, there are always individual manifestations and variations because EBS is a reaction of an individual personality. The selected method, which was used to detect the level of anxiety among students, allowed us to establish that medical students studying at the O.O. Bogomolets National Medical University feel the influence of a negative internal factor more than students studying at T.G. Shevchenko Kyiv National University. The reason for such a significant effect has not been established. Since it is known that nervous (anxious) stress is created by a chronic psycho-emotional atmosphere, a destabilizing environment, increased responsibility, and the complexity of the contingent, there is a need to study external factors that influence the development of the predictor in students of higher educational institutions.

Features of the possible manifestation and prevalence of internal risk factors of EBS are the basis of unhealthy behavior among student youth and indicate the need for a comprehensive approach to its prevention, timely detection, and the need for the development and application of modern adequate methods, forms and methods of prevention.

## REFERENCES


1. Gruzeva TS. Biostatistics: textbook. Vinnytsia: Nova Kniga. 2020, p.384.
2. Vodopyanova NE, Starchenkova ES. Sindrom vygoraniya: diagnostika i profilaktika [Burnout syndrome: diagnosis and prevention]. Moskva: Urayt. 2017, p.343 (In Russian).
3. Maslach C, Leiter MP. Understanding the burnout experience: recent research and its implications for psychiatry. World Psychiatry. 2016; 15(2): 103-111. doi: 10.1002/wps.20311.
4. Maslach C, Schaufeli WB, Leiter MP. Job burnout. Annual review of psychology. 2001; 52 (1): 397-422. doi: 10.1146/annurev.psych.52.1.397.
5. Dyrbye LN, Massie FS, Eacker A et al. Relationship between burnout and professional conduct and attitudes among US medical students. JAMA. 2010; 304(11): 1173-1180. doi:10.1001/jama.2010.1318.
6. Rotenstein LS, Torre M, Ramos MA et al. Prevalence of burnout among physicians: a systematic review. JAMA. 2018; 320 (11): 1131-1150. doi:10.1001/jama.2018.12777.
7. Vashaka T, Tukayev S, Palamar B et al. The Alexithymia correlation between individual-typological properties, emotional sphere and mental states of personality. Clinical and preventive medicine. 2019; 4 (9-10). doi: 10.31612/2616-4868.4(10).2019.04.
8. Tukaiev SV, Vasheka TV, Zyma IG. Psychological and neurophysiological aspects of the emotional burnout development. Actual aspects of internal medicine. Collective scientific monograph. Novosibirsk: Publishing House. «SibAK». doi: 10.13140/RG.2.1.2429.3845.
9. Tukaev SV, Dolgova EN, Vasheka TV et al. Individual'no-psihologicheskie harakteristiki uchashchejsya molodezhi, zanimayushchejsya raznymi vidami sporta [Individual and psychological characteristics of students engaged in different sports]. Sportyvna medytsyna i fizychna reabilitatsiia, 2017; 1: 64-71.
10. Reis D, Xanthopoulou D, Tsaousis I. Measuring job and academic burnout with the Oldenburg Burnout Inventory (OLBI): Factorial invariance across samples and countries. Burnout Research. 2015; 2(1): 8-18. doi: 10.1016/j.burn.2014.11.001.
11. Draga TM, Myalyuk SP, Krynytska IYa. Osoblyvosti syndromu emotsiinoho vyhorannia u medychnykh pratsivnykiv [Features of emotional burnout syndrome in medical workers]. Medsestrynstvo. 20176 p. 3. (in Ukrainian).
12. Andrushko JS. The genesis of personality anxiety as a leading emotional component. A question of psychology. Bulletin of the National Defense University of Ukraine. 2020; 1 (54).
13. Costa PTJr, McCrae RR. Professional Manual. Psychological Assessment Resources. Florida. 1992, p. 237-260.
14. Izard KE. Psikhologiya emotsii [Psychology of emotions]. S-Peterburg: Piter. 2012, p.464. (in Russian).
15. Spielberger Ch. Trevoga i trevozhnost' [Anxiety and anxiety] khrestomatiya: uchebnoe posobie. S-Peterburg: Per Se. 2008, p.240. (in Russian).

16. Goulman D. Emotsiinyi intelekt [Emotional intelligence]. Kyiv: Vivat. 2019, p.512. (in Ukrainian).
17. Boyko VV. Psihoenergetik [Psychoenergetics]. S-Peterburg: Piter. 2008, p.409. (in Russian).
18. Zajcev YA. Trevozhnost' v podrostkovom i rannem junosheskom vozrastah: diagnostika, profilaktika, korrekcija [Anxiety in adolescence and youth: diagnosis, prevention, correction] M.: KGPA. 2006, 1p.12. (in Russian).

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REVIEW ARTICLE

# EFFECT OF HORMONAL CONTRACEPTION ON DEPRESSION IN WOMEN

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**ABSTRACT**

Oral contraceptives are the most frequently chosen method of preventing pregnancy in Poland. Mood changes are one of the most common reasons why young women quit therapy. Depression is a severe disorder that affects millions of people around the world. Some long-term studies suggest an increased relative risk of antidepressant use during contraceptive use compared to non-users. Scientists note an increased risk of suicide as well. Other researchers suggest that there is insufficient evidence to support these findings. Some indicate strong correlation between most hormonal contraceptives and following usage of antidepressant drugs in female adolescents. There is still no consensus in the scientific community. Analyzes of many studies provide ambiguous information. Large-scale studies with properly selected test groups and particular therapies taken into consideration are required in order to accurately assess the risk of depression and mood disorders. In this article, we try to present different approaches to the subject of effects of various types of hormonal contraception methods on depression in women.

**KEY WORDS:** hormonal contraception, depression, estradiol, progestins

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## INTRODUCTION

Almost 10 million women use oral contraceptives (OC) in the United States. 25.3 % of women determined to prevent pregnancy chose OC [1]. It is also the most common method in Poland [2].

The main goal of OC is to prevent ovulation and implantation of the ovum. It also thickens the cervical mucus. Ethinylestradiolum reduces the frequency of menstrual bleedings, blocks the growth of ovarian follicles and prevents ovulation.

Combined hormonal contraception has been proven to be effective – Pearl Index between 0.1 and 0.8. For minipill the values are between 0.5 and 5, which also proves high efficiency. The Pear Index for 52 mg levonorgestrel IUD (Intra Uterine Device) is very high – from 0.09 to 0.11, but IUD with 13.5 mg of levonorgestrel has a 0.33 ratio.

According to a WHO report from 2020 more women than men are affected by depression. One in eight females during her life will suffer from depression. The illness may occur at various ages but most often the symptoms appear in patients aged 40 or older. Twice as many women than men get depressed. According to WHO estimates approximately 350 million people all around the world might be affected by depression which is 5-6% of world population [3].

Relying on data from Institute for Health Metrics and Evaluation (IHME) of Washington University in 2017 2.8 % of Poles suffered from depression which is 0.36 percentage point more than in 2012. Compared to other EU countries Poland had the lowest percentage of clinically depressed patients. However NFZ (Polish National Health Fund) emphasized that data from each country may differ depending on mental health awareness. Citizens of countries with lower stigmatization of ill and better access to specialist care are more likely to seek for it and get included in official statistics [4].

From 2013 to 2018 an increase of patients under 18 and over 65 treated for depression was noted in Poland. In 2018 2.1% of patients were underage and 97.9% – adults. 73% of people undergoing treatment were women [5].

## THE AIM

The aim of our work is to present different approaches to the subject of effects of various types of hormonal contraception methods on depression in women.

## REVIEW AND DISCUSSION

According to Alicia A. Walf and Cheryl A. Freye estradiol (E2) has various effects on the central nervous system

[6]. Antianxiety and antidepressant-like effects may depend upon many factors, like the regimen of E2 administration and interactions with the hypothalamic-pituitary-adrenal axis. Brain targets for estradiol's effects on anxiety and depression include the hippocampus and amygdaloid body. Administration of E2, compared to placebo, subcutaneously or to the hippocampus or amygdaloid body of rats after ovariectomy decreases anxiety and depressive behavior. Estrogen receptor (ER) antagonists in the hippocampus (but not amygdala) increase those effects of naturally susceptible female rats. Studies on mice suggest that anxiety and depressive behaviors may require estrogen receptors β. It is important to investigate alleged mechanisms and brain targets for estradiol to establish, if it is possible to enhance mood without proliferative effects in reproductive tissues.

The influence of hormonal levels on mood changes in women was also researched by Baca Garcia and associates. The researchers observed higher suicide rates in women during luteal phase in comparison to follicular phase [7].

Frequency of premenstrual dysphoric disorder (PMDD) varies between 1.2 and 6.4% [8]. Women affected by it experience predictable and cyclic psychological, behavioral and somatic symptoms which escalate in late luteal phase and disappear during menstruation. They repeat throughout most fertile years. Patients reported resolution of symptoms after suppression of endogenous ovarian hormone secretion with gonadotropin-releasing hormone (GnRH)-agonist treatment or hormonal contraception. Subjects were studied both during early and late luteal phase in the same menstrual cycle. 63 women with PMDD and 53 healthy participants were included. The PMDD group had significantly lower estrogen levels in comparison to the control group in early ($p < 0.001$) and late ($p = 0.026$) luteal phase. Further analysis indicated that PMDD patients had a higher progesterone level in luteal phase than women from the control group. Those findings show that progesterone induced symptoms of premenstrual dysphoric disorder especially in women with lower levels of estrogen in the early luteal phase.

## EFFECT OF PROGESTINS ON DEPRESSION

Theresa A. Lawrie and associates conducted research in which, compared with a placebo group, women receiving a progestin injection (norethisterone enanthate depot given within 48 hours after delivery) were significantly more likely to develop symptoms of depression within six weeks of delivery [9]. Two scales were used to assess symptoms of depression, MADRS (Montgomery-Åsberg Depression Rating Scale) and EPDS (Edinburgh Postnatal Depression Scale). Relative risk (RR) of scores >9 in MADRS and >11 in EPDS for women in the progestin group in the six weeks interview was 2.556 (95% CI 1.262–5.175) and 3.035 (95% CI 1515–6.080). The disadvantage of this study is that the follow-up period is too short, only 6 weeks.

Worly's team identified 26 studies in which there was a minimal association between methods that use progestins alone and depression [10]. There was no correlation with depression in five studies with progestin-based implants and in four out of five studies with levonorgestrel IUDs. After three attempts of intramuscular injection of medroxyprogesterone acetate researchers found no difference in the incidence of depression. For two progestin-only setups, studies show no worsening of depression, while one study has found an association between different forms of progestin-containing contraception and depression.

No effect on mood change in young women using depot medroxyprogesterone acetate as a form of contraception was demonstrated in a prospective study conducted on 63 patients by N.Gupta et al. [11].

Franca Fruzzetti and Tiziana Fidecicchi [12] report that there is no strong evidence to prove a connection between hormonal contraception (HC) and depression. They studied the influence of the progesterone on the neurotransmitters, especially the GABA pathway. They believe the undesirable influence on the mood affects only adolescents or women with a history of affective mood disorder. In that case, the authors suggest using progestogens without androgen or anti- androgen effects.

Slattery et al. conducted a study in order to determine if levonorgestrel administered through an intrauterine device increases the risk of anxiety, panic attacks, sleep disorder, restlessness and if so, to what extent [13]. To achieve this researchers used data of THIN database from Great Britain. They found a connection between exposure to levonorgestrel and increased risk of anxiety (hazard ratio = 1,18; 95%) and insomnia (hazard ratio = 1,22; 95%) in women without a prior record of these events. They established no relevant connection with panic attacks or restlessness.

## EFFECT OF TWO-COMPONENT DRUGS

Another analysis [14] shows a significant mood improvement in women taking oral contraceptives with levonorgestrel and ethinylestradiol for 3 months. This was a double blind, randomized, placebo-controlled study and the main outcome measure was PGWBI (Psychological General Well-Being Index).

Cecilia Lundin and her team [15] noticed a negative influence of hormonal contraception usage on mood only during the intermenstrual phase. Previous studies focused on proving the positive effects during premenstrual phase and menstruation. It's the time when most women experience problems like painful menstruation, premenstrual syndrome, premenstrual dysphoric disorder. A lot of them expect the reduction of the symptoms by hormonal contraception [16]. Results of this randomized and controlled study suggest that taking combined oral contraceptives (COC)-containing 1.5 mg E2 and 2.5 mg nomegestrol acetate – induces mild, but significant side effects. Intermenstrual phase (according to this study) lasts from day 5 of the cycle until day 21. The biggest differences have been noted between day 6 and day 9 of the cycle- when women taking placebo had late follicular phase. In this phase women taking placebo were exposed to increased estrogen levels until it reached the preovulation level. Lower concentration of endogenous estradiol or continuous exposure to COC might have affected the results of the study.

According to Neri et al. [17], tablets with 17-beta estradiol and nomegestrol acetate have a positive effect on the mental state of women. In a prospective observational study from 2017, anthropometric indicators and body composition parameters were analyzed, as well as symptoms related to the menstrual cycle and mental well-being. Improvement was observed in the last two categories, with no effect on the anthropometric parameters.

Shen suspects that adolescent girls may be more susceptible to the effects of exogenous hormones. An interesting discovery, although confirmed only on an animal model, is that female mice respond differently to allopregnanolone during puberty. Increased activity of the α4βδ GABAR at the beginning of adolescence promotes increased anxiety reactions [18]. Another reason may be found in the social relationships of teenage girls using hormonal contraception. Early sexual initiation has been associated with and increased risk of depressive symptoms and decreased self-esteem [19]. Scientists also stated that teens with depression were more likely to choose the IUD as a method of contraception [20].

## COMPARISON OF CONTRACEPTIVE METHODS

In 2016 Charlotte Wessel Skovlund's team published the results of a prospective cohort study involving over one million women living in Denmark. Data was collected from 1995 to 2013 [21]. The study group excluded those women who had already used antidepressants before 1995, as well as those who could not use them for health reasons. Danish researchers observed an increased risk of the first use of antidepressants during therapy with any type of hormonal contraceptive. One of the groups consisted of women using progestogen pills – relative risk 1.34 (95% CI 1.27-1.40). The relative risks of women using IUDs and transdermal patches were higher than those using the tablets, however the authors of the study associate this with a higher dose rather than with the route of drug administration. Additionally, it was noted that the analyzes limited to adolescents (15-19-years-old) showed a higher relative risk of starting antidepressant use and of first diagnosis of depression. Compared to those not treated with hormonal contraception, the relative risk for combined oral hormonal contraception was 1.8 (95% CI 1.75-1.84). With age, the relative risk of depression decreased. There was a correlation between the duration of hormonal contraception therapy and the relative risk of using antidepressants and the diagnosis of depression. Relative risk was highest after 6 months and then decreased (however, it was still higher compared to non-users – only after 4 years of treatment, relative risks were ~ 1).

Another analysis on the same study group assessed the relative risk of suicide attempts and suicide while using hormonal contraception [22]. Compared to women who had never used hormonal contraception, the relative risk of a suicide attempt was 1.97 (95% CI = 1.85-2.10) and for suicide was 3.08 (95% CI = 1.35-7.08). Suicide rates were highest after 2 months of drug use. The highest relative risks were observed in young female patients.

Bloch and associates noticed that changes in the ovarian hormones concentration are more important than the absolute level of hormones in the pathogenesis of mood deterioration. Menstruation, menopause, pregnancy and labour are the factors that allow depression to develop. [23].

Abrams analyzed the results of 119 women using a single-phase, three-phase or non-hormonal method of contraception [24]. For three months, the assessment of at least two complete menstrual cycles was performed. Patients using parenteral hormonal contraception reported fatigue, sadness, and deterioration of mood at the end of the cycle slightly more often. However, the difference was not significant and the researchers emphasize the lack of clinical relevance. Researchers connect this phenomenon to PMS, not to the influence of hormonal contraception on the mood of patients.

In a study conducted on over 75,000 women, the relationship between the use of hormonal contracep-

tion and the following use of antidepressants or the diagnosis of depression during the first 12 months after childbirth was assessed [25]. Less than half of the surveyed women (41.7%, n = 31506) started using hormonal contraception within 12 months after childbirth. Norethindrone-only tablets accounted for 63.1% of contraceptive initiation (n = 19,883), levonorgestrel-containing intrauterine systems 9.8% (n = 3096), etonogestrel subcutaneous implants 8.7% (n = 2730), ethinyl estradiol / norgestimate tablets 8.6% (n = 2718), ethinyl estradiol / norethindrone 5.3% tablets (n = 1675) and ethinylestradiol / etonogestrel vaginal rings 4.5% (n = 1404). The percentage of women taking antidepressants in the first year postpartum was 7.8% (the Keplan-Meier estimation). Studies have shown a connection between the use of hormonal contraception and subsequent depression and the use of antidepressants, however, this relationship has not been assessed in postpartum women.

Another research on women after childbirth shows a significant connection between hormonal contraception and depression [26]. Women (n=242) were randomly assigned to two groups. First group received DMPA (medroxyprogesterone acetate) and the second group received an intrauterine device containing copper 48 hours after labor. Patients were examined in the first and second month after delivery. Scholars used Beck Depression Inventory (BDI-II) and Edinburgh Postnatal Depression Scale (EPDS). EPDS results after the first month were significantly higher when women used DMPA than in the intrauterine device group. According to BDI-II results more women using DMPA had severe depression at months 1 and 3 than in the other examined group.

## A LINK BETWEEN CONTRACEPTION AND DEPRESSION IN ADOLESCENTS

McKetta and Keyes from the USA were looking for a link between usage of oral contraception and depression among female adolescents in National Comorbidity Survey Adolescent Supplement [27]. 4765 teenage women who reported current or previous oral contraception (OC) usage and no history of pregnancy were included in the study. They also reported the age of OC initiation. Previous and current depression episodes were included. It was stated that using OC does not cause increased risk of depressive disorders. Lack of influence on depression or worsening of previously present depressive state was also established in prospective study on a group of 39 adolescent women who had been using depot medroxyprogesterone acetate (DMPA) for 12 months.

Discontinuation rates of HC are high, especially among adolescents, and mood complaints are one of the most frequently mentioned reasons for treatment discontinuation.

Research among women aged 12-30 was conducted [28]. They were observed since first usage of hormonal contraceptives for the whole year or up to the point when they started taking antidepressants. Among HC users the absolute risk of using antidepressants was around 4% for all age groups. However, in young non-users of HC the risk was very low and increased in age up until age of 21 or older. At that age the risk reached the level of HC users. The results indicate strong correlation between most hormonal contraceptives and following usage of antidepressant drugs in female adolescents without previous psychiatric morbidity. The highest odds ratio were noticed in 12 to 14 year old girls using intravaginal rings or skin patches containing progesterone. This connection was permanent and high for most types of HC in adolescents but was lower or disappeared in women over 19. The influence of HC on mental health might vary due to personal traits, disorders such as premenstrual dysphoric disorder (PMDD), dysmenorrhea or different susceptibility to neuroactive metabolites of progesterone.

## CONCLUSIONS

Despite of the reported dependencies between use of hormonal contraceptives and increased risk of depression in women, the evidence still remains ambiguous. More large-scale studies with properly selected test groups and particular therapies taken into consideration are required in order to accurately assess the risk of depression and mood disorders. Shaffir's team [29] in 2016 described problems concerning those studies: lack of prospective studies, various methods of examining mood swings and the fact that researchers are adding women who take different types of contraception to one cohort.

While oral contraception is being commonly used, problem of depression occurrence and its relation to hormonal therapies remains underestimated. Depression belongs to disorders with multifactorial genesis. Detailed patient history regarding depression episodes should be obtained by doctors prescribing hormonal medications. On the other hand psychiatrists should take into consideration the possible effects of oral contraceptives on the mood changes and depression incidence. Hormonal contraception cannot be treated as an "on demand" therapy, but the patients should be informed in details about all the possible adverse effects to make a conscious decision.

## REFERENCES


1. Daniels K. Current Contraceptive Status Among Women Aged 15-49: United States, 2015–201, NCHS Data Brief No. 327, 2018.
2. Zgliczynska M, Szymusik I, Sierocinska A. Contraceptive Behaviors in Polish Women Aged 18-35-A Cross-Sectional Study. Int. J. Environ. Res. Public Health 2019;16(15):2723.
3. Depression – World Health Organization (WHO). https://www.who.int/news-room/fact-sheets/detail/depression". [Accessed August 10th, 2020].
4. IHME 2019 report: Changes in disease burden in Poland between 1990–2017 in comparison with other Central European countries: A systematic analysis for the Global Burden of Disease Study 2017. https://www.healthdata.org/research-article/changes-disease-burden-poland-between-1990%E2%80%932017-comparison-other-central-european. [Accessed May 10th, 2020].
5. NFZ o zdrowiu. Depresja https://ezdrowie.gov.pl/portal/home/badania-i-dane/zdrowe-dane/raporty/nfz-o-zdrowiu-depresja. [Accessed May 10th, 2020].
6. Walf AA, Frye CA. A review and update of mechanisms of estrogen in the hippocampus and amygdala for anxiety and depression behavior. Neuropsychopharmacology. 2006 June;31(6):1097-111.
7. Baca-Garcia E, Diaz-Sastre C, Ceverino A et al. Suicide attempts among women during low estradiol/low progesterone states. J Psychiatr Res. 2010 Mar;44(4):209-14.
8. Yen JY, Lin HC, Lin PC et al. Early- and Late-Luteal-Phase Estrogen and Progesterone Levels of Women with Premenstrual Dysphoric Disorder. Int J Environ Res Public Health. 2019 Nov 7;16(22):4352.
9. Lawrie TA, Hofmeyr GJ, De Jager M et al. A double- blind randomised placebo controlled trial of postnatal norethisterone enanthate: the effect on postnatal depression and serum hormones. Br J Obstet Gynaecol.1998 Oct;105(10):1082-90.
10. Worly BL, Gur TL, Schaffir J. The relationship between progestin hormonal contraception and depression: a systematic review. Contraception. 2018 Jun;97(6):478-489.
11. Gupta N, O'Brien R, Jacobsen LJ et al. Mood changes in adolescents using depot-medroxyprogesterone acetate for contraception: a prospective study. J Pediatr Adolesc Gynecol. 2001 May;14(2):71-6.
12. Fruzzetti F, Fidecicchi T. Hormonal Contraception and Depression: Updated Evidence and Implications in Clinical Practice. Clin Drug Investig. 2020 Dec;40(12):1097-1106.
13. Slattery J, Morales D, Pinheiro L et al. Cohort Study of Psychiatric Adverse Events Following Exposure to Levonorgestrel-Containing Intrauterine Devices in UK General Practice. Drug Saf. 2018 Oct;41(10):951-958.
14. Zethraeus N, Dreber A, Ranehill E et al. A first-choice combined oral contraceptive influences general well-being in healthy women: a double-blind, randomized, placebo-controlled trial. Fertil Steril. 2017 May;107(5):1238-1245.
15. Lundin C, Danielsson KG, Bixo M et al. Combined oral contraceptive use is associated with both improvement and worsening of mood in the different phases of the treatment cycle-A double-blind, placebo-controlled randomized trial. Psychoneuroendocrinology. 2017 Feb;76:135-143.
16. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD006586.
17. Neri M, Malune ME, Corda V et al. Body composition and psychological improvement in healthy premenopausal women assuming the oral contraceptive containing micronized estradiol (E2) and nomegestrol acetate (NOMAC). Gynecol Endocrinol. 2017 Dec;33(12):958-962.
18. Shen H, Gong QH, Aoki C et al. Reversal of neurosteroid effects at alpha4beta2delta GABAA receptors triggers anxiety at puberty. Nat Neurosci. 2007 Apr;10(4):469-77.
19. Lara LAS, Abdo CHN. Age at Time of Initial Sexual Intercourse and Health of Adolescent Girls. J Pediatr Adolesc Gynecol. 2016 Oct;29(5):417-423.
20. Francis J, Presser L, Malbon K et al. An exploratory analysis of contraceptive method choice and symptoms of depression in adolescent females initiating prescription contraception. Contraception. 2015 Apr;91(4):336-43.
21. Skovlund CW, Mørch LS, Kessing LV et al. Association of Hormonal Contraception With Depression. JAMA Psychiatry. 2016 Nov 1;73(11):1154-1162.
22. Skovlund CW, Mørch LS, Kessing LV et al. Association of Hormonal Contraception With Suicide Attempts and Suicides. Am J Psychiatry. 2018 Apr 1;175(4):336-342.
23. Bloch M, Schmidt PJ, Danaceau M et al. Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry. 2000 Jun;157(6):924-30.
24. Abrams LS, Skee DM, Natarajan J et al. Pharmacokinetics of a contraceptive patch (Evra/Ortho Evra) containing norelgestromin and ethinyloestradiol at four application sites. Br J Clin Pharmacol. 2002 Feb;53(2):141-6.
25. Roberts TA, Hansen S. Association of Hormonal Contraception with depression in the postpartum period. Contraception. 2017 Dec;96(6):446-452.

26. Singata-Madliki M, Hofmeyr GJ, Lawrie TA. The effect of depot medroxyprogesterone acetate on postnatal depression: a randomised controlled trial. J Fam Plann Reprod Health Care. 2016 Jul;42(3):171-6.
27. McKetta S, Keyes KM. Oral contraceptive use and depression among adolescents. Ann Epidemiol. 2019 Jan;29:46-51.
28. Zettermark S, Perez Vicente R, Merlo J. Hormonal contraception increases the risk of psychotropic drug use in adolescent girls but not in adults: A pharmacoepidemiological study on 800 000 Swedish women. PLoS One. 2018 Mar 22;13(3):e0194773.
29. Schaffir J, Worly BL, Gur TL. Combined hormonal contraception and its effects on mood: a critical review. Eur J Contracept Reprod Health Care. 2016 Oct;21(5):347-55.

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REVIEW ARTICLE

# PENITENTIARY MEDICINE IN THE CONTEXT OF NATIONAL HEALTH CARE REFORM IN UKRAINE

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## ABSTRACT

**The aim:** Identify the main issues in the penitentiary medicine functioning in the context of National Health Care Reform in Ukraine and determine the state of realization of the right to health care and medical assistance of convicts and detainees.

**Materials and methods:** This article used a set of general and special methods of scientific cognition. The empirical basis of the research consists of: international acts and standards in the penitentiary field and health care, statistics of the Ministry of Justice, reports of international organizations, the case law of the European Court of Human Rights (ECHR), scientific publications in databases of systematic reviews MEDLINE, PubMed, reports on the results of monitoring visits to prisons and pre-trial detention centers.

**Conclusions:** Penitentiary medicine continues to be a separate departmental system, which does not consider the positive changes in the National Medical Services System. Such a superficial imitation of the method of guaranteeing prisoners' rights to medical care is a kind of cargo cultism of public institutions designed to ensure non-discriminatory conditions for implementing the right to health care for all population segments.

**KEY WORDS:** health care and medical care in prisons and pre-trial detention centers; protection of prisoners' rights; mechanisms for ensuring the right to health care

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## INTRODUCTION

The proper organization of conditions for implementing the right to health care and medical assistance by convicts and detainees during their stay in penitentiary facilities and after release has become significantly relevant in recent years. And it's not just about the humanistic approach or the pursuit of human rights. The so-called "penitentiary medicine" issues are not limited to the penitentiary system's framework – they also affect society.

The Health Care System in Ukraine is based on such principles as the recognition of health care as a priority of society and the state, observance of human and civil rights and freedoms in the field of health care, and provision of related state guarantees; humanistic orientation; ensuring the priority of universal values over class, national, group or individual interests. The leading international documents that deal with the provision of necessary medical care to convicts and detainees include the following: the European Convention on Human Rights,1950; Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment, 1984; The United Nations Standard Minimum Rules for the Treatment of Prisoners, 1955; Basic Principles for the Treatment of Prisoners, 1990; European Penitentiary Rules / Recommendation №R (2006) 2 of the Committee of Ministers of the Member States of January 11, 2006; Guidelines for physicians concerning torture and other cruel, inhuman or degrading treatment or punishment about detention and imprisonment (Tokyo Declaration), 1975. In its judgments, the European Court of Human Rights notes that Article 3 of the European Convention on Human Rights obliges the state to take care of the physical well-being of persons deprived of their liberty. At the same time, the Court agrees that the quality of health care in penitentiary facilities may not always be the same as that provided in the best general care facilities. However, the state must ensure that the health and well-being of detainees are adequately protected by providing them with the necessary medical care (for example, decisions in cases

Kudla v. Poland, application № 30210/96, § 94, ECHR 2000-XI; Hurtado v. Switzerland of January 28, 1994, Series A, № 280-A; Melnik v. Ukraine, application № 72286/March 1 March 28, 2006, paragraphs 104–106; Farbtuhs v. Latvia, application № 4672/02 of December 2, 2004, p. 56).

Health support and medical care organization are essential issues in correctional facilities. Many convicts and detainees already have health problems when incarcerated due to their lifestyle or environment. It is well known that prisons concentrate on people with issues such as alcohol abuse, drug addiction, or risky behavior. Prisoners have a high proportion of people with mental and psychological disorders, which is why the level of suicide and self-harm in prisons is relatively high, and violence can be a daily occurrence. That is why places of imprisonment become dangerous for the health of prisoners and staff.

## THE AIM

Identify problematic issues in the penitentiary medicine functioning in the context of National Health Care Reform in Ukraine and clarify the state of implementing the right to health care and medical assistance to convicts and detainees.

## MATERIALS AND METHODS

The empirical data of the research include: international acts and standards in the field of execution of criminal sanctions and health care; statistics of the Ministry of Justice of Ukraine; reports of international organizations; the case law of the European Court of Human Rights; reports on monitoring visits to enforcement agencies punishments and pre-trial detention centers. To generalize the approaches in the organization of penitentiary medicine, we analyzed scientific publications in the databases of systematic reviews MEDLINE and PubMed. The working experience in the State Institution "Probation Center" came in handy when analyzing quantitative and qualitative indicators of the realization of the right of convicts to health care.

We used general and special scientific methods of cognition, particularly Comparative Law, which allowed us to study medical care organizations in penitentiary institutions in several countries and highlight their advantages and disadvantages.

## REVIEW AND DISCUSSION

The European Committee for the Prevention of Torture and Inhuman or Degrading Treatment or Punishment (CPT), after inspections of penitentiaries in Ukraine regarding medical care and health care for convicts, noted that the main shortcomings of medical assistance and health care are: inadequate conditions for keeping people, which leads to the creation of favorable conditions for the spread of diseases, in particular, tuberculosis; lack of necessary medicines, which is caused by insufficient funding for this area of activity; lack of medical staff, their inadequacy for the number of people held in penitentiary facilities as a result – periodic physical examination of prisoners, insufficient for prevention, detection (diagnosis) and treatment of diseases [1].

In turn, representatives of human rights organizations point to some other problems. According to the monitoring results, many penitentiary facilities lack proper attention and appropriate medical care for prisoners suffering from serious illnesses treated within such facilities. However, the prisoners often do not have access to adequate medical care, and then, by law, they must be transferred to a civilian hospital for good treatment. On the other hand, the penitentiary administration does not want to do so. It can only be compelled to do so by a decision of the European Court of Human Rights on interim measures under Rule 39 of the ECHR Rules. This decision obliges the state to transfer a sick prisoner to a specialized civilian hospital [2]. Researchers note that factors that increase the risk of disease, as well as specific conditions of detention and behavior of convicts, lead to the fact that therapeutic approaches to this category of patients in medical practice should be different [3].

One of the reasons for the lack of timely and proper treatment of convicts is the subordination of medical institutions to the Penitentiary System of the prison administration and not to the Ministry of Health, which is a problem that needs to be addressed [2]. That is why, according to human rights activists, the entire system of medicine should be restructured from penitentiary to general practice [4].

Currently, the Ministry of Justice of Ukraine is trying to continue the functioning of a completely autonomous system of penitentiary medicine. As a result, the health care reform implemented in Ukraine has completely bypassed approaches to providing medical services in places of deprivation of liberty. According to official data of the Health Care Center of the State Criminal Executive Service of Ukraine, obtained during the research, currently under the subordination of the Ministry of Justice: 80 medical units, 13 hospitals, and 4 paramedic stations. In them, prisoners and detainees can receive medical care and services even though the right to free choice of a doctor is enshrined in the

law. So, is the existence of an autonomous healthcare system in places of detention justified?

The study of the international experience of the countries of the former USSR, Europe, and the USA testifies to the existence of different approaches in the organization of medical care in penitentiary services. Thus, the implementation of the function of medical care can be divided into three models [5]:

*1. Departmental.* The staff and management of the penitentiary system provide medical care in penitentiary institutions. The penitentiary health care staff, material, and financial assets are at the disposal of the penitentiary system. As a rule, normative legal support of the medical care order and assessment of its quality is also assigned to the penitentiary system. Such a system exists in Ukraine, Russia, other countries of the former USSR, Asia, and some European countries (Ireland, Albania).

The main advantage of the departmental system is the relatively low financial costs. There are also advantages in the observance of regime measures in institutions and higher social protection of medical staff of penitentiary institutions. For example, to attract and retain medical staff in many countries, the penitentiary system provides many motivational measures (provision of official housing, health insurance for health workers, and others).

Despite all the positive aspects, the departmental system has serious shortcomings. Thus, the presence of a military medical staff closed system and lack of external control over medical care by supervisors, and independent NGOs causes the so-called "double loyalty" – the need to comply with the interests of management to the detriment of the patient in prison, and possible use of the disease and drug withdrawal as a method of exposure. There is also a low continuity of medical care and functional medical examination of patients with socially significant diseases after release.

*2. Out-of-department.* Medical care and assistance are provided by third-party organizations (commercial or civil health care systems) that are not under the control of the penitentiary system. Funding can be organized under different schemes. The closer the amount of medical care to national standards, the more expensive it is to the state and exceeds similar costs in civilian health care.

Such a model successfully exists in Norway, England, France, and Australia. In transition, Spain and Scotland. Under such a system, conditions are created for improving the quality of medical care for prisoners; there are opportunities for further development and improvement of the system of protecting prisoners' rights to provide quality medical care. Prisoners have the same status as all citizens of the country, and medical staff interact with the administration of correctional facilities but are independent of it. Under such a system, better health care is provided in prisons, and continuity in medical care to released prisoners is ensured [6].

Its shortcomings include the complexity of management, the loss of specific knowledge that prison medical staff had, and the high cost of providing medical care to other citizens.

*3. Mixed version* – used in the United States, characterized by a combination of organizational components of the above systems. Federal correctional facilities are funded from the state budget; health workers are subordinated to the national executive body (for example, the Ministry of Justice), are civil servants, and have appropriate titles, guaranteeing their high social security. Medical care for convicts in correctional facilities in some states (counties) is built in the same way as at the federal level, but funding is provided from the state budget. Medical care is provided by commercial organizations that have committed to medical care within the allocated funds [7].

To some extent, the advantages of this system include the above benefits of the departmental and non-departmental systems, and the disadvantages are similar.

A number of countries have succeeded in the complete integration of prison health care with national public health by transferring its responsibility and administration to the national health system and ministry of health; these include Norway; France; the United Kingdom; the Swiss cantons of Geneva, Vaud, Valais, and Neuchatel; New South Wales in Australia; Italy; Kosovo; Catalonia in Spain; and Finland [8]. Such a transition occurred at different times. For example, in the case of Norway, the Penitentiary Health Service has been run by the national health service since 1988. In England and Wales, this process began in 2000 and ended in 2006 [9]. Several other countries are now exploring the possibility or intention of making a similar transition, including Spain, Scotland, and others.

Ukraine had a departmental model of the penitentiary organization, according to which medical staff in each prison or pre-trial detention center subordinated to the administration of the institution (head of the institution and his deputy) and higher governing bodies – the Interregional Department for the Execution of Criminal Penalties and the relevant structural units of the Ministry of Justice. This model can be called departmental in its "pure form," and the results of its operation did not provide adequate medical care and led to numerous human rights violations and loss of

budget funds due to these violations in the European Court of Human Rights.

At the beginning of the reform (as of January 1, 2020), the total number of convicts and detainees in the institutions of the State Penitentiary Service of Ukraine amounted to 52,863 people. At the same time, the full-time staff of the State Penitentiary Service of Ukraine amounted to 2,781 positions, of which 2,530 (or 91%) were filled. And the penitentiary system included: medical units in 91 prisons, paramedic points – in 4 institutions, and 18 hospitals, of which 9 are multidisciplinary (including 1 psychiatric one), and 7 are tuberculosis hospitals. To change the situation, in pursuance of the order of the Cabinet of Ministers of Ukraine dated September 13, 2017, № 684-r, there was established the State Institution "Health Center of the State Penitentiary Service of Ukraine" (further – Health Center) which belongs to the Ministry of Justice of Ukraine. The structure of the Health Center includes the management, divisions of the staff, and branches in the regions (currently 20 of them). The whole team of the Health Center is still 2,781 units (including the management and administration – 81). Implementing practical activities to provide medical care to convicts and detainees in prison and pre-trial detention centers is entrusted directly to the relevant branches of the Health Centers in the regions.

However, such an update of the organizational structure did not ensure the achievement of the set tasks. On the contrary, it distanced convicts and detainees from receiving the necessary medical services and care. The reform of civilian medicine, which is based on the principle of guaranteeing a package of medical services and involving local budgets in their provision in the context of decentralization, does not consider in this system citizens who are in prison and pre-trial detention centers. Due to this approach, vulnerable categories of convicts will also not be able to use medical services immediately after their release from prison (until other social aspects are resolved).

In addition, creating a separate system of healthcare services requires significant budgetary expenditures, including for the maintenance of staff and healthcare facilities. Thus, according to the official data obtained during the study, despite the decrease in the number of prisoners (from 52,863 in 2019 to 42,848 in 2022), the costs of their medical care and maintenance of medical staff have not changed.

Researchers note that the practical implementation of the objectives of health care in prisons and pre-trial detention centers requires the support and permission of the institution's governor – for example, transferring inmates for medical interventions to outside facilities or the procurement and installation of health equipment in the institution. In this regard, the Mandela Rules said, "Clinical decisions may only be taken by the responsible health-care professionals and may not be overruled or ignored by non-medical prison staff" [10].

In Ukraine, the separation of penitentiary medicine from the administration of prisons and pre-trial detention centers has led to the removal of the heads of these facilities from health problems and, in some cases, to artificial barriers for convicts and prisoners to access medical services. Earlier, other authors drew attention to the fact that the penitentiary legislation of Ukraine does not provide mechanisms for exercising a specific right to health care, as well as the responsibility of officials and officials of the penitentiary service for inadequate medical care and harm to their health [11].

The mortality rate among prisoners, especially in adulthood (up to 50-55 years), remains extremely high; there are problems with quality medical examinations and providing complete secondary and tertiary medical, palliative care, providing medical care to those sentenced to life imprisonment, prisoners with mental disorders, various forms of addiction, dangerous chronic, infectious diseases, etc. The incidence (prevalence) in penitentiary institutions exceeds the national tuberculosis rate by more than 10 times, HIV infection by 25 times, viral hepatitis C by 15 times, alcohol and drug addiction by 20 times, etc.

The preventive direction of the activity of penitentiary medicine raises many questions. Regulatory procedures and stages of the patient's clinical route both in the penitentiary system and outside it (referral to state and municipal health care facilities) are over-regulated and lead to long-term patient transfer and, as a consequence, the growth of dangerous complications of diseases.

Another problem is that convicts and prisoners do not get social protection. Thus, during the entire period of the system's existence, no sick leave was issued, even for those who work and earn the appropriate contributions to the compulsory insurance. It is also the result of the separation of penitentiary medicine, which is not included in the electronic system for issuing sick leaves.

In such circumstances, it is difficult to eliminate the reasons that become the basis for appeals to the European Court of Human Rights about the inadequate conditions of detention convicts and detainees, their medical and logistical support, which primarily entails additional state costs, compensations, and causes the formation of a negative image of Ukraine in the world community, as well as budget losses.

The isolation of the medical care system of the State Penitentiary Service of Ukraine leads to high maintenance costs. The budget for 2020 for the maintenance of the Health Center, branches, and subordinate medical institutions provided UAH 589.9 million, which is UAH 11,591.7 per capita [12-15]. In 2021, UAH 566.7 million was spent [16]. For comparison, the per capita expenditure in the general system of the National Health Service of Ukraine is approximately UAH 3,000. At the same time, these funds do not create quality medical care. For example, 74% of the annual budget is spent on wages and salaries, and only 9.4% on medicines and dressings.

The health center's entire medical staff is proportional to the largest hospitals in Ukraine. For example, the number of hospital beds in Health Center facilities is 9.3 per 1,000, much higher than the average for Ukraine – 7.3 per 1,000 population. At the same time, each healthcare facility in the penitentiary system lacks the workload to ensure the quality of treatment and its cost-effectiveness. This burden on doctors is an example of inefficient use of funds and, above all, of poor quality, which threatens the life and health of the patient. For instance, according to official data in 2019, 479 patients with a diagnosis of ischemic heart disease were treated in Health Center hospitals, of which 81 patients died [12]. In 2021, the number of such persons was 347 and 74, respectively. The mortality rate for patients with this diagnosis is 15% and is three times higher than in the general system, even in those who treat the most severe patients. Malignant mortality is 22%, twice the average for the public health system. The presence of subordinate hospitals only creates the illusion of access to medical care. Convicts and detainees often need a long transfer to a medical facility, but this does not guarantee that the facility will provide the necessary assistance. In this regard, researchers point out that hospitals do not have psychiatric wards and generally involve a limited number of psychiatric specialists. This situation is, therefore, incapable of providing prisoners with adequate psychiatric services [13].

In the UK, research into prisoners' use of hospital care noted that moving away from the Prison Medical Service being responsible for prison health care is believed to have improved the quality of prison health care [14, 9]. In 2016, Public Health England conducted a rapid review to understand how this move had affected it. It found that the consensus was that the move had resulted in significant improvements to the quality of care through, among other factors, improved partnership working, professional development of the health care workforce, and increase [15, 9].

The need to fully transfer penitentiary medicine in Ukraine to the National Health Care System is supported by the existing difficulties in cooperation between the penitentiary and public healthcare facilities. Thus, payments to health care facilities of the public system for provided medical services are made by electronic referrals when the facilities of the penitentiary system do not have the technical capacity to provide electronic referrals. As a result, the health care facilities of the general health care system have no incentive to work with the prison, as the cost of medical services provided to convicts and prisoners is not reimbursed.

Interestingly, 1,594 convicts and detainees have concluded declarations with family doctors. All declarations were signed before being imprisoned. That is, double funding is provided for these 1,594 people. However, convicts are not provided with access to their family doctors, and they are forced to apply only to the medical staff of the Center for Health of the penitentiary system.

## CONCLUSIONS

The article gives grounds to state that over time, the problems of medicine in the penitentiary system in Ukraine, despite all the measures taken, do not decrease but only change. The implemented measures have only a point effect and do not significantly change the situation. Penitentiary medicine, as a separate departmental structure, is a valuable element that requires constant co-financing and will continue to do so until a complete duplication of the public sector health care system is established.

Penitentiary medicine today has lost its connection with the civilian health sector and exists as autonomously as possible. At the same time, it continues to use the services of civilian medicine outside the established procedure and free of charge for the providers of such services. Convicts and prisoners are not included in the general medicine of society. And this does not allow for the introduction of progressive ways and methods of treatment in the penitentiary system, requires much higher unjustified costs, and complicates further treatment after release. Convicts and prisoners cannot receive services and facilities for all other population categories.

Therefore, the only way to solve the situation in Ukraine is to maximize the integration of penitentiary medicine with the national health care system, making it practical and efficient. In addition, it will ensure that convicts and prisoners have unhindered access to quality medical care, improving the population's overall health.

## REFERENCES


1. Dopovid Ukrainskomu Uriadu shchodo vizytu v Ukrainu, zdiisnenoho Yevropeiskym komitetom z pytan zapobihannia katuvanniam chy neliudskomu abo takomu, shcho prynyzhuie hidnist, povodzhenniu chy pokaranniu (KZK) z 1 po 10 hrudnia 2012 r. [Report to the Ukrainian Government on a visit to Ukraine by the European Committee for the Prevention of Inhuman or Degrading Treatment or Punishment from 1 to December 10, 2012]. http://khpg.org/index.php?id=1379842217 [date access 03.02.2023] (in Ukrainian).
2. Porushennia prava viazniv na okhoronu zdorovia ta medychnu dopomohu [Violationoprisoners's" right to health care and medical assistance]. http://khpg.org/index.php?id=1427750983 [date access 03.02.2023] (in Ukrainian).
3. Petryshyn OV, Serohina SH, Romanov MV. Penitentiary healthcare: legal and practical aspects. Wiad Lek. 2019; 72(12): 2591-2595. doi: 10.36740/WLek201912233.
4. Dostup do medychnoi dopomohy u mistsiakh nesvobody [Access to medical care in places of detention]. http://khisr.kharkov.ua/index.php?id=1425562854 [date access 03.02.2023] (in Ukrainian).
5. Yakovets IS, Hel AP. Systema nadannia medychnoi dopomohy v ustanovakh vykonannia pokaran: suchasnyi stan ta shliakhy reformuvannia [The system of providing medical care within penal institutions: current state and ways of reforming]. Bulletin of the Criminological Association of Ukraine. 2016; 3 (14): 151-167 (in Ukrainian).
6. Bengoa A, Mateo-Abad M, Zulaika D et al. Availability and use of healthcare resources in prisons according to the transference model: a comparative study in Spain. Rev Esp Sanid Penit. 2018;20(1):21-29.
7. Shalev N. From public to private care, the historical trajectory of medical services in a New York City jail. Am J Public Health. 2009;99(6):988-995. doi:10.2105/AJPH.2007.123265,
8. Pont J, Enggist S, Stöver H et al. Prison Health Care Governance: Guaranteeing Clinical Independence. American Journal of Public Health. 2018; 108:472-476. doi: 10.2105/AJPH.2017.304248.
9. Hutchings R, Davies M. How prison health care in England works. https://www.nuffieldtrust.org.uk/resource/prison-health-care-in-england [date access 03.02.2023]
10. UN Standard Minimum Rules for the Treatment of Prisoners. https://ajph.aphapublications.org/doi/10.2105/AJPH.2017.304248 [date access 03.02.2023]
11. Teremetsky VI, Muzychuk OM, Salmanova EY et al. Problems of medical protection of persons sentenced to imprisonment. Wiad Lek. 2018;71(9):1777-1780.
12. Zvit pro diialnist Tsentru okhorony zdorovia Derzhavnoi kryminalno-vykonavchoi sluzhby Ukraini v 2020 r. [Report on the activities of the Health Center of the State Penitentiary Service of Ukraine in 2020]. https://coz.kvs.gov.ua/?page_id=160 [date access 03.02.2023] (in Ukrainian)
13. Yanovska OG, Chugaevska AV, Ivanov MS. Cargocultism of psychiatric care in custody. Wiad Lek. 2021;74(11):2916-2921. doi: 10.36740/WLek202111210.
14. Davies M, Rolewicz L, Schlepper L, Fagunwa F. LockedOutPrisoners's" use of hospital care. Nuffield Trust. https://www.nuffieldtrust.org.uk/research/locked-out-prisoners-use-of-hospital-care [date access 03.02.2023]
15. Public Health England. Rapid Review of Evidence of the Impact on Health Outcomes of NHS Commissioned Health Services for People in Secure and Detained Settings to Inform Future Health Interventions and Prioritisation in England. Public Health England. 2016.
16. Zvit pro diialnist Tsentru okhorony zdorovia Derzhavnoi kryminalno-vykonavchoi sluzhby Ukraini v 2021 r. [Report on the activities of the Health Center of the State Penitentiary Service of Ukraine in 2021]. https://coz.kvs.gov.ua/wp-content/uploads/2022/02/%D0%95%D0%BA%D0%BE%D0%BD%D0%BE%D0%BC%D1%96%D0%BA%D0%B0-%D1%84%D1%96%D0%BD%D0%B0%D0%BD%D1%81%D0%B8-%D1%82%D0%B0-%D0%BC%D0%B0%D0%B9%D0%BD%D0%BE%D0%B2%D1%96-%D0%B2%D1%96%D0%B4%D0%BD%D0%BE%D1%81%D0%B8%D0%BD%D0%B8-%D1%83-2021-%D1%80%D0%BE%D1%86%D1%96-1.doc [date access 03.02.2023]



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REVIEW ARTICLE

# HYPOGLYCEMIA IN PATIENTS WITH COVID-19: A COINCIDENCE OR A TREND?

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## ABSTRACT

**The aim:** The purpose of this work is to analyze the available scientific information on causes and risk factors of hypoglycemia during treatment of patients with COVID-19.

**Materials and methods:** A search and analysis of full-text articles was carried out in the PubMed, Web of Science, Google Scholar, and Scopus databases. The search was conducted using the keywords: «hypoglycemia in COVID-19 patients», «treatment of COVID-19 and hypoglycemia» and «COVID-19 vaccination and hypoglycemia» from the beginning of the pandemic in December 2019 to July 1, 2022.

**Conclusions:** Hypoglycemia can be an incidental clinical finding. But it can also be a natural consequence of treatment if it is carried out without taking into account the possible hypoglycemic effects of drugs and without careful monitoring of the patient's condition. In the case of determining the program of treatment and vaccination against COVID-19 in patients with DM, the known and possible hypoglycemic effects of drugs and vaccines should be taken into account, the level of glycemia should be carefully controlled, and sudden changes in the type and dose of drugs, polypharmacy and the use of dangerous combinations of drugs should be avoided.

**KEY WORDS:** COVID-19, hypoglycemia, treatment, vaccination

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## INTRODUCTION

In the early 20s of the 21st century, humanity witnessed an unprecedented coronavirus disease (COVID-19) pandemic caused by SARS COV-2. COVID-19 is confidently and aggressively spreading around the planet, particularly in Ukraine, as of July 22, 2022, there were 5,021,612 confirmed cases of COVID-19 with 108,699 deaths (case fatality rate – 2.16%) [1]. The main risk factors for developing COVID-19 and its severe course are advanced age, arterial hypertension, diabetes mellitus (DM), and cardiovascular and cerebrovascular diseases. In particular, the risk of death from COVID-19 may be up to 50% higher in patients with concomitant diabetes than in non-diabetics. In these patients, significant fluctuations in blood glucose levels are observed, probably due to irregular diet, reduced physical activity, and the use of glucocorticoids [2]. Significant changes in blood glucose levels often lead to hypoglycemia.

According to American Diabetes Association (ADA), hypoglycemia can be defined as «any abnormally low plasma glucose concentration that can cause potential harm to the subject.» Current ADA Guidelines distinguish three levels of hypoglycemia. Level 1 hypoglycemia is defined as blood glucose <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as the threshold for the neuroendocrine response to glucose lowering in nondiabetic individuals, and a measured glucose level <70 mg/dL (3.9 mmol/L) is considered clinically important (regardless of the severity of acute hypoglycemic symptoms). Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate intervention to reverse the hypoglycemic event. Finally, level 3 hypoglycemia is defined as a severe event characterized by a change in mental and/or physical functioning that requires the assistance of another person for recovery [3].

Hypoglycemia is a factor that limits the possibilities of treatment in diabetes, which must be treated carefully and critically to avoid complications. The lockdown due to the COVID-19 pandemic has further complicated the problem of hypoglycemia by restricting access to food, clinics, medical services, and medicines [4].

It is also known that hypoglycemic reactions often occur against the background of treatment of COVID-19,

in particular with some antiviral agents, glucocorticosteroids, antibiotics, etc. The question arises: are cases of hypoglycemia in patients with COVID-19 isolated random clinical phenomena, or is this a natural result of treatment? The search for an answer to this question was the reason for conducting this study.

## THE AIM

The aim is to discover the causes of hypoglycemia during treatment in patients with COVID-19 and propose recommendations for its prevention.

## MATERIALS AND METHODS

A search and analysis of full-text articles from the PubMed, Web of Science, Google Scholar, and Scopus databases were conducted to solve the task. The search was conducted using the keywords: «hypoglycemia in COVID-19 patients», «treatment of COVID-19 and hypoglycemia» and «COVID-19 vaccination and hypoglycemia» from the beginning of the pandemic in December 2019 to July 1, 2022. The statistical results of the research are presented in absolute (n) and relative (%) values, the assessment of the risk of occurrence of the event was carried out using the odds ratio (OR) and their confidence intervals (CI), the results were considered statistically significant when $p < 0.05$.

## REVIEW AND DISCUSSION

A total of 186 publications were found as a result of the search. The analysis of literary sources made it possible to demonstrate the influence of individual drugs and methods of therapy and prevention used in patients with COVID-19. The possibility of developing hypoglycemia against the background of pharmacotherapy and the use of biological drugs for COVID-19 is summarized in Table I.

**Antiviral drugs** block the maturation of the virus and the penetration of the virus into the cell. Among the new antiviral drugs, molnupiravir is an innovative oral antiviral drug with broad activity against coronaviruses, including SARS-CoV-2. A randomized, placebo-controlled trial of A.J. Bernal, published in February 2022, confirmed the superiority of molnupiravir over placebo in ambulatory adult patients with mild to moderate COVID-19, provided treatment was started within 5 days of symptoms onset. Adverse effects were reported in 216 of 710 participants (30.4%), but the incidence of hypoglycemia was not reported [5]. Studies of the viral protease inhibitor camostat mesylate have shown a reduction in glycemic levels, which may be a potential alternative antiviral treatment option for patients with DM [6]. Administration of other antiviral drugs (lopinavir/ritonavir, remdesivir, darunavir/cobicistat) for COVID-19 is accompanied by infrequent moderate hyperglycemia [6].

**Interleukin-6 (IL-6) receptor blockers.** IL-6 is a pleiotropic cytokine that activates and regulates the immune response to infections. Elevated concentrations of IL-6 are associated with severe outcomes of COVID-19, including respiratory failure and death, although the role of IL-6 in disease pathogenesis is unclear. Among IL-6 receptor blockers for the treatment of COVID-19, WHO recommends tocilizumab or sarilumab [7]. **Tocilizumab** is used to treat moderate to severe COVID-19 pneumonia by targeting IL-6 receptors and reducing cytokine release. Intriguingly, there is evidence that optimal treatment of COVID-19 infection with tocilizumab is not achieved during hyperglycemia in both diabetic and non-diabetic patients [8].

Recommendations concerning **Janus kinase (JAK) inhibitors**, specifically baricitinib, ruxolitinib, and tofacitinib, for patients with severe or critical COVID-19 were published on 14 January 2022 as the eighth version of the WHO living guideline and in the BMJ as Rapid Recommendations [7]. The drugs tofacitinib, ruxolitinib, and baricitinib are used in the treatment of patients with a severe or critical course of COVID-19. Evidence has demonstrated that each of these therapies lowers glycemia in patients with and without diabetes [9].

**Chloroquine,** a drug obtained from the bark of the cinchona tree, has long been used to treat various diseases, including malaria, and was accidentally shown to reduce hyperglycemia [10]. It is known that chloroquine has an immunomodulatory and hypoglycemic effect, and causes changes in insulin metabolism through cell receptor signaling and post-receptor clearance [11]. In diabetic animals, chloroquine has been shown to increase serum insulin levels even without treatment with exogenous insulin [10].

**Hydroxychloroquine (HCQ)** is an antimalarial drug that has gained global news and media attention and has been used in the treatment of patients with COVID-19. This drug has been used based on its antimicrobial and antiviral properties, despite the lack of definite evidence of clinical efficacy.

Hypoglycemia and QT prolongation are known and frequent side effects of HCQ [6]. 33.56% of patients who prophylactically received 400 mg of hydroxychloroquine in combination with conventional antihyperglycemic agents without dose adjustment reported hypoglycemia [4]. Hypoglycemia can be seen as a side effect of HCQ use in COVID-19 infection, even in patients without chronic diseases and diabetes.

**Table I.** Occurrence of hypoglycemia when using means of treatment and prevention of COVID-19

| Drug class | Name of the drug | Features of changes in blood glucose level | References |
|---|---|---|---|
| Antiviral drugs | Camostat mesylate<br>Lopinavir/ritonavir<br>Remdesivir<br>Darunavir/cobicistat | Infrequent moderate hypoglycemia | [5,6] |
| IL-6 receptor blockers | Tocilizumab<br>Sarilumab | Hypoglycemia is possible | [6-8] |
| Janus kinase inhibitors | Tofacitinib<br>Ruxolitinib<br>Baricitinib | Decrease blood glucose levels in diabetic and nondiabetic patients | [7,9] |
| Anti-infective agents | Hydroxychloroquine<br>Chloroquine | In diabetic and nondiabetic patients, hypoglycemia occurs frequently | [4,6,10,11] |
| Glucocorticosteroids | Dexamethasone | Both hyperglycemia and hypoglycemia can occur. Hypoglycemia is often observed after withdrawal of GCS. | [6,12,13] |
| Macrolides | Azithromycin<br>Clarithromycin | Hypoglycemia is rare, but in combination with hydroxychloroquine – up to 42.8% | [14-16] |
| Fluoroquinolones | Ciprofloxacin<br>Moxifloxacin<br>Levofloxacin | Frequent. Hypoglycemia is the most common side effect of fluoroquinolones treatment | 14,17,18][ |
| Selective serotonin reuptake inhibitor | Fluvoxamine | Can cause both hyperglycemia and hypoglycemia | [7] |
| Analgesics, antipyretics | Paracetamol (acetaminophen) | Hypoglycemia occurs in case of overdose | [19,20] |
| Antidiabetic drugs | Metformin<br>Sulfonylurea<br>Insulin<br>DPP-4 inhibitors | All drugs in this group can cause hypoglycemia, especially in combination with other medications used for the treatment of COVID-19 | [4,21,22] |
| ACE inhibitors | Lisinopril<br>Captopril | Hypoglycemia can occur both in patients with and without DM | [22-24] |
| Vaccination | Covishield<br>mRNA-based vaccines:<br>Pfizer-BioNTech<br>Moderna | All vaccines can cause hyperglycemia after the first dose. Hypoglycemia is also possible for mRNA-based vaccines | [6,25,26] |

Note: GCS – glucocorticosteroids; ACE – angiotensin-converting enzyme; DM – diabetes mellitus

**Glucocorticosteroids (GCS).** It is known that GCS suppress the activity of inflammatory cytokines, which leads to decreasing edema, fibrin deposition, capillary leakage, and migration of inflammatory cells, thereby suppressing inflammation and blocking the cytokine storm [6]. Recent clinical trials have confirmed that dexamethasone is an effective treatment for patients with COVID-19 who require mechanical ventilation. However, it is also known that GCS drugs affect carbohydrate metabolism and disrupt glycemic control. Thus, a study by D.J. Douin et al. showed that taking ≥320 mg methylprednisolone equivalents was associated with 4 additional days spent with glucose either <80 mg/dL or >180 mg/dL (OR=4.00, 95% CI = 2.15-5.85, p<0.001). Thus, the use of GCS in patients with COVID-19 is associated with a higher frequency of both hyperglycemia and hypoglycemia [12]. In addition, it should be taken into account that hypoglycemia is often observed after the withdrawal of corticosteroids. In 60% of patients after discontinuation of GCS L.G. Strongin et al. (2022) reported on clinically significant, often nocturnal episodes of hypoglycemia, that were not detected by routine methods [13].

**Macrolides.** When using macrolides (azithromycin or clarithromycin), hypoglycemia was observed in 3.72% of patients [14]. **Azithromycin** suppresses the synthesis of polypeptides and proteins and has immunomodulatory and antiviral effects. Several clinical trials have shown conflicting results regarding its effectiveness [7].

Hypoglycemia was the most common side effect of the **combination of hydrochloroquine and azithromycin** and was observed in 69 of 161 patients (42.86%) [15]. In a cohort of 21 patients with COVID-19 on hemodialysis, treated with HCQ and azithromycin, 5 (23.8%) patients experienced hypoglycemia [16].

**Fluoroquinolones (FQ)** are wide-spectrum synthetic antimicrobial agents with strong antiviral activity. The fluoroquinolones (ciprofloxacin and moxifloxacin) can

inhibit the replication of SARS-CoV-2 by showing a stronger ability to bind to its core protease than chloroquine. In addition, FQ have demonstrated numerous immunomodulatory effects, leading to attenuation of the inflammatory response through proinflammatory cytokines inhibition [17]. However, FQ use is often accompanied by hypoglycemic reactions. Thus, in the message of A. Althaqafi et al. (2021), hypoglycemia was registered in 2179 patients (35.1%) who received fluoroquinolones in eleven studies with 6208 patients. Among all FQ, moxifloxacin is the most associated with dysglycemia, and ciprofloxacin the least [18]. The absolute risk of hypoglycemia was 10.0 events per 1000 for moxifloxacin, administration of levofloxacin had also a higher risk of hypoglycemia than macrolides (OR-1.79; 95% CI 1.33-2.42). A significant increase in the risk of hypoglycemia was also observed among patients receiving moxifloxacin concomitantly with insulin (OR, 2.28; 95% CI, 1.22-4.24) [14].

**Fluvoxamine** is a selective serotonin reuptake inhibitor (SSRI) with antiviral and anti-inflammatory effects [7]. It can cause both hyperglycemia and hypoglycemia.

OTHER DRUGS USED IN PATIENTS WITH COVID-19 AND RELATED DISEASES

**Paracetamol (acetaminophen)** is recommended for the treatment of hyperthermia. However, in the case of an overdose of acetaminophen, hepatotoxicity occurs with manifestations of severe hypoglycemia, coagulopathy, and metabolic acidosis [19], sometimes with a fatal outcome [20].

**Antidiabetic drugs.** Almost all antihyperglycemic drugs can worsen the course of COVID-19, regardless of their class. Administration of an antihyperglycemic drug can lead to side effects, including episodes of hypoglycemia, diarrhea, lactic acidosis, and an increased risk of cardiovascular and hepatic hazards. These adverse effects associated with antihyperglycemic drugs pose a threat to the development of severe complications of COVID-19 [21].

K. Shah et al. studied 146 patients with type 2 diabetes (T2DM) who presented to the emergency department during quarantine with symptoms of hypoglycemia. It turned out that hypoglycemia most often occurred against the background of the use of a combination of metformin and sulfonylurea (65.75%), followed by insulin (33.56%) [4].

**Dipeptidyl peptidase-4 inhibitors (DPP-4i)** are considered safe for patients with T2DM. However, the combination of these agents with other drugs used to treat COVID-19 produces undesirable hypoglycemic effects. Thus, in a large study, C.Y. Ray et al. (2021) analyzed data from 77,047 patients using DPP-4i. An increased risk of hypoglycemia was observed with the combination of DPP-4i with bumetanide (OR 2.44; 95% CI, 1.78-3.36), captopril (OR 2.97; 95% CI, 2.26-3.90), colchicine (OR 1.87; 95% CI, 1.44-2.42), acetaminophen (OR 2.83; 95% CI, 2.44) [22]. Physicians who prescribe DPP-4i should consider the potential risks associated with the simultaneous use of other drugs.

In addition, COVID-19 may limit the choice of available antihyperglycemic agents, which may further increase the risk of severe complications of diabetes and COVID-19 itself [21].

**Angiotensin-converting enzyme (ACE) inhibitors** are among the most common drugs used to treat concomitant hypertension and diabetes. They are considered the first line of treatment for hypertension in this population. ACE inhibitors can increase insulin sensitivity, which can lead to an approximately 3- to 4-fold increase in the risk of hypoglycemia in patients with diabetes, especially those receiving other hypoglycemic agents, including sulfonylureas [23]. Previous studies have shown a potential association between ACE inhibitors used in combination with sulfonylureas and severe hypoglycemia [24]. Cases of recurrent hypoglycemia in non-diabetic patients treated with ACE inhibitors, in particular lisinopril, have also been reported [23]. There are also data on hypoglycemia in the background of captopril administration [22].

VACCINATION

All vaccines have been designed to increase immunity to the infection of COVID-19, which allows for the prevention of the disease. The mechanisms linking vaccines against COVID-19 and changes in glucose homeostasis have not been definitively discovered. As a rule, antiviral vaccines can cause unstable blood glucose levels. It is not just a reaction to the virus but the vaccine excipients.

G. di Mauro et al. (2022) reported 4275 events with impaired glucose metabolism after the administration of vaccines. The most frequently registered events belong to the group «high glucose level» (n = 2012; 47.06%), followed by «hypoglycemia» (n = 954; 22.32%). Covishield, Pfizer-BioNTech, and Moderna have been associated with hyperglycemia after the first dose [6]. In addition, mRNA vaccines against COVID-19 were associated with an increased frequency of reports of alterations in glucose homeostasis compared with viral vector vaccines. In particular, the frequency of reports of hypoglycemia after the use of mRNA vaccines was significantly higher (OR 1.62; 95% CI 1.41-1.86) compared to vaccination with vaccines based on viral vectors [25].

Adverse effects associated with vaccination vary considerably by age and sex, with more severe effects seen in women and young adults. It is noteworthy that women show a stronger immune response against

pathogens and vaccines but also a greater susceptibility to autoimmune diseases [26].

To date, the effect on the level of glycemia of such treatment methods as plasma of convalescents, monoclonal antibodies, and vaccination with vaccines not mentioned above (for example, Johnson & Johnson) remains unknown [6].

The conducted study showed that hypoglycemia can occur with the use of drugs of almost all pharmacotherapeutic groups used for the treatment (and vaccine prophylaxis) of patients with COVID-19. In addition, many patients with DM have chronic complications that contribute to the occurrence of hypoglycemia in the event of a disease with COVID-19.

Diabetic kidney disease (DKD) is a significant risk factor for the development of hypoglycemia. Factors contributing to the risk of hypoglycemia in DKD are reduced renal clearance of insulin, reduced breakdown of insulin in peripheral tissues, reduced renal gluconeogenesis, and impaired renal excretion of antidiabetic drugs. In particular, in the study by K. Shah et al., among patients with symptomatic hypoglycemia, almost a third of patients (32.88%) had diabetic kidney disease [4]. In the case of a severe course of DKD, patients with COVID-19 often develop renal failure, which significantly worsens the treatment results.

The presence of diabetic micro- and macroangiopathy and concomitant arterial hypertension in the patient is also important. Patients with arterial hypertension, micro-, macro-vascular complications of diabetes, and concomitant complications had a higher tendency to risk of hypoglycemia (46.58%, 33.56%, and 23.29%, respectively) than patients without these complications [4].

And finally, another phenomenon that is observed during the development of a viral infection in patients with DM is **the mutually aggravating effect of diseases**. Thus, DM is a risk factor affecting the progression and prognosis of COVID-19. In a study by W. Guo et al. (2020), it was found that patients with COVID-19, who had no other comorbidities except diabetes, had a high risk of developing severe pneumonia, the release of enzymes associated with tissue injuries, excessive uncontrolled reactions on inflammation, and hypercoagulable state associated with dysregulation of glucose metabolism [27]. In addition, the level of serum inflammatory biomarkers, such as IL-6, C-reactive protein, serum ferritin, prothrombin index, and D-dimer, were significantly higher ($p<0.01$) in diabetic patients compared to non-diabetic patients. which indicates the development of a wider complex of inflammatory reactions in diabetic patients, and this, in turn, over time leads to a rapid deterioration of the course of COVID-19 [27]. Impaired innate immunity, pro-inflammatory cytokine milieu, reduced ACE2 expression, and use of renin-angiotensin-aldosterone system antagonists in people with diabetes contribute to a poor prognosis in COVID-19 [9].

Both hypoglycemia and hyperglycemia have a negative impact on mortality and length of stay in the hospital with COVID-19 [28]. A large US multicenter study of 1,544 patients with COVID-19 from 91 hospitals in 12 states found that hypoglycemia at any time during the hospital stay in both diabetic and nondiabetic patients increased the risk of death (OR 2.2; 95% CI 1.35-3.60) [29].

Regarding the mechanisms of the negative impact of hypoglycemia on the course of COVID-19, some researchers suggest that hypoglycemia leads to an increase in the pro-inflammatory factor lipopolysaccharide during active infection of COVID-19 [30]. Lipopolysaccharide enhances monocyte glucose transporter overexpression to provide monocytes with sufficient glucose to fight infection but at the same time can trigger a cytokine storm that worsens the outcome of the COVID-19 disease [30]. Hypoglycemia can also cause an increase in counterregulatory hormonal adrenergic activity, leading to further inflammatory stress [31].

Thus, hypoglycemia, in addition to being a risk factor for cardiovascular and all-cause mortality in patients with diabetes, may be a trigger for the "cytokine storm" during COVID-19 disease and negatively impact mortality and length of stay in the hospital with COVID-19 [30].

In turn, COVID-19 can worsen the course of diabetes in patients. As highlighted by E. Maddaloni, and R. Buzzetti (2020), the interaction between COVID-19 and diabetes may be bidirectional, as SARS-CoV-2 can potentially worsen the course of existing diabetes or even the predisposition to diabetes in individuals without diabetes [32].

Thus, COVID-19 can also present with dyspeptic symptoms, such as vomiting and diarrhea, which aggravate dehydration [33]. COVID-19 uses the angiotensin-converting enzyme type 2 (ACE-2) receptor as a "gateway" to invade human target cells [34]. This enzyme is expressed by various tissues and cell types, including the lungs, as well as the endocrine part of the pancreas [34]. Direct β-cell damage, cytokine-induced insulin resistance, hypokalemia, and drugs used to treat COVID-19 may contribute to impaired glucose control in people with DM. This complex two-way interaction between COVID-19 and diabetes creates a vicious cycle in which COVID-19 worsens dysglycemia and diabetes exacerbates the severity of COVID-19 [9].

In addition to all of the above, there are also **«organizational factors,»** which in turn cause problems in the treatment and monitoring of the patient's condition. In a

large study by I.A. Kshanti et al. (2021) with 1124 patients with diabetes aged 18 years and older participating authors studied the correlation between difficulties in diabetes management and related complications during the COVID-19 pandemic. It was established that 69.8% of patients experienced difficulties in treatment. Difficulties included attending a diabetes consultation 30.1%, accessing medication 12.4%, checking blood glucose levels 9.5%, controlling diet 23.8%, and doing regular exercise 36.5%. Complications related to diabetes occurred in 24.6% of subjects. Those who had difficulty managing diabetes during the COVID-19 pandemic were 1.4 times more likely to have diabetes complications (OR: 1.41, 95% CI: 1.09-1.83) than those who did not have [35].

Among 667 Americans aged 18-90 years with diabetes (type 1 diabetes (T1DM): 18%; T2DM: 82%), 19% and 17% reported problems accessing diabetes care and test strips, respectively. More than a quarter reported problems getting sugar-lowering drugs from the pharmacy, and more than a third reported problems consulting diabetes service providers. The pandemic led to non-adherence to the therapeutic regimen (14%), medication rationing (17%), and reduced monitoring (16%). Many found it difficult to monitor and control hypoglycemia (12%-15%) and lacked social support to help manage the risk (19%). Almost half reported a decrease in physical activity [36]. In this category of patients, the frequency of severe and mild hypoglycemia was 0.68 (95% CI from 0.5 to 0.96) and 2.75 (95% CI from 2.4 to 3.1) events per person per month, respectively [36].

Quarantine led to food restrictions in some cases. And due to the absence of a balanced diet, a deficit of electrolytes and trace elements quickly develops, carbohydrate metabolism is disturbed, and as a result, hypoglycemia develops.

Thus, the analysis of hypoglycemia causes during the treatment of patients with COVID-19 allows us to formulate the following recommendations:

- In patients undergoing outpatient or inpatient treatment for COVID-19, it is necessary to ensure careful control of the level of glycemia. Glycemic monitoring should be especially thorough in patients of the risk group (diabetes mellitus, prediabetes) and patients with a severe course of COVID-19.
- In patients with COVID-19 and concomitant DM, the dosage of oral antidiabetic drugs may need re-adjustment depending on blood glucose parameters and prevailing conditions. Serious changes in hypoglycemic drugs should be avoided, and treatment modifications should be carried out gradually.
- The known and possible hypoglycemic effects of drugs should be taken into account when determining the treatment program for COVID-19 in patients with diabetes mellitus.
- Polypharmacy and dangerous pharmacotherapeutic combinations should be avoided as much as possible when forming a treatment program.
- In the case of vaccination, clinicians should consider the possibility of hypoglycemia in high-risk patients (with diabetes, prediabetes) or patients with a history of COVID-19.

## CONCLUSIONS

1. Hypoglycemia can be an accidental clinical finding. But it can also be a natural consequence of treatment if it is carried out without taking into account the possible hypoglycemic effects of drugs and without careful monitoring of the patient's condition.
2. Hypoglycemia is caused by the mutually aggravating influence of diabetes and COVID-19, the high frequency of hypoglycemic reactions to various groups of drugs used in patients with COVID-19, and deficiencies in the organization of outpatient and inpatient care.
3. In order to prevent hypoglycemic states, patients should avoid sudden changes in the means of treatment for COVID-19, the type and dose of hypoglycemic drugs, carefully monitor the level of glycemia, avoid polypharmacy, and the use of combinations of drugs that are dangerous for hypoglycemia.

## PROSPECTS FOR FURTHER RESEARCH

There is no doubt that it is necessary to continue the search for new optimal methods of treatment and prevention of COVID-19, taking into account the pathogenesis of comorbid conditions, in particular diabetes, which will make it possible to improve the prognosis and quality of life of such patients.

## REFERENCES

1. WHO. Coronavirus (COVID-19) data. https://www.who.int/data#reports [date access 14.01.2023].
2. Pathan F, Selim S, Fariduddin M et al. Bangladesh Endocrine Society (BES) Position Statement for Management of Diabetes and Other Endocrine Diseases in Patients with COVID-19. Diabetes Metab Syndr Obes. 2021;14:2217-2228. doi: 10.2147/DMSO.S293688.
3. American Diabetes Association Professional Practice Committee; 6. Glycemic Targets: Standards of Medical Care in Diabetes–2022. Diabetes Care, 2022; 45(1):S83–S96. doi:10.2337/dc22-S006.

4. Shah K, Tiwaskar M, Chawla P et al. Hypoglycemia at the time of Covid-19 pandemic. Diabetes Metab Syndr. 2020;14(5):1143-1146. doi: 10.1016/j.dsx.2020.07.003.
5. Jayk Bernal A, Gomes da Silva MM, Musungaie DB et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2022;386(6):509-520. doi: 10.1056/NEJMoa2116044.
6. Parise R, Deruiter J, Ren J et al. Impact of COVID-19 therapy on hyperglycemia. Diab Vasc Dis Res. 2022;19(3):14791641221095091. doi: 10.1177/14791641221095091.
7. Siemieniuk RA, Bartoszko JJ, Zeraatkar D et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980. doi: 10.1136/bmj.m2980.
8. Marfella R, Paolisso P, Sardu C et al. Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes Metab. 2020;46(5):403-405. doi: 10.1016/j.diabet.2020.05.005.
9. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. Diabetes Metab Syndr. 2020;14(4):513-517. doi: 10.1016/j.dsx.2020.04.049.
10. Mahmoud AB, Alghriany AA, Shakor AB. The effect of chloroquine induced hypoglycemia on the levels of major blood serum proteins in diabetic mice. Egypt Acad J Biol Sci C Physiol Mol Biol. 2014; 6(2):138-148. doi: 10.21608/EAJBSC.2014.16041.
11. Hage MP, Al-Badri MR, Azar ST. A favorable effect of hydroxychloroquine on glucose and lipid metabolism beyond its anti-inflammatory role. Ther Adv Endocrinol Metab. 2014;5(4):77-85. doi: 10.1177/2042018814547204.
12. Douin DJ, Krause M, Williams C et al. Corticosteroid Administration and Impaired Glycemic Control in Mechanically Ventilated COVID-19 Patients. Semin Cardiothorac Vasc Anesth. 2022;26(1):32-40. doi: 10.1177/10892532211043313.
13. Strongin LG, Nekrasova TA, Belikina DV et al. Disglikemiya pri COVID-19 i sakharnom diabete 2 tipa: osobennosti glikemicheskogo profilya u gospitalizirovannykh patsiyentov i rol' steroid-indutsirovannykh narusheniy [Dysglycemia in COVID-19 and Type 2 Diabetes Mellitus: Peculiarities of the Glycemic Profile in Hospitalized Patients and the Role of Steroid-Induced Disorders]. Probl Endokrinol (Mosk). 2022;68(2):56-65. doi: 10.14341/probl12840. (in Russian).
14. Chou HW, Wang JL, Chang CH et al. Risk of severe dysglycemia among diabetic patients receiving levofloxacin, ciprofloxacin, or moxifloxacin in Taiwan. Clin Infect Dis. 2013;57(7):971-80. doi: 10.1093/cid/cit439.
15. Abbas HM, Al-Jumaili AA, Nassir KF et al. Assessment of COVID-19 Treatment containing both Hydroxychloroquine and Azithromycin: A natural clinical trial. Int J Clin Pract. 2021;75(4):e13856. doi: 10.1111/ijcp.13856.
16. Giaime P, Guenoun M, Pedinielli N et al. Hydroxychloroquine and azithromycin tolerance in haemodialysis patients during COVID-19 infection. Nephrol Dial Transplant. 2020;35(8):1346-1353. doi: 10.1093/ndt/gfaa191.
17. Karampela I, Dalamaga M. Could Respiratory Fluoroquinolones, Levofloxacin and Moxifloxacin, Prove to be Beneficial as an Adjunct Treatment in COVID-19? Arch Med Res. 2020;51(7):741-742. doi: 10.1016/j.arcmed.2020.06.004.
18. Althaqafi A, Ali M, Alzahrani Y et al. How Safe are Fluoroquinolones for Diabetic Patients? A Systematic Review of Dysglycemic and Neuropathic Effects of Fluoroquinolones. Ther Clin Risk Manag. 2021;17:1083-1090. doi: 10.2147/TCRM.S284171.
19. Levine M, Stellpflug SJ, Pizon AF et al. Hypoglycemia and lactic acidosis outperform King's College criteria for predicting death or transplant in acetaminophen toxic patients. Clin Toxicol (Phila). 2018;56(7):622-625. doi: 10.1080/15563650.2017.1420193.
20. Mahadevan SB, McKiernan PJ, Davies P, Kelly DA. Paracetamol induced hepatotoxicity. Arch Dis Child. 2006;91(7):598-603. doi: 10.1136/adc.2005.076836.
21. Sibiya N, Mbatha B, Arineitwe C et al. Covid 19 May Limit the Use of Anti-hyperglycemic Agents. Does it Call for the Development of New Anti-hyperglycemic Agents? Curr Diabetes Rev. 2022;18(3):e060821195364. doi: 10.2174/1573399817666210806114200.
22. Ray CY, Wu VC, Wang CL et al. Hypoglycemia Associated With Drug-Drug Interactions in Patients With Type 2 Diabetes Mellitus Using Dipeptidylpeptidase-4 Inhibitors. Front Pharmacol. 2021;12:570835. doi: 10.3389/fphar.2021.570835.
23. Elshimy G, Techathaveewat P, Alsayed M et al. Simple Reason for Hypoglycemia: ACE Inhibitor-induced Severe Recurrent Hypoglycemia in a Nondiabetic Patient. Cureus. 2019;11(8):e5449. doi: 10.7759/cureus.5449.
24. Hee Nam Y, Brensinger CM, Bilker WB et al. Angiotensin-Converting Enzyme Inhibitors Used Concomitantly with Insulin Secretagogues and the Risk of Serious Hypoglycemia. Clin Pharmacol Ther. 2022;111(1):218-226. doi: 10.1002/cpt.2377.
25. di Mauro G, Mascolo A, Longo M et al. European Safety Analysis of mRNA and Viral Vector COVID-19 Vaccines on Glucose Metabolism Events. Pharmaceuticals (Basel). 2022;15(6):677. doi: 10.3390/ph15060677.
26. Bunders MJ, Altfeld M. Implications of Sex Differences in Immunity for SARS-CoV-2 Pathogenesis and Design of Therapeutic Interventions. Immunity. 2020;53(3):487-495. doi: 10.1016/j.immuni.2020.08.003.
27. Guo W, Li M, Dong Y et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020:e3319. doi:10.1002/dmrr.3319.
28. Klonoff DC, Messler JC, Umpierrez GE et al. Association Between Achieving Inpatient Glycemic Control and Clinical Outcomes in Hospitalized Patients With COVID-19: A Multicenter, Retrospective Hospital-Based Analysis. Diabetes Care. 2021;44(2):578-585. doi: 10.2337/dc20-1857.
29. Piarulli F, Lapolla A. COVID 19 and low-glucose levels: Is there a link? Diabetes Res Clin Pract. 2020;166:108283. doi: 10.1016/j.diabres.2020.108283.

30. Zhang B. Expert Consensus on Telemedicine Management of Diabetes (2020 Edition). Int J Endocrinol. 2021;2021:6643491. doi: 10.1155/2021/6643491.
31. Kesavadev J, Misra A, Saboo B et al. Blood glucose levels should be considered as a new vital sign indicative of prognosis during hospitalization. Diabetes Metab Syndr. 2021; 15(1): 221-227. doi: 10.1016/j.dsx.2020.12.032.
32. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev. 2020:e33213321. doi: 10.1002/dmrr.3321.
33. Orioli L, Hermans MP, Thissen JP et al. COVID-19 in diabetic patients: related risks and specifics of management. Ann Endocrinol (Paris). 2020: S0003-4266(20)30068-8. doi: 10.1016/j.ando.2020.05.001.
34. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev. 2020. doi: 10.1210/endrev/bnaa011.
35. Kshanti IA, Epriliawati M, Mokoagow MI et al. The Impact of COVID-19 Lockdown on Diabetes Complication and Diabetes Management in People With Diabetes in Indonesia. J Prim Care Community Health. 2021;12:21501327211044888. doi: 10.1177/21501327211044888.
36. Ratzki-Leewing AA, Ryan BL, Buchenberger JD et al. COVID-19 hinterland: surveilling the self-reported impacts of the pandemic on diabetes management in the USA (cross-sectional results of the iNPHORM study). BMJ Open. 2021;11(9):e049782. doi: 10.1136/bmjopen-2021-049782.

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REVIEW ARTICLE

# STATE REGISTRY OF HUMAN GENOMIC INFORMATION IN UKRAINE: HOW TO ACHIEVE A BALANCE BETWEEN LAW, MEDICINE AND ETHICS

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## ABSTRACT

**The aim:** The purpose of this study is to analyze the provisions of the Law of Ukraine "On State Registration of Human Genomic Information" and to make proposals for its improvement taking into account international experience.

**Materials and methods:** The study was conducted on the basis of the analysis of normative material, investigative and judicial practice, decisions of the ECtHR, the position of experts involved in the process of identification of deceased persons, which was expressed during the Second All-Ukrainian Forum of Forensic Experts on June 17, 2022, and a working meeting of the leadership of the KNDISE, DSU "Main Bureau of Forensic Medical Examination of the Ministry of Health of Ukraine" with a representative of the European Training Center for Identification of Victims of Natural Disasters and Forensic Examination in Central Europe (ETAF) (Germany).

**Conclusions:** The Law of Ukraine «On the State Register of Human Genomic Information» is a progressive step towards normalizing the use of DNA analysis as an evidence tool. The detailed regulation of the types of information and subjects subject to DNA testing, taking into account the procedural status of the person, the gravity of the crime or official duties, fully complies with international standards. At the same time, the issue of legal certainty and compliance with the principle of confidentiality requires additional elaboration, since the provision of genomic information obtained in accordance with this law to the authorities of foreign states is possible only if these authorities and the relevant competent authority of Ukraine can establish such a regime of access to information that makes it impossible disclosure of information for other purposes or its disclosure in any way, including through unauthorized access. The procedure for selecting, storing, and using genomic information and enshrining it in this law requires unification, as the extensive departmental approach creates risks for the quality of the law, improper use of information, and minimizes the guarantee of its protection.

**KEY WORDS:** DNA, examination, evidence

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## INTRODUCTION

Nobel laureate Jennifer Dudna in her book "Breaking DNA" calls scientists to a broader understanding of their own fields and the application of knowledge to solve interdisciplinary problems [1]. One of these problems is the use of a person's genetic profile in criminal proceedings. DNA profiling is a modern procedure for establishing a system of identification features of a person based on a unique genetic composition, which contributes to a more accurate level of proof of the connection of the suspect to the scene of the incident, involvement in criminal acts (by biological traces on the instruments of the crime), etc. Testimony of witnesses under certain conditions can be unreliable, especially in situations of testimony regarding the event of a crime they witnessed (peculiarities of perception (psychological, physical, situational), the period of time that has passed since the event, pressure from interested parties).

In the paper, "The Neuroscience of Memory: Implications for the Courtroom," the researchers note that changing testimony during cross-examination due to forgetting, the dimming of the replay effect, can cast doubt on eyewitness testimony. Instead, the results of DNA analysis are recognized as scientifically based, which minimizes the risk of their appeal [2]. Back in 1990, the Council of Europe discussed the existence of a dual relationship between biomedical sciences and law. On the one hand, the law should provide answers to some questions caused by the progress of biomedicine. On the other hand, biomedical sciences can be used by law as auxiliary (for example, identification by DNA analysis - genetic dactyloscopy). The expansion of the use of this method led to a number of procedural, moral and ethical issues (taking DNA samples from relatives of the suspect), professional and accreditation requirements for laboratories, the regime of protection, preservation and use of genomic information [3].

## THE AIM

The purpose of this study is to analyze the provisions of the Law of Ukraine "On State Registration of Human Genomic Information" and to make proposals for its improvement taking into account international experience.

## MATERIALS AND METHODS

The study was conducted on the basis of the analysis of normative material, investigative and judicial practice, decisions of the ECtHR, the position of experts involved in the process of identification of deceased persons, which was expressed during the Second All-Ukrainian Forum of Forensic Experts on June 17, 2022, and a working meeting of the leadership of the KNDISE, DSU "Main Bureau of Forensic Medical Examination of the Ministry of Health of Ukraine" with a representative of the European Training Center for Identification of Victims of Natural Disasters and Forensic Examination in Central Europe (ETAF) (Germany).

## REVIEW AND DISCUSSION

Modern possibilities of molecular genetic examination, i.e. the study of human biological material, which is carried out with the aim of obtaining its genomic information, is a tool for improving the quality of justice. Such an interdisciplinary approach (medical and legal) corresponds to the tasks defined by the Strategy for the Development of the Justice System and Constitutional Judiciary for 2021-2023, which states that the improvement of the justice system will contribute to the establishment of the legal order, which is based on a high level of legal culture, the activities of all subjects social relations on the basis of the rule of law and the protection of human rights and freedoms, and in the event of their violation - their fair restoration in a reasonable time frame [4,5].

The use of human biological material for legitimate purposes of justice and law and order requires careful legislative regulation with a balance between the right to non-interference in private life, protection of personal data and public safety. As Yan Bernaziuk notes, the issue of understanding compliance with the principle of proportionality as a criterion for ensuring the necessary (fair) balance between public (public) and private interests is complex in theory and practice [6].

In the judiciary of Ukraine, the conclusions of DNA expertise are quite successfully used as a source of evidence. Yes, criminal proceedings were opened under Part 1 of Article 115 of the Criminal Code of Ukraine ("Murder") due to the discovery of an unidentified corpse of a man with traces of violent death in a reservoir. In the course of the pre-trial investigation, a forensic molecular genetic examination was conducted to establish all the necessary information and further identification of the corpse, and biological samples were also taken for the DNA profile of the daughter of the missing person. During the verification of the above-mentioned DNA profile, probable matches of kinship with the DNA profile of an unidentified corpse were established [7]. DNA profiling has been used quite successfully in criminal proceedings for crimes such as murder and rape. A seven-year-old girl was raped and killed in the Kherson region. Based on the comparison of the DNA profile with the biological materials found on the body and clothes of the victim, as well as the rope with which the rapist twisted the bag with the child's body, the crime was quickly solved with the DNA of the suspect. This method is an important source of evidence in the investigation of traffic accidents, illegal possession of vehicles, etc. [8].

The difficulty in using the possibilities of genetic examination was, first of all, the lack of a database of DNA profiles, which complicated the process of searching for suspects and increased the time of the investigation; the absence of a special law left open questions regarding the types of such databases, the subjects for which such data is collected, storage periods, grounds for destruction, etc.

As a result of military aggression by the Russian Federation, not only military personnel, but also a significant number of civilians became victims. Eight mass graves of civilians were discovered in Kyiv region. In total, out of 1,202 bodies of citizens discovered in the Kyiv region, the identities of almost 280 of them remain undetermined. As part of cooperation with the International Commission on Missing Persons (ICMP), Ukrainian prosecutors obtained DNA samples for the purpose of their identification. [9] It turned out to be impossible to identify the bodies of those killed at Azovstal, which necessitates a DNA examination. Currently, France has handed over a mobile laboratory to Ukraine for prompt resolution of issues of identification and identification of war victims in the de-occupied territories [10].

Currently, there is an urgent need to carry out DNA analysis for the identification of persons who were killed at the beginning of hostilities in the east of Ukraine in 2014. Thus, on November 5, 2014, the State Service for Veterans Affairs and Participants of the Anti-Terrorist Operation published a letter with information on the conduct of DNA examinations of the bodies of the dead and missing in the area of the anti-terrorist operation, in which it was noted that the conduct of DNA examinations is within the competence of the Ministry of Internal Affairs of Ukraine , in the system of which 17

laboratories have been created for carrying out DNA examinations. Relatives of the dead and missing should contact the district police department. On the basis of the relevant open criminal proceedings, the internal affairs authorities provided the relatives with a referral for a free DNA analysis. Identification of the bodies relied on the State Expert Forensic Center of the Ministry of Internal Affairs [11].

According to Art. 26 of the Law of Ukraine «On the National Police», the police, using the means of the information and communication system, fills and maintains in an up-to-date state the registers and databases (banks) of data included in the unified information system of the Ministry of Internal Affairs of Ukraine (part 1). Collection, accumulation, storage, use and destruction of genetic data (DNA samples) are carried out in accordance with the law (part 2) [12]. However, the Law of Ukraine «On the National Police» does not contain any additional provisions regulating the scope of powers to collect DNA and other personal data; there is no differentiation regarding the categories of persons whose DNA and other personal data may be collected; correlations between the need to collect personal data and the severity of the relevant crime have not been determined; the procedural guarantees of individuals regarding the collection, storage, and disposal of data are not regulated.

At the same time, Ukraine has not adopted a special law on the settlement of these issues, in accordance with international standards, ECtHR practice and the experience of EU countries.

According to the practice of the ECtHR, the collection of even publicly available data may fall within the scope of Article 8 of the Convention if such data are «systematically collected and stored in files held by the authorities». Any discretionary powers entrusted to national authorities (for example, the police) should be limited to a sufficiently clearly defined scope and method of their implementation [13]. These safeguards «are particularly relevant in the context of the protection of special categories of more 'sensitive' data, in particular information about DNA, which contains a person's genetic code, which is of great importance to both the individual and his/her family». The court noted that, when considering the issue of such taking of DNA material, «national courts are obliged to take into account the circumstances of each specific case, the personality of the convicted person and explain the reasons for their assumption that criminal proceedings against this person for similar crimes will be conducted in the future.» [14].

In the case «S. and Marper v. the United Kingdom (S. and Marper v. the United Kingdom)» regarding obtaining DNA data from a detained minor, the ECtHR found that in England and Wales there was no difference in the rules for collecting DNA according to the severity of the crime and the age of the offender. The limited possibilities for the justified person to delete data from the national database and to destroy the materials were regulated... in particular, there was no provision for an independent review of the justification for storage according to certain criteria, including factors such as the seriousness of the offense [15].

Ralph Roche, analyzing the powers of the National Police of Ukraine regarding the collection of DNA, came to the conclusion of the need for a detailed normative regulation of the following issues: Who decides on the collection of biometric material in each specific case? Are they approved by a judge (for example, relying on the relevant provision of the Criminal Procedure Code of Ukraine to ensure that this can be done only by the decision of the investigating judge on the basis of a substantiated submission by the prosecutor)? Under what conditions is biometric material collected - is there a possibility of depriving a person of his freedom for this purpose? Can the officials responsible for taking the sample use reasonable force to enforce the demand for the sample? Are there any time limits on taking samples, such as after the investigation begins or after the investigation is completed? Can a person be compelled to attend a police station or other premises for the purpose of providing samples if they have not been taken during any period during which such persons have been detained? If so, under what conditions? Who is responsible for creating a profile for inclusion in the database based on the sample? What security measures are in place to ensure that all access to personal databases is recorded? The requirement should be the recording of each access to personal data bases and the justification of such access as a necessary prerequisite. It is necessary to clearly outline the circumstances under which personal data can be transferred to other state bodies. It is necessary to determine the duration of the personal data storage period. These periods should vary according to the seriousness of the case resulting in the investigation of a particular person, regardless of whether he has been found guilty or not, as well as the level of risk that such person may pose. It is worth introducing differentiation between separate categories of persons whose personal data can be entered into the database. Control measures should be put in place so that there is a body represented by medical, ethical and legal experts with relevant experience who can determine the strategic principles of the operation of the database to ensure that the personal data stored in it are used only for the purposes provided by law, and

scientific achievements in the field of DNA were taken into account [16].

Worthy of attention is the positive experience of Poland, where the DNA data storage system was registered on April 23, 2007, the management of which is entrusted to the General Inspector of Personal Data Storage, the administrator is the head of the Polish police. The list of persons whose data is entered in this register is contained in the Criminal Procedure Code of Poland: persons with unknown data; individuals who try to hide their data; unidentified corpses; traces of unknown perpetrators of crimes; persons posing a threat (Article 74, Article 192a). Currently, the database contains 70,000 DNA profiles, the storage period is 20 years, and for particularly serious crimes - 35 years [17].

In Belgium, DNA is allowed to be taken from people who have been convicted of «serious crimes», which are clearly defined and include crimes such as rape and murder. A prosecutor or a judge may order the collection of DNA samples from persons suspected of crimes punishable by imprisonment for more than 5 years. Samples are not entered into the database, except in cases where a person has been convicted of a serious crime. There is a database of profiles obtained from persons convicted of serious crimes and a separate database of profiles obtained from material found at the scene of a crime.

In Ireland, DNA collection is governed by the Criminal Justice Act 2014, which created the DNA database. The general rule is that the police can only take a sample from a person aged 14 and over who has been arrested on suspicion of committing a crime punishable by imprisonment for at least five years. If the person has not been convicted, the DNA profile can be kept for a maximum of six years (three years for children). A number of precautions are taken in the process of collecting and analyzing DNA samples.

In 2015, Switzerland approved the Counter-Terrorism Strategy, which focuses on the use of DNA profiling and the creation of databases of persons involved in terrorist activities [18].

In Bulgaria, in 2020, the police successfully solved the crime of attacking the journalist Slavi Angelov on the basis of collected and analyzed biological materials, which were used to establish the DNA profile of the accused [19].

In Serbia, to implement the decision in the case of Zorica Jovanović, a state DNA registry was created to search for missing (abducted) children (infants) [20]. In the case of Dragan Petrović v. Serbi ECtHR pointed out that the procedure for taking samples for DNA profiling was not regulated in the Criminal Procedure Code of Serbia, on the basis of which relevant changes were made in 2011 [21].

In New Zealand, in 1995, a law on criminal investigations was adopted, which also regulated the procedure for taking DNA samples. In 2020, an independent commission, after conducting an analysis of the use of powers by law enforcement agencies, submitted a report to the Parliament for discussion and amendments to the current legislation (strengthening supervision). After the identified gaps and shortcomings, a decision was made to develop a new law on the regime of DNA and its use in judicial proceedings [22].

The analysis of the Law of Ukraine «On State Registration of Human Genomic Information» gives reason to pay attention to certain provisions that require clarification or are debatable. First of all, in Art. 2 states that one of the laws, according to which the database will be created, is the Law of Ukraine «On the Protection of Personal Data», this provision is consistent with Art. 3, which states the principle of confidentiality, and also recognizes the effectiveness of international agreements. In this aspect, there are certain risks for Ukraine associated with gaps in joining international agreements. In particular, on October 10, 2018, the Protocol on Amendments to the Convention on the Protection of Individuals during Automatic Processing of Personal Data (ETS No. 108) was opened for signature, the purpose of which was to modernize this Convention taking into account new challenges in the field of protection of individuals during the processing of personal data data that arose after its adoption in 1980. The Protocol provides an appropriate and comprehensive legal framework to facilitate the exchange of data across borders with effective safeguards for use. However, Ukraine, among other states (Turkey, Moldova, Romania, Azerbaijan), did not sign or ratify the modernized Convention («108+») (2018).

With regard to confidential data, the processing of personal data that reveals racial or ethnic origin, genetic data, biometric data that is recognized as confidential due to their risk factor, or personal data that relates to the state of health or sex life is carried out only if there is appropriate safeguards that provide protection against the risk of unjustified bias resulting from the use of such data, in particular against illegal discrimination. Thus, in order to ensure the proper use of genetic data bases in compliance with the principle of confidentiality, the exchange of such information within the framework of international cooperation, Ukraine should join this document [23]. Poland signed the Protocol on Amendments to this Convention on May 16, 2019 and ratified it on 10 June 2020.

Secondly, since DNA profiling is a sensitive procedure related to personal life, every citizen should be aware of the legal regulation of this procedure, that is, the law should be accessible, understandable and predictable.

However, the law of Ukraine contains a significant number of blanket (reference) norms that do not ensure the quality of the law, in particular: «the procedure for the mandatory state registration of human genomic information is approved by the Cabinet of Ministers of Ukraine» (Part 4, Article 5); the procedure for conducting voluntary state registration of human genomic information and the fee for providing services for voluntary state registration of human genomic information are determined by the Cabinet of Ministers of Ukraine (part 8 of Article 6); in the event of the introduction of martial law, the selection of biological material ... is carried out in a mandatory manner from military personnel, police officers, members of the rank and file of the civil defense service, as well as members of voluntary formations of territorial communities, categories of persons, the order and terms of the selection of biological material, as well as the place the storage of selected biological material in such cases is determined respectively by the Ministry of Defense of Ukraine, the Ministry of Internal Affairs of Ukraine, the Security Service of Ukraine, the State Security Office of Ukraine, the intelligence agency, the State Service for Special Communications and Information Protection of Ukraine, and in the case of voluntary formations of territorial communities - by the Cabinet of Ministers of Ukraine (Part 2 of Article 8); the procedure for selection and referral for molecular genetic examination (research) to establish genomic information, as well as the procedure for storing biological material of prisoners of war are approved by the Cabinet of Ministers of Ukraine (Part 6, Article 9); molecular genetic examination (research) for the implementation of voluntary state registration of genomic information is carried out on a paid basis by subjects whose competence, according to the legislation, includes the conduct of molecular genetic examination (research), in accordance with the procedure established by the Cabinet of Ministers of Ukraine (Part 3 of Art. 10); the procedure for accessing genomic information registered in the Electronic Register and its use is determined by the holder of the Electronic Register (part 3 of Article 16), etc. Such a number of bylaws, which will be adopted by an extensive system of bodies, increases legal uncertainty. In addition, the law stipulates the introduction of martial law as a mandatory condition for the selection of DNA samples from military personnel and policemen, although in other states such a procedure is mandatory upon recruitment. It is obvious that during the introduction of martial law, the procedure for taking samples from a large number of people will become much more complicated.

Thirdly, control over the observance of human and citizen rights during state registration of genomic information is carried out by the Commissioner of the Verkhovna Rada of Ukraine for Human Rights (Part 1 of Article 19). It is obvious that a collegial body (commission) should be created for control, which should include, according to the experience of other states, doctors, lawyers, public representatives, and human rights defenders. The grounds, terms of such inspection, reporting procedure, etc. are not regulated.

Fourthly, the Criminal Procedural Code of Ukraine should be supplemented with provisions regarding the possibility of collecting genetic information of the suspect's relatives (in which cases this procedure may be mandatory (forced), and when - voluntary), in order to avoid a contradiction with Art. 63 of the Constitution of Ukraine, according to which a person is not liable for refusing to testify or explain about himself, family members or close relatives, whose circle is defined by law.

## CONCLUSIONS

The Law of Ukraine «On the State Register of Human Genomic Information» is a progressive step towards normalizing the use of DNA analysis as an evidence tool. The detailed regulation of the types of information and subjects subject to DNA testing, taking into account the procedural status of the person, the gravity of the crime or official duties, fully complies with international standards. At the same time, the issue of legal certainty and compliance with the principle of confidentiality requires additional elaboration, since the provision of genomic information obtained in accordance with this law to the authorities of foreign states is possible only if these authorities and the relevant competent authority of Ukraine can establish such a regime of access to information that makes it impossible disclosure of information for other purposes or its disclosure in any way, including through unauthorized access. The procedure for selecting, storing, and using genomic information and enshrining it in this law requires unification, as the extensive departmental approach creates risks for the quality of the law, improper use of information, and minimizes the guarantee of its protection.

## REFERENCES

1. Dudna D, Sternberh S. Zlamaty DNK. Redahuvannia henoma ta kontrol nad evoliutsiieiu. [Break the DNA. Genome editing and the control of evolution]. K. 2019, p. 272. (in Ukrainian).
2. How Is DNA Profiling Used to Solve Crimes? https://online.maryville.edu/blog/how-is-dna-profiling-used-to-solve-crimes/ [date access 07.12.2022]

3. Analysis for Police and Criminal Justice Purposes Secretariat Memorandum prepared by the Directorate of Legal Affairs. Working party on genetic testing for police and criminal justice purposes (CAHBI/CDPC-GT) DNA. 1990. https://rm.coe.int/09000016809d6fef [date access 07.12.2022]
4. Zakon Ukrainy Zakon Ukrainy "Pro derzhavnu reiestratsiiu henomnoi informatsii liudyny" vid 9 lypnia 2022 r. [ The Law of Ukraine «On State Registration of General Human Information» 09 July, 2022]. https://ips.ligazakon.net/document/view/ji03492g?an=&ed=2022_07_09&dtm= [date access 07.12.2022] (In Ukrainian).
5. Stratehiia rozvytku systemy pravosuddia ta konstytutsiinoho sudochynstva na 2021-2023 roky, zatv. Ukazom Prezydenta Ukrainy vid 11 chervnia 2021 roku [Strategy for the development of the justice system and constitutional judiciary for 2021-2023, approved. Bydecree of the President of Ukraine dated June 11, 2021]. https://zakon.rada.gov.ua/laws/show/231/2021#Text [date access 07.12.2022] (In Ukrainian).
6. Bernaziuk YaO. Pryntsyp proportsiinosti u praktytsi Yevropeiskoho sudu z prav liudyny [The principle of proportionality in the practice of the European Court of Human Rights]. Expert: paradigms of legal sciences and public administration. Kyiv: Interregional Academy of Personnel Management. 2021;6(18):197-214. doi:10.32689/2617-9660-2021-6(18)-197-214. (In Ukrainian).
7. Ukhvala Vynohradivskoho raionnoho sudu Zakarpatskoi oblasti vid 18.06.2019 roku. Sprava № 299/1531/18. [Decision of the Vynogradivskyi District Court of the Transcarpathian Region dated June 18, 2019. Case No. 299/1531/18.]. https://zakononline.com.ua/court-decisions/show/82482131 [date access 07.12.2022] (in Ukrainian).
8. Zastupnyk holovy Natspolitsii Maksym Tsutskiridze: Znyklyi nachshtabu Odeskoho zahonu morskoi prykordonnoi okhorony Chertkov mav znachni borhovi zoboviazannia [Deputy Head of the National Police Maksym Tsutskiridze: Chertkov, the missing Chief of Staff of the Odesa Maritime Border Guard Unit, had significant debts]. https://mvs.gov.ua/uk/press-center/news/zastupnik-golovi-nacpoliciyimaksimcuckiridze-zniklii-nacstabu-odeskogo-zagonu-morskoyi-prikordonnoyi-oxoroni-certkov-mav-znacni-borgovizobovyazannyaza-dekilka-dniv-do-zniknennya-vin-prograv-veliku-sumu-v-kazino [date access 07.12.2022] (in Ukrainian).
9. Kyivshchyna: prokuratura otrymala pershi DNK dlia identyfikatsii zhertv ahresii rf u Makarovi [Kyiv region: the prosecutor's office received the first DNA to identify the victims of Russian aggression in Makarov]. https://www.unn.com.ua/uk/news/1975197-kiyivschinaprokuratura-otrimala-pershi-dnk-dlya-identifikatsiyi-zhertv-agresiyi-rf-u-makarovi [date access 07.12.2022] (in Ukrainian).
10. Identyfikatsiia zhertv viiny. Frantsiia peredala Ukraini mobilnu laboratoriiu DNK [Identification of war victims. France handed Ukraine a mobile DNA laboratory]. https://news.liga.net/ua/politics/photo/identifikatsiya-jertv-voyny-frantsiya-peredala-ukraine-mobilnuyulaboratoriyu-dnk-foto 21.07.2022 [date access 07.12.2022] (In Ukrainian).
11. Informatsiia shchodo zdiisnennia DNK-ekspertyz til zahyblykh ta znyklykh bezvisty v zoni provedennia antyterorystychnoi operatsii: Lyst Derzhavnoi sluzhby Ukrainy u spravakh veteraniv viiny ta uchasnykiv antyterorystychnoi operatsii vid 5 lystopada 2014 roku [Information regarding DNA examinations of the bodies of the dead and missing in the area of the anti-terrorist operation: Letter of the State Service of Ukraine for war veterans and participants of the anti-terrorist operation dated November 5, 2014]. https://ips.ligazakon.net/document/FN006736 [date access 07.12.2022] (in Ukrainian).
12. The Law of Ukraine "On the National Police" dated July 2, 2015. https://zakon.rada.gov.ua/laws/show/580-19#Text [date access 07.12.2022]
13. «Rotaru proty Rumunii (Rotaru v Romania)», rishennia Yevropeiskoho sudu z prav liudyny vid 4 travnia 2000 roku [ «Rotaru v Romania», decision of the European Court of Human Rights dated May 4, 2000.]. http://eurocourt.in.ua/Article.asp?AIdx=212 [date access 07.12.2022] (in Ukrainian).
14. Antonio PERUZZO against Germany and Uwe MARTENS against Germany. Applications nos. 7841/08 and 57900/12. https://hudoc.echr.coe.int/fre#{%22itemid%22:[%22001-121998%22]} [date access 07.12.2022]
15. Marper S, Marper V. the United Kingdom (Applications nos. 30562/04 and 30566/04): https://rm.coe.int/168067d216 [date access 07.12.2022]
16. Roche R. Comments on the provisions of the law of Ukraine on national police concerning the creation of databases for storage of personal data, including dna and other biometric material. 2017.
17. Polska baza danych DNA. http://forensicwatch.pl/web/polska-baza-danych-dna [date access 07.12.2022]
18. Switzerland and Counter-terrorism. https://rm.coe.int/0900001680a47bbb [date access 07.12.2022]
19. Slavi Angelov. 2020. https://rm.coe.int/bulgaria-reply-en-bulgarian-newspaper-editor-slavi-angelov-severely-be/1680a3d258 [date access 07.12.2022]
20. Fifteen "missing babies" applications pending in Strasbourg. https://rm.coe.int/rfe-interview-with-fsundberg/16809949eb [date access 07.12.2022]
21. Action Plan Dragan Petrović v. Serbia. Application no. 75229/10. The judgment of 14 April 2020, final on 14 August 2020. https://hudoc.echr.coe.int/fre#{%22itemid%22:[%22002-12789%22]} [date access 07.12.2022]
22. The Use of DNA in Criminal Investigations. Te Whakamahi i te Ira Tangata i ngā Mātai Taihara. December 2018. Wellington, New Zealand. https://www.lawcom.govt.nz/sites/default/files/projectAvailableFormats/DNA%20IN%20CRIMINAL%20INVESTIGATIONS%20-%20IP43%20-%20Final.pdf [date access 07.12.2022]

23. Akhtyrska N. Pravova rehlamentatsiia natsionalnykh reiestriv biolohichnykh danykh liudyny [Legal regulation of national registries of human biological data]. Scientific Bulletin of the Uzhhorod National University. Series: Law. 2022;69:385-390. doi: 10.24144/2307-3322.2021.69.65 (in Ukrainian).

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REVIEW ARTICLE

# HARM TO LIFE AND HEALTH AS A RESULT OF ACTS OF ILLEGAL ADOPTION: CRIMINAL LEGAL AND MEDICO-PSYCHOLOGICAL ASPECTS

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## ABSTRACT

**The aim:** To study the harm that can be a result of acts of illegal adoption and find out the effects on child life and health.

**Materials and methods:** The following methods were used: system-structural, regulatory, dialectical and statistical processing, The article provides data of the Court Administration of Ukraine of 2001-2007 on the conviction of 5 individuals involved in illegal adoption. Also data of the Unified Register of Court Decisions of Ukraine as of the 4th of September 2022 have been processed which served as the basis of illegal adoption criminal proceedings with only 3 guilty verdicts out of total number which came into force. In addition, the article provides examples that have been published in the Internet, media of Poland, the Netherlands, US and Ukraine.

**Conclusions:** It has been proved that acts of illegal adoption constitute criminal offence which not only infringes upon orphaned children settling procedures established by law, but also can be used for the "pseudo adoption" purposes, which can result in the following acts of violence against minors: physical, mental, sexual, psychological abuse, etc. The article considers their effect on life and health.

**KEY WORDS:** orphanhood, rights of the child, violation of the law

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## INTRODUCTION

According to the international documents on protection of children's rights: if a child lacks temporary or constant parental care, it has the right for special protection and help of the State. No family to a child is the evidence of violation of its family right provided by the Convention of the Rights of Child, article 20. That's why public attention in most countries is focused on comprehensive protection of rights of juveniles, especially on childhood and orphanhood problems that require special and extraordinary action from the State. Regretfully, orphanhood remains unresolved social problem not only in our country, but in many countries abroad. Increased number of orphans is the result of pandemics, natural disasters and catastrophes and other adverse situations that lately have been widely spread which impairs man'd health to a degree that leads to increased mortality rate among adult population. Today, the orphanhood problem is acute more than ever and tends to increase as a result of the Russian aggression.

This is the reason why the orphanhood problem can be addressed by finding home for such children by way of adoption as the best form of protection of orphaned child rights and interests. Institution of adoption is one of priority parenting forms. It guarantees harmonious all-round personal development, provides caring and loving family, meets basic needs of child, required for its physical and psychological development.

According to M. Skiepko and J. Brągoszewska adoption makes child feel safe, ensures natural (family) development conditions. Furthermore, it allows child to avoid mental, physical and social delay, gives opportunities for all-round development, forms standards of conventional social behaviour [1].

Institution of adoption is undoubtedly one of legal protection forms of children. It exists across EU countries. Protection of children's rights and interests is the comprehensive institution which is the part of the single international system of protection of human rights and freedoms. The international documents such as the Universal Declaration of Human Rights (1948), international Covenant on Civil and Political Rights, international Covenant on Economic, Social and Cultural Rights (1966), European Convention on the Protection of Human Rights and Fundamental Freedoms (1950), Hague Convention on Adoption (1967), UN Convention

on the Rights of Child (1989), Convention on Protection of Children and Cooperation in Respect of International (Inter-country) Adoption (1993), European Convention on the Exercise of Children's Rights (1996), etc. not only establish the right of child, but also determine organisational and legal framework for adoption as one of priority forms of legal protection of children's rights.

As adoption is aimed at finding an appropriate family with strong relationships for an orphaned child and let the child exercise its right for family care and all-round physical and psychological personal development, actions against the established adoption procedures violate children's rights international standards.

For example, the European Convention on Adoption of Children, article 15 includes the regulation that prohibits any illicit profiting from adoption, in other words it prohibits adoption on commercial or any other basis. Similar regulations are included in the Convention on Protection of Children and Cooperation in Respect of International Adoption (1993), article 32: "No one should receive undue financial or other benefits from international adoption activities, executives, administrators, and officials involved in adoption are not entitled to remuneration for the provided services", etc.

In this way, the global community shall address orphanhood problems in compliance with international documents on the protection of rights and interests of child given that legal protection of children's rights is not only an independent institution which is a part of the international system of the protection of human rights and freedoms, but is also supported and protected by international, constitutional, civil, family, criminal, and other legal provisions.

As illegal acts of adoption cause significant harm not only to child's interests, but also to its health and even life, criminal law of a number of countries of the world criminalise infringement upon social relationship in respect to adoption

For example, criminal liability for illegal acts of adoption is established in a number of countries of Europe and world: article 124 /a of the Criminal Code of Albania [2]; article 211a of the Criminal Code of Poland [3]; article 364 of the Criminal Law Act of Israel [4]; articles 221, 222 of the Criminal Code of Spain [5]; § 236 of the Criminal Code of Germany [6]; article 227-12 of the Criminal Code of France [7]; article 174 of the Criminal Code of Azerbaijan [8], article 173 of the Criminal Code of Georgia [9], article 172 of the Criminal Code of Tajikistan [10], etc.

## THE AIM

Study potential harm resulting from illegal acts of adoption and their adverse effect on life and health of adopted child, which substantiates feasibility of criminalisation of such offences.

## MATERIALS AND METHODS

When preparing this article, the authors used the system-structural method to study adoption institution as a legal object. The regulatory study was also used to analyse international documents on the protection of human and children's rights and criminal law of other countries that includes criminal ban of illegal adoption acts. The dialectical method was used to analyse institution of adoption in terms of relationship and interaction as the basic category, which allows a child to exercise its right for family care, but in case adoption procedure established by law is violated, life and health of a minor could be endangered. In addition, the statistical processing method was used, but due to the highly latent nature of illegal adoption acts, the authors had limited information about their actual status. However, the analytical data of the Court Administration of Ukraine of 2001-2007 provide information about 5 individuals convicted for illegal acts of adoption in 2003. According to the Unified Registry of the Court Decisions as of the 4th of September 2022, 25 criminal proceedings for illegal acts of adoption have been initiated, only 3 of which ended up in a guilty verdict in Ukraine. Furthermore, the authors give examples of illegal acts of adoption published in the Internet, media of Poland, the Netherlands, US and Ukraine.

## REVIEW AND DISCUSSION

Based on article 13 of the Declaration of Social and Legal Principles of the Protection and Welfare of Children, Especially when Children are Transferred for Parental Care and Adoption on National and International Level (1986), the main purpose of adoption is ensuring stable family for a child deprived of care of its parents. The European Convention on Adoption of Children includes an important article 11 which states that following adoption the child acquires status of a full member of the family of adoptive parents and has the same rights and responsibilities as their own children. The above international documents prove that adoption is one of the most prioritised forms of care of orphaned children or children deprived of parental care.

We'd like to note that the law of a number of world countries provides both national and inter-country adoption. However, the provisions of international documents on the protection of children's rights and law of a number of countries that ban acts of adoption recognised illegal are the most important.

For example, the European Convention on Adoption of Children, article 15 prohibits any illicit profiting from transferring a child for adoption, in other words it prohibits adoption on commercial or any other basis. Similar regulations are included in the Convention on Protection of Children and Cooperation in Respect of International Adoption (1993), article 32: "No one should receive undue financial or other benefits from international adoption activities, executives, administrators, and officials involved in adoption are not entitled to remuneration for the provided services".

The UN Convention on the rights of Child and Optional Protocol on Human Trafficking, Child Prostitution and Child Pornography include provisions that prohibit profiting from adoption, kidnapping, illegal removal of children from their own country, and provide legal actions to support prevention of the above offences.

The most countries of the world therefore recognise adoption acts illegal when a child is transferred for a fee in view of "legal" adoption in the future [11].

The above socially dangerous acts are pretty common in many countries and it's very difficult to estimate their exact number. Here's a few examples of illegal adoptions in the US which provide evidence of illegal methods of obtaining children for the purpose of adoption. For example: purchase of children from poor families, or kidnap them from their house, street or pre-school institution; force their biological parents whose mental state is not too stable to issue a consent to the adoption or obtain the consent by fraud. Then the illegally obtained children are "legalised" with the help of the national adoption system: by fake birth certificates and other fake documents required for the adoption to hide true origin of the child. This allows to identify the child as an alleged legal orphan [12]. This "adoption fraud" unfortunately exists in Ukraine where criminal groups are engaged in illegal adoption [13].

According to the Ministry of Justice, Poland has around 2000 illegal adoptions a year [14]. The offence is so widely spread that adoption centres are saying about the adoption "grey zone" in Poland. There are numerous Internet ads entitled "Belly's growing and looking for a family for the baby", "Belly to let", "Baby for ultimate family", "Baby for a childless couple" offering to give birth to a child and give it away right after the birth. There are also "customers" ads offering "adoption of unwanted babies". The ads offer a baby price of a few Zloty to hundred thousand Zloty. The money is paid during pregnancy and down payments are made as a financial support. The websites have over 400 visitors per day. Total number is already over 1.3 million visitors. These acts are highly harmful for the society and, according to experts, family and administrative law can't efficiently combat them, as they can't prevent potential criminals from continuing their profitable practice, especially so, when biological parents are often involved [15].

The Netherlands even imposed a moratorium on adoption from abroad when a government commission discovered that some children had been kidnapped or purchased like a commodity from their biological parents [16].

Unfortunately, illegal acts of adoption in Ukraine often stay out of respective criminal statistics due to their hidden nature. According to V. Haltsova, illegal acts of adoption are combined with other offences, such as abuse of office, proposal, promise, giving/receiving of undue benefits in the process of adoption, official forgery, human trafficking, etc., which promote illegal adoption. That is why the above criminal offences are the subjects of proceedings. Such cases are more common in legal practice [17]. For example: according to the statistics of the State Court Administration of Ukraine of 2001-2007, 2 persons have been convicted under article 169, part 2 of the Criminal Code of Ukraine in 2003, 1 person in 2005, 2 persons in 2006 [18]. As of 4 September 2022, the Unified Registry of Court Decisions includes data about 25 proceedings initiated for illegal acts of adoption, out of which only 3 guilty verdicts were pronounced [19].

Despite this, the law of Ukraine was under massive attack during adoptions, especially so during adoptions by foreigners. This had effect of a "criminal business". Foreigners and different adoption agents from the USA, Canada, Italy, France, and other countries applied to Ukrainian orphanages for the adoption of Ukrainian children. It looked like "mass pilgrimage" That is when massive violations and abuse have been discovered in inter-country adoption. Under simplified procedure Ukrainian children have been transferred to foreign adoptive parents without due examination and establishing their prospects of settling, which resulted in the inter-country adoption moratorium for a few years [20].

In the mid-90s four persons ended up on the dock in Lviv, including Deputy Head of Lviv region, chief physicians of two hospitals, and a social welfare officer. They transferred 1360 infants to foreigners for adoption. Investigators could only find 50 infants, fate of the others remained unknown [21]. Illegal adoption is definitely a concealed minor trafficking practice. For example: maternity house often told mother that her baby died at birth while the baby was alive and hospital manager and doctors transferred it for adoption [22].

Unfortunately there was a number of criminal groups with international connections that included orphanage officials who had numerous criminal contacts with doctors. For the purpose of adoption of Ukrainian

orphans by foreigners, the doctors came up with fake diseases for babies, which enabled foreigners to adopt them out of turn

As rightly observed by T. Cholan, the public danger of illegal adoption as criminal offence is that it disregards the principle of child as the highest social value from birth, as a result of which it becomes an "item" of an illegal agreement (in broad sense and in the eyes of civil law) on transferring child to individuals who may not meet requirements provided in the law [23].

As a rule, violation of the existing adoption law of Ukraine often takes shape of mediation, coercion, or blackmailing of parents with the purpose of adoption, falsification of documents required for adoption, separation of siblings and other illegal acts during adoption.

Indeed, the consequence of illegal adoption is that the child's security is at risk in many vital, psychological and legal aspects [15]. Public relations therefore require further legal protection using criminal law, which ensures protection of human rights in today's world [24].

We believe that public danger of acts of illegal adoption is that they not only violate adoption procedure established by the law of Ukraine and undermine moral foundations of the society, including right to adoption, but they can also affect the normal development and parenting of minors [17]. This doesn't exclude harm to life and health of adopted child. Here's a few examples.

In most cases after the adoption of Ukrainian orphans by foreigners, the State loses contact with them and has no information about the fate of these children, their living and parenting conditions. These children might have been adopted for other than parenting and personal development purposes. It is possible that their adoptive parents may use them for personal gain, in other words it was an act of "pseudo adoption" aimed at transplantation of donor organs rather than parenting, In some cases foreign parents adopted or applied for adoption to involve children in child pornography, use them in harmful production, force them to beg, etc.

The world knows the case when John Walter Kruger from the US adopted three boys in Ukraine. In a year police established facts of sexual abuse of the adopted boys. After that the children were returned to Ukraine. There also were cases when lonely elderly foreigners adopted minors to make children look after them, and instead of family the children got into slavery [25].

In result of illegal adoption children may experience physical, sexual, mental violence that harms their physical health, sexual immunity, mental development, etc. As a result, children may suffer from bodily injuries, or irreparable consequences for their health – disability, or even suicide or death. Minors may also suffer from mental disorders resulting from separation with their siblings. Such actions are recognised as illegal. Law of Ukraine prohibits such adoption actions that separate siblings as provided in article 210 of the Family Law of Ukraine. Separation of siblings is only possible under grave circumstances and on the consent of guardianship authority. 17 October 2018 the Supreme Court (case 333/3340/16-ts) issued an order on this providing explanation of grave circumstances under which siblings can be separated. Separation is only allowed if it meets best interests of children, namely: brother and sister never lived together, or their cohabitation is undesirable due to dangerous disease of one of the children [19].

Based on this, a criminal proceeding under article 169 part II of the Criminal Code of Ukraine was initiated against director of orphanage K. in Cherkasy region as brother and sister B. were adopted by different families and taken to Italy and Canada.

It should be noted that following the Russian aggression forced removal of Ukrainian children from temporarily occupied territories became massive. Children are removed for their further illegal adoption by citizens of Russia. For this purpose the aggressor is drafting a law on simplified registration of orphaned children. As of 2 May 2022 up to 181 children have been removed to Russia, only 1 200 of which are orphans, who in most cases have parents, caregivers and relatives [27]. Such actions are a gross violation of the Geneva Convention (IV) of 1949 art. 4, 49 and 147 on protection of civilians during war, which provides for occupant's obligation to keep civil status of children intact and UN Convention on the Rights of the Child of 1989.

It's hard to disagree with Elvira C Loibl that this is harmful for emotional and mental development of children as they have already had deep cultural and social self identification, especially teenagers, and identify themselves with the country of residence. So forced removal seriously traumatises them as cultural and social identity is essential for them [28]. Following separation which is an illegal act of adoption minors are seriously traumatised. As they have parents, relatives and caregivers they feel loss and can't forget their families. This may result in serious consequences for their life and health.

In this regard, psychologist O. Turina says that mental damage unlike physical damage which is always external, may be of intramental nature – mind is able to traumarise itself by thoughts, memories, emotions and affections it produces. Such mental damage is invisible and can be identified with the help of indirect characteristics where emotional pain dominates [29]. Furthermore, according to experts acts of illegal separation may affect mental condition and development of child

so much that it may feel "abandoned", "alienated", "violated", "humiliated", etc. Child feels "abandoned", when it lacks physical contact with mother, which results in the future in all kind of addictions, symbiotic relations, infantilism and fears [29]. The trauma of "alienation" is related to not having mama around who soothes and supports crying baby. People with this trauma live feeling lack of attention from people around them, they constantly strive to win their attention, they prone to manipulations, don't enjoy life [29]. The trauma of "violence" is present when child is systematically ill-treated, injured. It leads to psychopathy or builds psychopathic, asocial character. The trauma of "humiliation" is the blow to child's ego, it humiliates, despises, diminishes self-esteem, which causes mental disorders in "ego concept" and inferiority complex. Mental traumas of humiliation, violence, rejection, betrayal also occur in adulthood. As a rule, adults reconstruct their childhood traumas, but with now with their partners and family. That's why S. Freud mentioned "fate neurosis" resulting from childhood traumas [29]. So when children lose their parents, siblings, it causes mental trauma for them resulting from separation at illegal adoption. In the future, it may lead to depression, aggression, fits of rage, drug abuse, insomnia, and other serious consequences for child life and health [29].

## CONCLUSIONS

Adoption is an important institution of protection of children rights. It's meant to ensure their all-round and harmonious development and enables them to exercise their right for parenting in family.

International acts on the protection of children rights at adoption and laws of many countries include provisions that prohibit remuneration for adoption. Such remuneration is recognised illegal in criminal codes of many countries and has mediation nature. In addition, acts of illegal adoption may lead to separation of siblings, families and caregivers, during the Russian aggression in particular. This violates international law and leads to serious mental traumas.

Acts of illegal adoption are socially dangerous – not only they violate the adoption procedure established by existing law of Ukraine, but also infringe on protection of childhood – a very important public realm, rights and legitimate interests, cause significant harm to development and parenting of minors, their life and health.

Acts of illegal adoption of minors can lead to physical, mental, sexual, psychological and other kinds of violence. This occurs due to not uncommon cases of so called "pseudo-adoption" with the purpose of involvement of a child in porno business, donorship, begging or hard physical work. It can be accompanied by beating, bodily injures, tortures, mental violence, ill-treatment.

In case of separation of siblings or other family members at illegal adoption, children are seriously traumatised and the trauma may stay with them for the rest of their life.

Illegal adoption often leads to the dander of life and health of minors, especially so if it resulted in drug or alcohol abuse, disability, mental disorder, suicide, death, etc.

So governments must take all steps to continue combat acts of illegal adoption by imposing further criminal sanctions on them and strengthen punishment for them while involving international institutions that protect minors from infringement on their rights for physical, intellectual, psychological cultural and personal development.

## REFERENCES


1. Skiepko M, Brągoszewska J. Zaburzenia psychiczne u dzieci adoptowanych Psychiatric disorders inadopted children. Psychiatr. Psychol. Klin. 2009;9 (3):207-213.
2. Criminal Code of the Republic of Albania (1995, amended 2017). Legislationline. https://www.legislationline.org/download/id/8235/file/Albania_CC_1995_am2017_en.pd [date access 20.07.2022].
3. Kodeks karny. https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU19970880553/U/D19970553Lj.pdf [date access 20.07.2022].
4. Zakon ob ugolovnom prave Izrailya [Israel's Criminal Law]. 2010. http://crimpravo.ru/ codecs/izr/2.pdf[date access 18.07.2022]. (in Russian).
5. Ugolovnyiy kodeks Ispanii [Spanish Criminal Code]. Moskva: Zertsalo. 1998, p.218. (In Russian).
6. Ugolovnyiy kodeks FRG [Criminal Code of the Federal Republic of Germany]. Moskva: Zertsalo. 2000, p.208. (In Russian).
7. Ugolovnyiy kodeks Frantsii [Criminal Code of France]. SPb: Yurid. tsentr Press. 2002, p.650. (in Russian).
8. Ugolovnyiy kodeks Azerbaydzhanskoy Respubliki [Criminal Code of the Republic of Azerbaijan]. Baku: Yurid. lit. 2000, p.224. (in Russian).
9. Ugolovnyiy kodeks Gruzii [Criminal Code of Georgia]. SPb.: Yurid. tsentr Press. 2002, p.352. (in Russian).
10. Ugolovnyiy kodeks Respubliki Tadzhikistan [Criminal Code of the Republic of Tajikistan.]. SPb: Yurid. tsentr Press. 2001, p.410. (in Russian).
11. Cantwell N. The sale of children and illegal adoption. Terre des Hommes Netherlands. 2017. https://defenceforchildren.nl/media/1945/the-sale-of-children-and-illegal-adoption.pdf [date access 22.07.2022].

12. Loibl E. The Transnational Illegal Adoption Market: A Criminological Study of the German and Dutch Intercountry Adoption Systems.The Hague:Eleven International Publishing. 2019. https://intercountryadopteevoices.com/2019/09/21/adoptee-activism-in-america/ [date access 27.07.2022].
13. Orlovskyi R, Us O, Shevchuk V. Committing a Criminal Offence by an Organized Criminal Group. Pakistan Journal of Criminology. 2022;14(2): 32–45.
14. Rząd zaostrza prawo za handel dziećmi. Eksperci: Nielegalne adopcje zejdą do podziemi. https://wiadomosci.dziennik.pl/wydarzenia/artykuly/612252,nielegalne-adopcje-handel-dziecmi-resort-sprawiedliwosci.html [date access 22.07.2022].
15. Sejm rozpatrzy zmiany w kodeksie karnym: nielegalna adopcja dzieci. https://www.prawo.pl/prawo/projekt-zmian-w-kk-nielegalna-adopcja-dzieci,464703.html [date access 27.07.2022].
16. U Niderlandakh zamorozyly protseduru usynovlennia hromadianamy ditei z-za kordonu [In the Netherlands, the procedure for adoption of children from abroad by citizens has been frozen]. https://www.ukrinform.ua/rubric-world/3186953-u-niderlandah-zamorozili-proceduru-usinovlenna-ditej-zza-kordonu.html [date access 22.07.2022]. (in Ukrainian).
17. Gal`czova VV. Kry`minal`na vidpovidal`nist` za rozgoloshennya tayemny`ci usy`novlennya (udocherinnya) ta nezakonni diyi shhodo usy`novlennya (udocherinnya) [Criminal liability for disclosing the confidentiality of adoption (adoption) and illegal actions related to adoption (adoption)]. Kharkiv: Pravo. 2015, p. 248. (in Ukrainian).
18. Dovidka Derzhavnoi Sudovoi Administratsii Ukrainy [Certificate of the State Judicial Administration of Ukraine] 20.06.2007 r.№ 14-3950/07.(in Ukrainian).
19. Yedynyi reiestr sudovykh rishen Ukrainy [Unified register of court decisions of Ukraine].https://reyestr.court.gov.ua/ [date access 16.07.2022]. (in Ukrainian).
20. Bozhyk VO. Kryminalno-pravova okhorona mizhderzhavnoho usynovlennia [Criminal protection of interstate adoption]. Aktualni problemy derzhavy i prava. Odesa. 2009;47:80. (in Ukrainian).
21. Lukyanenko A. Skandalnoe delo o torgovle novorozhdennyimi v Odesskoy oblasti [Scandalous case of trafficking in newborns in Odessa region]. Zakon.kz. http://www.zakon.kz/175515-skandalnoe-delo-o-torgovle.html. [date access 16.07.2022]. (in Russian).
22. Ukhvala Kolehii suddiv Sudovoi palaty Verkhovnoho Sudu Ukrainy u kryminalnykh vid 22 sichnia 2008 roku [Decision of the Board of Judges of the Judicial Chamber of the Supreme Court of Ukraine in criminal cases, consisting of: presiding judge S. M. Mishchenko, judges S. M. Vus, V. F. Shkolyarov dated January 22, 2008]. Yedynyi derzhavnyi reiestr sudovykh rishen. http://www.reyestr.court.gov.ua/Review/2036669. [date access 16.07.2022]. (in Ukrainian).
23. Cholan T. Sotsialna zumovlenist vstanovlennia kryminalnoi vidpovidalnosti za nezakonni dii shchodo usynovlennia [Social conditioning of establishing criminal liability for illegal adoption actions]. Naukovyi chasopys Natsionalnoi akademii prokuratury Ukrainy. 2016;4(12): 178–185. (in Ukrainian).
24. Haltsova VV, Kharytonov SO, Khramtsov OM et al. Criminal law as a means of protecting human rights and freedoms in the modern world. Journal of the National Academy of Legal Sciences of Ukraine. 2021;28(3): 248-256. doi: 10.37635/jnalsu.28(3).2021.248-256.
25. Ukrainskykh ditlakhiv viddaly na usynovlennia pedofilu [Ukrainian children were given up for adoption by a pedophile]. OBOZREVATEL. https://incident.obozrevatel.com/ukr/crime/65341-ukrainskih-ditlahiv-viddali-na-usinovlennya-pedofilu.htm [date access 17.07.2022]. (in Ukrainian).
26. Seliuk M. Dytiachyi test na zrilist [Children's maturity test]. Den. 2006;6(2):98. (in Ukrainian).
27. Makaliuk B. Nezakonno kradut i tak samo khochut vsynovliuvaty. Yak ta kudy Rosiia deportuie ukrainskykh ditei [They steal illegally and also want to adopt. How and where is Russia deporting Ukrainian children]. https://vikna.tv/video/lyudy/nezakonno-kradut-i-tak-samo-hochut-vsynovlyuvaty-yak-ta-kudy-rosiya-deportuye-ukrayinskyh-ditej/ [date access 16.07.2022]. (in Ukrainian).
28. Loibl EC. The aftermath of transnational illegal adoptions: Redressing human rights violations in the intercountry adoption system with instruments of transitional justice. Childhood. 2021; 28(4): 477–491. doi:10.1177/09075682211064430.
29. Turynina OL. Psykholohiia travmuiuchykh sytuatsii [Psychology of traumatic situations]: navch. posib. dlia stud. vyshch. navch. zakl. Kyiv: DP "Vyd. dim "Personal". 2017, p.160. (in Ukrainian).

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REVIEW ARTICLE

# ENSURING THE RIGHT TO HEALTH CARE FOR GROUPS VULNERABLE TO HIV IN PENITENTIARY INSTITUTIONS AND PRE-TRIAL DETENTION CENTERS IN UKRAINE

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## ABSTRACT

**The aim:** To consider the problems of penitentiary health care for groups vulnerable to HIV in penitentiary institutions and pre-trial detention centers in Ukraine, and to determine the state of implementation of the rights of prisoners to health care.

**Materials and methods:** When writing this article, the authors used a number of scientific and special study methods: regulatory method, dialectical method, statistical method. We also conducted an anonymous survey of 150 released persons from penitentiary institutions and 25 medical workers from 7 penitentiary institutions and correctional colonies in different regions of Ukraine to assess the quality and availability of medical care for convicts vulnerable to HIV infection, tuberculosis, and viral hepatitis.

**Conclusions:** The right to health-care of convicted prisoners must be ensured in compliance with the principle of free choice of specialist according to health-care law, health-care standards and clinical protocols (in other words, amount and standards of health-care available for prisoners must be the same as that available for other people).

In practice prisoners are thrown out of the national health-care system, and the Ministry of Justice is unable to meet all needs. This can have a disastrous result as the penitentiary system will produce sick people who pose threat for civil society.

**KEY WORDS:** medical services, convicted patients, treatment in correctional facilities, prison health-care

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## INTRODUCTION

It is important to perceive the right to health of prisoners as a special case of the state's responsibility to a person, as a manifestation of the state's social function. This takes into account both the medical component (the presence and functioning of treatment and prevention facilities) and the state component (the creation within the state of conditions under which human health and the right to health care will be ensured the most).

At the same time, the right to medical care has a complex nature in relation to the person himself/herself, and his/her state of health, and consists of the possibility of a person realizing his/her right to receive such care in the event of an illness or pathological condition. It is especially important to note that a person cannot fully realize his/her right to life when he/she is deprived or limited in the right to medical assistance.

Starting with the adoption of the Universal Declaration of Human Rights (1948), the right to health is reflected in all important international legal documents devoted to medicine and the social security of citizens. The statement of the Declaration that everyone has the right to such a standard of living, including food, clothing, housing, medical care, and necessary social services, as is necessary for the maintenance of health and well-being, became the rule and model for the drafting of national legal norms.

Based on this and the content of medical law, the right to health care must be understood as the constitutionally established opportunity of each person to be provided with conditions established by the state under which social and environmental rights and legal guarantees in the field of health care, the right to free medical care in medical institutions as well as other factors contributing to the strengthening and protection of human health can be realized to the maximum extent possible.

## THE AIM

To consider the problems of penitentiary health care for groups vulnerable to HIV in penitentiary institutions and pre-trial detention centers in Ukraine , and to determine the state of implementation of the rights of prisoners to health care.

## MATERIALS AND METHODS

When writing this article, the authors used a number of scientific and special study methods: regulatory method, dialectical method, statistical method. We also conducted an anonymous survey of 150 released persons from penitentiary institutions and 25 medical workers from 7 penitentiary institutions and correctional colonies in different regions of Ukraine to assess the quality and availability of medical care for convicts vulnerable to HIV infection, tuberculosis, and viral hepatitis.

The survey was conducted in June 2021. Research questions were developed taking into account the basic health needs of these people. Due to the COVID-19 epidemic, access to inmates and staff has been limited. Therefore, the survey covered only those correctional facilities to which the researcher had access. At the same time, it was possible to cover all types of security institutions in three regions and various categories of inmates.

## REVIEW AND DISCUSSION

If the state assumed the function of punishing persons and limited the possibilities of mobility of prisoners by placing them in specialized institutions, it should provide the opportunity for such persons to undergo medical treatment and examinations, O. Petryshyn, S. Seriogina, and M. Romanov emphasize that [1, 2]. This is explained by the fact that a person's ability to move is not limited by conditions that lead to loss of health, but by the very fact of placing him/her in special institutions and isolating him/her from access to benefits provided by society. Therefore, the state has to provide such persons with the opportunity and access to medical care and return a physically healthy person to society.

Working in prisons, all medical staff must always remember that their primary duty to any prisoner who is their patient is to treat him/her. This is emphasized in the first of the UN Principles of Medical Ethics, which refer to the role of medical personnel, particularly doctors, in protecting prisoners and detainees from torture and other cruel, inhuman, or degrading treatment or punishment [3]. Medical personnel is obliged to provide them with the protection of physical and mental health and treatment of diseases of the same quality and level as those who are not imprisoned or detained, especially doctors entrusted with the medical care of prisoners and detainees [4].

The International Council of Prisons Medical Services reaffirmed this principle by adopting the Athens Oath [5]: We, prison health workers, meeting in Athens on September 10, 1979, hereby commit ourselves to the spirit of the Hippocratic Oath, that we will endeavor to provide the best medical care for those incarcerated in prisons for any reason, without prejudice and within the framework of our respective professional ethics. This principle is especially important for doctors. In some countries, full-time doctors can spend their entire careers working in prisons. In such situations, it is almost inevitable that these doctors establish a close relationship with the management of the penitentiary institution and may be members of the senior management of the penitentiary institution. One consequence of this may be that the warden occasionally looks to the doctor for assistance in the management of troublesome prisoners. For example, security officers may ask a doctor to sedate inmates who are being violent to other inmates or staff. In some cases, the administration of penitentiary institutions may require doctors to provide them with confidential information about a person's HIV status. Physicians must never forget that their relationship with each inmate must be primarily a doctor-patient relationship. A physician should never do anything to or cause patients to do anything that is not in their best clinical interests. Similarly, as with all other patients, doctors should always seek the patient's consent before taking any clinical action, unless the patient is clinically incompetent to give such consent. An online diploma course entitled Doctors Working in Prison: Human Rights and Ethical Dilemmas, provided free by the Norwegian Medical Association [6] on behalf of the World Medical Association, addresses many of these issues. See also the World Medical Association Declaration on the Starving, adopted by the 43rd World Medical Assembly, Malta, November 1991 and revised by the World Medical Association General Assembly in Pilanesberg, South Africa, in October 2006 [7]. Similar provisions are enshrined in Ukrainian legislation, which allows us to assert its compliance with generally recognized rules and approaches. The norms of various normative acts establish that those sentenced to convicted persons continue to be citizens of their state who have subjective rights and bear civil duties, albeit with restrictions on the legal status of a citizen. This directly follows from the content of Part 3 of Article 63 of the Constitution of Ukraine, which states that "an imprisoned person enjoys all the rights of a person and a citizen, except for restrictions defined by law and established by a court verdict". Furthermore, as defined

in numerous judgments of the ECHR, any restriction is acceptable only when it is established by law and is necessary for a "democratic society". It is this criterion that is determined in the context of European control.

The European Court of Human Rights constantly reminds us that in general prisoners continue to enjoy all the fundamental rights and freedoms guaranteed by the Convention, except for the right to liberty, when lawful imprisonment exclusively falls under the scope of Article 5 of the Convention. The right of every person to health and medical care declared in the Constitution of Ukraine is one of the basic rights in the legal status of a person.

The state guarantees all citizens the realization of their rights in the field of health care, including persons who are detained and serving prison sentences. According to Art. 3 of the Constitution of Ukraine, along with other freedoms and rights in Ukraine, human health is recognized as the highest social value. By guaranteeing citizens the realization of their rights, the state, among other things, undertakes to ensure that every citizen has the right to health care, medical assistance, and medical insurance (Article 49).

Article 6 of the Law of Ukraine "Fundamentals of the Legislation of Ukraine on Healthcare" enshrines a list of key elements that make up the content of the right to health: a) the standard of living, including food, clothing, housing, medical care, and social service, and other provisions, which are necessary for the maintenance of human health; b) a natural environment that is safe for life and health; c) sanitary-epidemic well-being of the territory and settlement where he/she lives; d) safe and healthy conditions of work, study, living, and recreation; d) qualified medical and rehabilitation assistance, including the free choice of a doctor and a rehabilitation specialist, the choice of treatment and rehabilitation methods in accordance with the recommendations of a doctor and a rehabilitation specialist, the choice of a health care facility; e) reliable and timely information about the state of one's health and the health of the population, including existing and possible risk factors and their degree, etc. [8-17].

That is, the legislator does not limit the right to health care exclusively with procedures or acts of a purely medical nature, but includes a significant list of guarantees for a person in various spheres of his/her life. And all of them create the content of the right to health care, which must also be guaranteed to prisoners and detainees.

According to the same law, medical care is defined as the activity of professionally trained medical workers, aimed at prevention, diagnosis, and treatment in connection with diseases, injuries, poisoning, and pathological conditions, as well as in connection with pregnancy and childbirth (Article 1). *Health insurance* is a type of personal insurance in case of loss of health due to illness or accident. Therefore, all these three key rights belonging to the medical field (the right to health, medical care, and health insurance) must be provided by the state. Regarding prisoners and detainees, the following question arises – do these rights belong to them in full or do the specifics of the conditions in which these persons are, or other circumstances make it possible to limit the content or scope of these rights? This issue is especially acute during the medical reform taking place in Ukraine [8], during the pandemic [9], and during military operations [10].

In the course of the study, an anonymous survey of medical workers at the Health Center of the State Criminal Enforcement Service of Ukraine (hereinafter referred to as the State Penitentiary Service of Ukraine) was conducted to assess the quality and availability of medical care for prisoners vulnerable to HIV, TB, and HC. It should be noted that from the moment of formation of the Health Center of SCES, a certain "isolation" of personnel from communication with outsiders is noted, as well as there is no access to official statistical data. In such conditions, it was not possible to conduct a large-scale survey, so the research managed to cover only 25 employees of medical units from 7 penal institutions and remand detention centers in different regions. At the same time, one of the conditions for participation in the survey was providing the respondents with a guarantee of complete anonymity without specifying even the name of the institution in which they work.

Among those who participated in the survey, 30% are doctors, 50% are paramedics, 10% are nurses, 5% are chiefs/heads of the medical departments, and 5% have no position. The majority of employees have sufficient work experience: 35% of respondents have worked for up to 3 years, 38% – from 4 to 8 years; 24% – from 9 to 15 years old; 3% – over 15 years. Over the past 3 years, most of the interviewed workers have received additional training on providing medical care to prisoners who are at risk of HIV/TB/VH. However, such training was mainly carried out either in the form of self-education of the employee (43% of respondents indicated this) or during seminars/trainings by non-governmental organizations (87%). According to the answers, only 3% of employees took part in the courses organized directly in the penitentiary institutions (hereinafter PIs) or pre-trial detention centers (PTDCs) with funds from the state budget, and another 12% received knowledge in this field during advanced training. All this points to the lack of systematicity in training and improving the qualifications of medical personnel, in particular, in HIV/TB/HG issues.

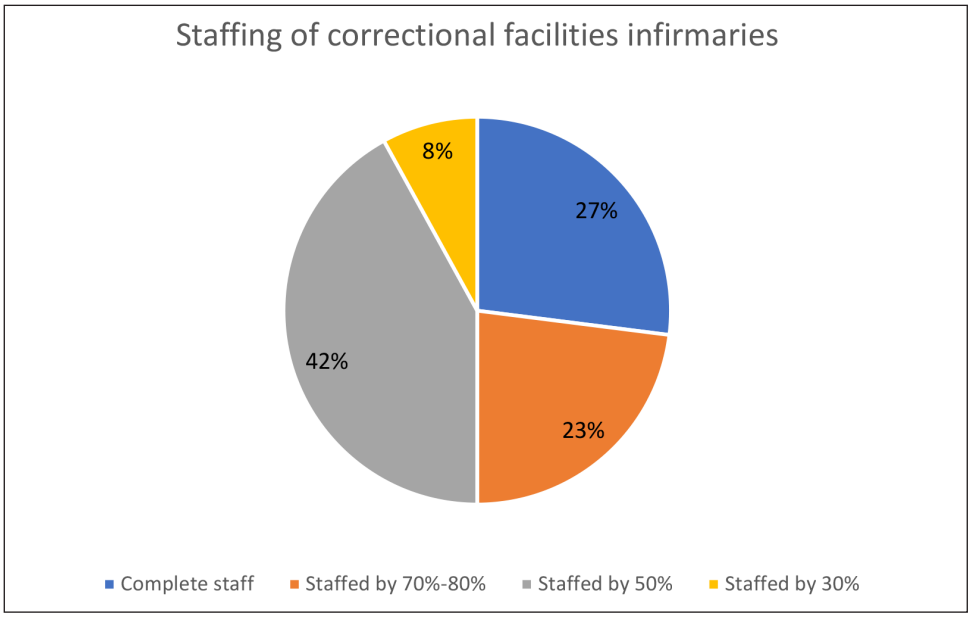


**Fig. 1.** Staffing of correctional facilities infirmaries

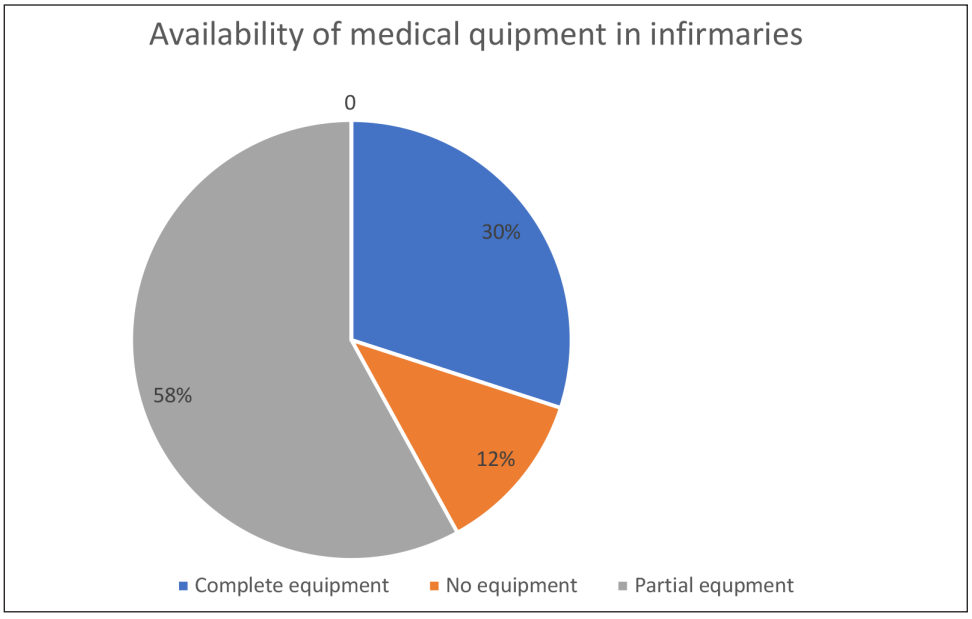


**Fig. 2.** Availability of medical quipment in infirmaries

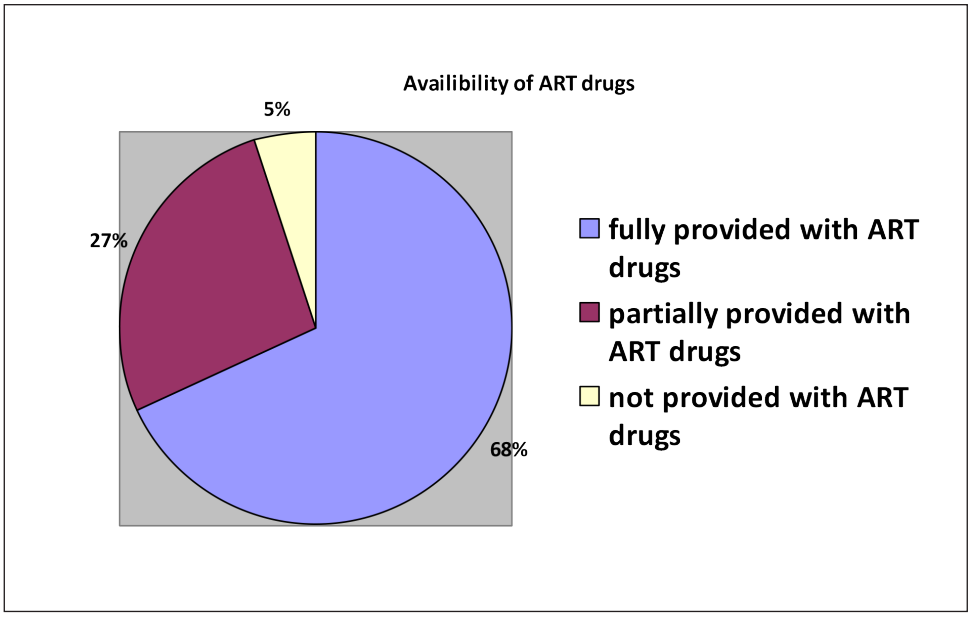


**Fig. 3.** Availability of ART drugs

The staffing of full-time positions in PIs and PTDCs is also insufficient. The interviewed personnel state that the medical department is fully staffed only in 27% of cases; up to 70-80% – 23% of respondents; up to 50% – 42% of questionnaires, up to 30% and less – 8% of respondents. (Fig. 1).

Medical units are not fully provided with licenses for the provision of medical care: only 37% of respondents referred to their availability. The state of technical support of medical units is also at inadequate level. Thus, in 58% of the questionnaires, the employees noted that the medical department is only partially equipped with the necessary equipment; according to 12% of respondents, it is not staffed at all; and only 30% of the respondents referred to complete equipment. (Fig. 2).

At the same time, in the comments, the respondents noted that even if the appropriate equipment is available in the medical department, it is either in a faulty condition, or there are no necessary materials, reagents, etc. for its intended use.

It is necessary to pay attention to a certain improvement in the provision of HIV tests. 75% of employees indicated their availability in the required amount, 22% indicated partial provision, and only 3% indicated their absence (with a note on procedural problems in obtaining them). The assessment of provision of facilities with drugs for ART is similar: fully provided – 68%; partially secured – 27%; unsecured – 5%. (Fig. 3).

The issue of the motivation of newly arrived detainees and prisoners to undergo such testing, as well as, in the future, to undergo treatment, remains quite problematic. Therefore, according to respondents' estimates, approximately 20–30% of newly arrived detainees and prisoners refuse to take the test (72% of respondents believe so); 12% determined this indicator at the level of 40%; 8% – at the level of 50% or more; 7% – at the level of 10%.

The situation with convicts receiving ART is a little better. According to respondents' estimates, no more than 10% of people refuse such treatment (82% of respondents indicated this). At the same time, the main reason is "protest mood" and the desire to resign due to health reasons (20% of respondents); indifference to one's own health (17% of respondents); mistrust on the part of prisoners in the administration of the PIs and treatment in general (15% of respondents). Only 8% of personnel cite a lack of awareness about the need for treatment and the lack of medicine in PIs as the reason.

The situation with the prevention and treatment of hepatitis is worse. Thus, the following answers were received to the question regarding the assessment of the situation with the provision of the medical units with rapid tests for the determination of HCV: available in the required amount in 62% of cases, 36% – for partial provision, completely absent in 2%. At the same time, the number of prisoners who, according to medical professionals, refuse this type of testing is smaller: up to 10% of newly arrived prisoners and detainees (89% of respondents believe so); 3% – determined this indicator at the level of 30-40%; 6% – at the level of 50% or more. One of the reasons is the lack of necessary medicines. In particular, according to estimated data, about 40% of prisoners do not receive treatment for viral hepatitis in PIs due to lack of medicine; 5% of people do not receive treatment due to indifference to their own health; due to mistrust of prisoners in the administration of the PIs and treatment in general, and insufficient awareness of the need for treatment – 4%.

Among the main problems that have a negative impact on the proper provision of the right to medical assistance, the respondents included the following: heavy workload due to lack of staff – 64%; low motivation due to unsatisfactory wages – 58%; pressure from the PIs administration – 27%; lack of necessary medical drugs – 23%.

The answers to the questions about measures to be taken to improve "penitentiary medicine" turned out to be quite similar and generally predictable: update medical equipment – 78% of respondents; increase the financial support of employees – 96%; make capital repairs in the wards and the medical office – 58%; provide HIV and HCV tests – 23%; provide medicines for HIV and HCV – 47%; conduct systematic training and consultations on the treatment of prisoners – 44%. Some personnel indicated the expediency of returning certified status for medical workers, as well as preferential retirement and additional payments for work with a complex category of patients.

The conducted survey confirms that the quality and accessibility of medical care for prisoners vulnerable to HIV, TB, and HCV do not meet the standards currently. The main problems with which staff associate existing gaps in work include personnel and material support, social protection, working conditions, uneven load, lack of equipment and medicines, training, and professional development.

In the course of the research, we also studied the attitude of the prisoners (after their release) to various forms of medical care, and the quality and availability of medical care for those vulnerable to HIV, TB, and HCV. Due to quarantine restrictions, the survey managed to cover 150 people released from PIs from 14 regions of Ukraine.

The vast majority of prisoners who took part in the survey were persons aged 18 to 25 years – 32% of them. Among those who are serving multiple sentences, there are slightly fewer prisoners of the same age – 23%, while the main part is between the ages of 35 and 50 – 49%. In general, the age of the respondents was distributed as follows: from 18 to 25 years old – 32%; from 25 to 35 years old – 28%; from 35 to 50 years old – 27%; from 50 to 60 years old – 12%; over 60 years old – 1%. The ratio of men to women is 17% and 83%, respectively.

21% of the prisoners serving prison sentences covered by the questionnaire have one previous conviction; 24% – two; 20% – three; 6% – from four to seven convictions. Detained for the first time – 29% of respondents. Among those surveyed, 58% had previously served sentences in prisons, and 44% were on the records of criminal enforcement inspectorates (probation bodies). Among the respondents, the total term of detention in the colony was distributed as follows: up to 1 year – 10%; from 1 to 3 years – 15%; from 3 to 5 years – 29%; from 5 to 10 years – 34%; from 10 to 15 years – 10%; over 15 years – 2%. That is, almost half of the prisoners served prison terms exceeding 5 years.

According to the data of this study, although 60% of prisoners have a clear plan for their actions after release, a large number do not have such a plan (27%), and 13% of respondents doubt the possibility of such planning. Similar were the answers to the question: "Do you believe that you will be able to live normally in freedom without breaking the law?": "Yes" – 58%; "No" – 15%; "It is difficult to answer" – 27%. The lack of skills and desocialization of prisoners is also confirmed by the fact that 51% of them do not plan to seek help after release; 23% – hope exclusively for the help of relatives; plan to visit relevant state (15%) and public institutions (11%). A significant number of released people have bad habits: 57% smoke; "like to drink" – 76%; use drugs – 24%. At the same time, 36% of respondents refer to the presence of any disease, and 21% refer to the group of disabilities, and limitations of working capacity. At the same time, 8% of those interviewed confirmed that they had an HIV diagnosis, 6% had hepatitis, and 18% had TB.

During the period of serving the sentence, 47% of the respondents applied for medical assistance in the pre-trial detention center or PIs. 21% wrote that they had reasons for such an appeal, but did not do that because of despair at "prison medicine". At the same time, every third of those who applied received the necessary help. The treatment or counseling provided was mostly for minor health problems (for example, SARS or HIV testing). The most common reasons for refusing medical assistance, treatment, or diagnosis were: lack of need – in 21% of cases; absence of a doctor of the appropriate profile – in 34%; lack of funding – in 42%; lack of necessary medicines – in 38%. Part (17%) of the respondents indicated that they did not receive the necessary help, treatment, or counseling as a result of the negative attitude of the staff of the PIs or PTDCs towards them. 7% of people who took part in the survey are taking ART therapy at the time of discharge; 2% indicated that they did not do this due to the lack of drugs. At the same time, 48% of prisoners among those who addressed this issue could not receive the necessary diet during treatment.

One of the negative aspects of treatment in places of detention remains the attitude of medical workers to the preservation of medical secrecy. In particular, 57% indicated that doctors always inform the staff of the colony about the presence of a diagnosis, which, in their opinion, poses a danger to others.

Communication with doctors and other specialists is also difficult: 47% determined that a doctor's appointment takes place once a week; 24% – once a month; 18% – every day and 11% – immediately after appeal. At the same time, 76% of respondents encountered problems when visiting the medical unit, and 54% of them noted that they encountered cases when the colony's employees did not take prisoners to the medical unit for various reasons. If prisoners are usually taken from the residential area to the medical unit in the morning, then in the workhouse it is determined by the work schedule and the end of working hours. After all, access to the medical unit takes from three hours to one or two days (from the moment the application is submitted).

Released people were offered to choose the type of examinations (analyses) available to them personally during the period of punishment. The results showed limitations in this area: determination of TORCH infections – 1%; HIV testing – 76%; general blood test – 34%; immunodiagnostics – 23%; viral load – 18%; fluorography – 84%. The list of specialists to whom you may appeal turned out to be limited (according to those released ones): therapist – 56%; dentist – 48%; physiologist – 89%; ophthalmologist – 35%; infectious disease doctor – 55%; gynecologist – 2%; dermatologist – 28%.

None of the interviewees tried to get a doctor's consultation "from the outside", citing the lack of funds to pay for these services. However, 32% of respondents noted that they had reasons for such a consultation.

The conducted survey of released people confirms that the state of ensuring the quality and availability of medical care for prisoners vulnerable to HIV, TB, and viral hepatitis is at an insufficient level. The main problems with which the prisoners associate existing gaps in work include personnel and material support of medical units; equipment and medicines; negative attitude of medical staff towards prisoners; the negative influence of other employees of PIs and PTDCs on medical workers (lack of real separation); inability to earn money while serving the sentence and pay for the services of doctors.

The Criminal Procedure Code of Ukraine enshrines the right to medical assistance and treatment, without establishing that this should take place in some special institution exclusively of the penal system, conditions, or form. Provisions of the Procedure for the provision of medical assistance to those sentenced to imprisonment,

approved by a joint order of the Ministry of Justice and the Ministry of Health of Ukraine dated August 15, 2014. No. 1348/5/572 [11] initially do not contradict this norm of the law, because in fact they only state what kind of medical care can be provided in the health care facilities of the SCES. It is emphasized that the prisoner has the right to freely choose a doctor, or a health care facility and to choose treatment methods in accordance with his recommendations.

The Criminal Procedure Code of Ukraine stipulates that only the procedure for obtaining medical assistance and treatment should be determined by this Code and the regulatory legal acts of the Ministry of Justice of Ukraine. As it follows from the analysis of other regulatory documents, the order is an act that establishes *the mechanism* for realizing the rights and obligations of individuals and legal entities, the procedure for applying the regulatory act, and *the conditions* for carrying out certain activities [12]. Hence, if the regulatory legal act of the Ministry of Justice of Ukraine is to determine the procedure itself, then its content should reflect a clear mechanism, procedure, and conditions for receiving medical assistance and treatment on a general basis for all, and not establish restrictions, in particular, regarding the place of receiving the corresponding services.

Instead, currently, the by-laws establish obstacles to the access by detainees and prisoners to services. Thus, the same Procedure for the provision of medical assistance to those sentenced to imprisonment, approved by the order of the Ministry of Health and the Ministry of Justice of Ukraine dated 15.08.2014 No. 1348/5/572, establishes both the right of the detained person to freely choose a doctor is established and only one form of interaction with him at the same time – by visiting of such a specialist to the PIs. The order or algorithm of other possible contacts is not regulated by departmental orders.

The medical units of the penal institutions are currently outside the scope of the outlined procedure since the chief administrator of budget funds did not conclude an agreement on medical care with them. The appropriate technical conditions for the implementation of the HIS (Hospital Information System) and its integration with the E-Health system have not been created, and the issue of obtaining medicines by electronic prescription has not been resolved. Medicinal products from the registry of the "Affordable Medicines" program can be obtained only by electronic prescription. Prisoners do not conclude a declaration with the doctors of the Health Center of SCES of Ukraine and, therefore, are not included in the program of such medical guarantees. Those who have such declarations with doctors "from the outside" are not provided with access to them, even though the penal institutions have all the possibilities for this.

Currently, communication with a doctor of a health care institution of the Ministry of Health of Ukraine can be provided remotely. In the system of the Ministry of Health, a system of remote consultation of primary care physicians has been launched [13], and elements of telemedicine are also being implemented [14]. The rules of the internal procedure of penal institutions [15] establish that payphones are installed in the place designated by the administration of the penal institution for telephone conversations and the availability of mobile (mobile) means of communication, which are registered with the institution, is ensured. The procedure for providing prisoners with access to the Internet [16] ensures the possibility of access to this network. In particular, the Internet access service, the use of IP telephony, and the use of video communication via the Internet are provided to prisoners in the Internet classroom.

As we see, the current regulations do not ensure a special definition of the algorithms for using the specified means of communication to contact a family doctor. As a result, in practice, the staff of the penal institutions, who are quite often mistakenly guided by the rule: "detainees and prisoners are allowed only what is expressly prescribed", do not provide the possibility of phone calls and the use of the Internet for consultations with a medical worker of the Ministry of Health of Ukraine.

It is clear that being in conditions of isolation, prisoners are actually deprived of both contacts and the possibility of earning money to receive paid out-of-office consultations with doctors. Therefore, the only option is to contact the medical departments of institutions.

## CONCLUSIONS

Convicted prisoner first of all is a patient who has the same rights as other people, and the existing legal acts provide no restrictions of the rights of convicted prisoners to publically accessible health-care (or any of its specific forms).. The right to health-care of convicted prisoners must be ensured in compliance with the principle of free choice of specialist according to health-care law, health-care standards and clinical protocols (in other words, amount and standards of health-care available for prisoners must be the same as that available for other people).

In practice prisoners are thrown out of the national health-care system, and the Ministry of Justice is unable to meet all needs. This can have a disastrous result as the penitentiary system will produce sick people who pose threat for civil society.

It makes no sense to continue funding of HCC PSU as the main health-care provider. The right to health-care of convicted prisoners must be ensured in compliance

with the principle of free choice of specialist according to health-care law, health-care standards and clinical protocols (in other words, amount and standards of health-care available for prisoners must be the same as that available for other people). These very provisions should be determining when assessing current status and establishing feasible algorithms and procedures of exercising the health-care rights of convicted prisoners.

## REFERENCES


1. Analiz vidpovidnosti Kryminalno-vykonavchoho kodeksu Ukrainy yevropeiskym standartam ta rekomendatsiiam Yevropeiskoho komitetu iz zapobihannia katuvanniam ta zhorstokomu povodzhenniu [Analysis of the compliance of the Criminal Code of Ukraine with European standards and recommendations of the European Committee for the Prevention of Torture and Cruel Treatment]. http://library.khpg.org/index.php?id=1184074406[date access 25.07.2022] (in Ukrainian)
2. Petryshyn O, Serohina S, Romanov M. Penitentiary healthcare: legal and practical aspects. Wiadomości Lekarskie. 2019; 72(12/2): 2591-2595. doi: 10.36740/WLek201912233.
3. Principles of medical ethics relevant to the role of health personnel, particularly physicians, in the protection of prisoners and detainees against torture and other cruel, inhuman or degrading treatment or punishment. General Assembly resolution 37/194, 18 December 1982. https://www.ohchr.org/en/instruments-mechanisms/instruments/principles-medical-ethics-relevant-role-health-personnel [date access 28.07.2022]
4. Moeller L, Stöver H, Jürgens R et al. Health in prisons: a WHO guide to the essentials in prison health. Copenhagen: WHO Regional Office for Europe. 2007. https://apps.who.int/iris/bitstream/handle/10665/107829/E90174.pdf?sequence=1&isAllowed=y [date access 28.07.2022]
5. Ethical codes and declarations relevant to the health professions. An Amnesty International compilation of selected ethical texts. The Oath of Athens (International Council of Prison Medical Services. 1979, p.40. https://www.amnesty.org/en/wp-content/uploads/2021/06/act750041994en.pdf [date access 11.08.2022]
6. Health care staff. http://www.apt.ch/en/knowledge-hub/detention-focus-database/health-care/health-care-staff [date access 11.08.2022]
7. WMA declaration of Malta on hunger strikers: adopted by the 43rd World Medical Assembly, St. Julians, Malta, November 1991and revised by the by the 68th WMA General Assembly, Chicago, United States, October 2017. https://www.wma.net/policies-post/wma-declaration-of-malta-on-hunger-strikers/ [date access 11.08.2022]
8. Melnychenko O, Chovpan G, Udovychenko N et al. The medical reform: realities and prospects for Ukraine. Wiadomości Lekarskie. 2021;74(5):1208-1212. doi: 10.36740/WLek202105130.
9. Ivats-Chabina A, Korolchuk O, Kachur A, Smiianov V. Healthcare in Ukraine during the epidemic: difficulties, challenges and solutions. Wiadomości Lekarskie. 2021;74(5):1256-1261. doi: 10.36740/WLek202105139.
10. Zhdan V, Holovanova I, Khorosh M. Bielikova I. et al. Analysis of the legislstive activity of the Ministry of Health jf Ukraine in the conditions of the Russian-Ukraine war in 2022. Wiadomości Lekarskie. 2022;75(6):1425-1433. doi: 10.36740/WLek202206101.
11. Pro zatverdzhennia Poriadku orhanizatsii nadannia medychnoi dopomohy zasudzhenym do pozbavlennia voli [On the approval of the Procedure for the provision of medical care to those sentenced to imprisonment]. https://zakon.rada.gov.ua/laws/show/z0990-14#Text [date access 11.08.2022] (in Ukrainian).
12. Termin «Poriadok» [The term "Order"]. https://zakon.rada.gov.ua/rada/term/22341 [date access 11.08.2022] (in Ukrainian).
13. Ukrainski likari teper mozhut provodyty konsultatsii onlain [Ukrainian doctors can now conduct consultations online]. 10/04/2020. https://www.ukrinform.ua/rubric-society/3003188-ukrainski-likari-teper-mozut-provoditi-konsultacii-onlajn.html [date access 11.08.2022] (in Ukrainian).
14. Telemedytsyna v praktytsi simeinoho likaria, feldshera ta medsestry [Telemedicine in the practice of a family doctor, paramedic and nurse]. 29/04/2020. https://telemed24.ua/articles/telemedycyna-v-praktycy-simeynogo-likarya-medsestry-feldshera [date access 11.08.2022] (in Ukrainian).
15. Pro zatverdzhennia Pravyl vnutrishnoho rozporiadku ustanov vykonannia pokaran [On the approval of the Rules of Internal Procedure of Penitentiary Institutions]. https://zakon.rada.gov.ua/laws/show/z1010-18#Text [date access 28.07.2022] (in Ukrainian).
16. Pro zatverdzhennia Poriadku orhanizatsii nadannia zasudzhenym dostupu do hlobalnoi merezhi Internet [On the approval of the Procedure for the organization of providing convicts with access to the global Internet network]. https://zakon.rada.gov.ua/laws/show/z1280-17#n16 [date access 28.07.2022] (in Ukrainian).
17. Law of Ukraine "Fundamentals of the Legislation of Ukraine on Healthcare". https://zakon.rada.gov.ua/laws/show/2801-12#Text [date access 18.08.2022]

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REVIEW ARTICLE

# SALE OF FALSIFIED MEDICINES VIA THE INTERNET IN UKRAINE: PROBLEMS OF DETECTION AND COUNTERACTION

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## ABSTRACT

**The aim:** The purpose of the article is to identify and analyze problematic theoretical and practical aspects related to the sale of counterfeit medicines via the Internet and measures to counteract the spread of their counterfeit products, as well as to search for evidence-based ways to improve the regulatory and legal mechanism that regulates the activities of the pharmaceutical business in Ukraine.

**Materials and methods:** The research based by the analysis of international acts, conventions and national legislation of Ukraine in the sphere of trade medicines via the Internet, scientific achievements in this area. Methodologically, this work is based on the system of methods, scientific approaches, techniques and principles with the help of which the realization of the research aim is carried out. There have been applied universal, general scientific and special legal methods.

**Conclusions:** Analyzed the legal regulation of online sales of medicines. Made the conclusion about necessity implementation of projects to create forensic records which have shown their effectiveness in the fight against counterfeit medicines in European countries.

**KEY WORDS:** medicines, falsification of medicines or circulation of falsified medicines, pre-trial investigation, electronic evidence

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## INTRODUCTION

Technological progress and the Covid-19 pandemic, in particular, have made their own adjustments to the life of every person. More and more services are moving online, technology saves time and money during online shopping and quarantine measures encourage a decrease in contacts between people. Global digitalization has a number of advantages: the convenience of various services, time savings, cashless payments, no need to leave the house, but there is one predominant drawback – the complication of monitoring such online transactions.

The sphere of protection of the health of each person is complex, providing the interconnection of various aspects of the general problem of the comprehensive protection of human rights. In the context of a fundamentally new demographic situation, which has developed in connection with the Covid-19 pandemic, as well as the spread of various diseases, there is an increased need for access to health services, including safe and effective medicines.

The UN Human Rights Council in resolution 32/15 points out that access to medicines is one of the fundamental elements in the progressive realization of the full realization of the right of every person to the highest attainable standard of physical and mental health. This main human rights mechanism of the UN system confirmed the commitment of Member States to ensure that all their citizens have non-discriminatory access to essential medicines as well as their affordability and high quality [1].

Ensuring wide online access to medicines requires state control of safety, quality and their effectiveness. At the same time, a wide range of pharmaceutical services provided via the Internet gives rise to a large number of counterfeit and illegal drugs. The issues of circulation of medicines and their falsification are among the most urgent in people's lives. Ensuring the safety of drug circulation is today an interdisciplinary subject of research for jurisprudence, medicine, ethics, sociology and a number of other fields of activity.

## THE AIM

The purpose of this article is to identify problematic theoretical and practical aspects related to the online sales of medicines in the pharmaceutical market and measures to counteract the spread of their counterfeit products via the Internet, as well as to search for evidence-based ways to improve the regulatory and

legal mechanism that regulates the activities of the pharmaceutical business in Ukraine.

## MATERIALS AND METHODS

The object of the research were scientific publications of Ukrainian scientists, normative legal acts in the field of circulation and control of medicines, international legal acts in the field of circulation of medicines, Directives of the European Union. Methodologically this work based on the system of methods, scientific approaches, techniques and principles with the help of which carried out the realization of the research aim. In the article were used statistical data, expert opinions, doctrinal ideas and reviews. Universal, general scientific and special legal methods were used in particular, the comparative legal method, the system-structural method, the method of generalization, the method of analysis and synthesis.

## REVIEW AND DISCUSSION

Until September 17, 2020 Ukraine did not provide for the possibility of online trade in medicines. At the same time, the Licensing conditions for the implementation of economic activities for the production of medicines, wholesale and retail trade in medicines, import of medicines (except for active pharmaceutical ingredients), approved by the Resolution of the Cabinet of Ministers of Ukraine dated November 30, 2016 № 929 in paragraph 27 provide for a ban on the sale of medicines remotely and through electronic commerce as well as by mail and through any establishments, except for pharmacies and outside them [2].

Decree of the Cabinet of Ministers of Ukraine dated March 23, 2020 № 220 amendments were made to the above Licensing Conditions, according to which licensees who have a license to carry out economic activities in the retail trade in medicines are allowed to trade in medicines remotely [3]. However, in accordance with the Law of Ukraine «The Protection of the Population from Infectious Diseases» [4] and the Law of Ukraine «The Legal Regime of the State of Emergency» [5], the right to sell medicines remotely is granted only temporarily – for the period of quarantine.

The Law of Ukraine «On Amendments to Article 19 of the Law of Ukraine «On Medicines» regarding the implementation of electronic retail trade in medicines» dated September 17, 2020 supplemented the above article with the following provision: «The business entity, who has a license to carry out economic activities in the retail trade in medicines, can carry out retail trade in medicines using information and communication systems remotely (electronic retail trade in medicines)». This law also lists the requirements that must be met by such business entities so, without compliance with such requirements, trade should be recognized as illegal [6].

On September 22, 2021, the Cabinet of Ministers of Ukraine, by Resolution № 1002, made changes to the Licensing conditions for the implementation of economic activities for the production of medicines, wholesale and retail trade in medicines, import of medicines (except for active pharmaceutical ingredients) and approval of the Standard form of the contract on the delivery of medicines to the consumer, which provide for the introduction of electronic trade in medicines, according to which electronic retail trade of medicines and their delivery to the final to the consumer will be carried out only through pharmacies and their structural subdivisions, which are included in the List of business entities that have the right to carry out electronic retail trade of medicines [7].

The possibility of distance selling medicines is also expressly provided for in Article 85c of Directive 2001/83 / EC of the European Parliament and of the Council of the European Union of 06.11.2001 «On the Code of Community Laws for Medicinal Products for Human Use» [8].

Should paying attention to the MEDICRIME Convention (Council of Europe Convention on the counterfeiting of medical products and similar crimes involving threats to public health), which Ukraine was one of the first to sign. This document is an international instrument of criminal law in the field of combating counterfeit medicines. The Convention obliges all signatory states to establish criminal liability for the commission of crimes related to the falsification of medicines [9].

In Finland, the United Kingdom, Poland and the United States allowed by legislation the sale of medicines via the Internet and their delivery by mail, which provides for certain regulatory requirements for such activities. In addition, for example, in Finland, allowed distance selling of prescription drugs.

The market of legal medicines always accompanies the market of counterfeit ones. Unfortunately, more and more cases of counterfeit medicines are being traded through the Internet. These actions are qualified under Part 2 of Art. 321-1 of the Criminal Code of Ukraine (falsification of medicines or circulation of counterfeit medicines) [10]. According to part 2 hours 1 tbsp. 2 of the Law of Ukraine «On Medicines» a counterfeit medicines is a medicines that is deliberately labeled not identical (not corresponding) to the information (one or more of them) about the medicines with the corresponding name entered in the State Register of Medicines of Ukraine, as well as medicinal a drug deliberately counterfeited in another way and does

not correspond to the information (one or more of them), including the composition of the drug with the corresponding name entered in the State Register of Medicines of Ukraine [11].

The study of falsification of medicines was highlighted in the works of O. Huk [12], R. Daraha [13], I. Kovalenko [14], A. Lytvyn [15], V. Tkalich [16], B. Shchur [17], N. Eiben [18] and others. O. Huk stressed that the counterfeiting of medicines on the Ukrainian pharmaceutical market is facilitated by: the presence of a system of further sales of counterfeit and substandard medicines alongside illegal production; sale of medicines by wholesale companies and with the help of Internet resources; creation and state support of the over-the-counter drug consumption industry [12]. I believe that I. Kovalenko was right when said, that the biggest danger is the sale of medicines over the Internet, which attracts criminals with the opportunity to act anonymously. The level of falsification in this segment of the market reaches 50% [14].

It should be noted that the sale of counterfeit medicines via the Internet contains the same signs as the sale of such medicines through offline sales namely the signs specified in Art. 2 of the Law of Ukraine «On Medicines» [11]: non-identical labeling to information about the medicines with the corresponding name entered in the State Register of Medicines of Ukraine; fake in another way and does not correspond to the information about the medicines with the corresponding name entered in the State Register of Medicines of Ukraine. Taking this into account, the corpus delicti will not differ, the only difference is the method of treatment – remote sales via the Internet.

From the point of view, it is possible to grow conclusions, which are medically owned as they are not registered in Ukraine, but they are falsified, «de jure» they are not considered. For example, it is clear that if the medicines is registered in Ukraine at a dose of 10 mg and the drug product is registered at a dose of 5 mg, it is not included in the State Register of Medicanes of Ukraine. In this way, the addition of the drug at a dose of 5 mg according to the dignified legislation of Ukraine, will not be falsified [19].

The specifics method of treatment complicates the process of investigating falsification. The difficulty lies in identifying offenders because the use of Internet resources provides almost complete anonymity, payment can be made to the accounts of nominees or using cryptocurrencies the movement of which cannot be tracked. V. Shevchuk, I. Parfylo and M. Sokolenko were right when wrote that, electronic traces make up only 23.4% of the total set of traces detected during the investigation of falsification of medicines[20].

After the stage of detection of falsification, the formation of an evidence base will be based meeting the conditions for the admissibility of evidence when it is presented for trial becomes an obstacle. First of all, the main evidence of the fact of falsification of medicines is a forensic chemical-pharmaceutical examination of the medicine. But the search for the perpetrator is also important. In the case of a non-cash payment for an Internet order in the national currency of Ukraine the bank that carried out this transaction may at the request of the investigator, provide information about the recipient of the payment, his bank account, passport data. All this simplifies the search for a criminal who probably sold counterfeit medicines but, at the same time, does not exclude the possibility of opening a bank account for a figurehead who has nothing to do with these acts.

Another piece of evidence can be a web page at a separately created Internet address or a page on social networks that is one that does not have a separate domain, but has an individualized Internet address through counterfeit medicines were sold. In this case, the problem arises of their reflection in the procedural documents of the pre-trial investigation, which is due to the absence of the concept of «electronic evidence» in the criminal procedure legislation.

Based on the analysis of judicial practice, it can be argued that such evidence (websites, files, databases) was obtained using a standard set of investigative actions (temporary access to things and documents, search, removal of information from electronic information systems, etc.), while were drawn up as documents, expert opinions, physical evidence, which later presented in court, which is incorrect and, according to all the rules, for examining evidence in criminal proceedings, should be recognized as inadmissible. This is also noted by the authors of Report on Ukraine № 2016 / DGI / JP3608 dated 03.11.2016, prepared by the Office of the Cybercrime Program with the support of Council of Europe experts. They believe that such a phenomenon as electronic evidence should be defined by fixing a special definition of the concept of electronic evidence or by making such changes to the general definition of evidence [21].

At this stage, in accordance with Part 2 of Art. 264 of the Code of Criminal Procedure of Ukraine does not require the permission of the investigating judge to obtain information from electronic information systems or part of it access to which is not limited to its owner, owner or holder or is not associated with overcoming the logical protection system [22]. So, the receipt of data from the company's web page is legal and given the practice is formalized by an inspection with a protocol. At the same time, such an approach violates the princi-

ple of full, comprehensive, objective, direct clarification of all circumstances, since information contained on the Internet can be quickly deleted, coded, changed, and the like. Therefore, when working with such information, it is imperative to understand what is the original and what is a copy.

Returning to the identification of the offender and given the likely anonymity of the page on social networks, it seems possible to obtain information from providers that can determine the IP address of the computer from which the correspondence was carried out, but this does not protect against the possibility of the criminal using shared computers or simple destruction devices. At this stage, the innovative technologies and legislation of Ukraine, which are available to investigators are exhausted, therefore, given the widespread judicial practice, the only possible way to identify the offender is to conduct such an undercover investigative and search action as control over the commission of a crime in the form of an operational/control purchase.

Thus, given the imperfection of the methods for investigating this category of crimes, complicated by their commission using the Internet, there is a real need to create detailed control over the circulation of drugs sold remotely. To do this, you can refer to the experience of those countries in which this system is already implemented. First of all, the EU countries separately regulate the requirements for online pharmacies, that is, since 2014 the legal framework for the common logo of online pharmacies has been adopted, defined by the Directive of the European Commission 2001/83 / EC, as amended by Directive 2011/62/Eu [23]. On the official page of the EMA (Europian medicines agency) there is a list of official sites for all EU countries where the online sale of medicines is allowed, so the consumer can make sure that the online pharmacy is legal before buying, firstly, using a special mark and, secondly, by finding links to the pharmacy website on this page [24]. That is, this regulation provides only control over drugs that are sold in licensed pharmacies. In addition, the International Working Group on Combating Counterfeit Medicines (IMPACT) was created within the framework of the WHO, which approved a document dedicated to the fight against falsified medicines with help of innovative information technologies, which allow quick and effective detection of falsified medicines throughout the global supply system [25].

Another positive example of the implementation of an effective investigative tool is the Fakeshare project, which was introduced in 2013 to protect the European population from the risks associated with the sale of counterfeit medicines. This project is funded European commission under the program «Prevention of and Fight against Crime» [26]. The essence of the project is to create a web space with limited space for the exchange of reports on the investigation of cases of illegal online pharmacies between health regulators, law enforcement and customs authorities.

Coordination and optimization of initiatives is provided with the help of information technology. From analysis of scientific sources, we can make the conclusion that the use of computer software systems and networks to process and distribute information, technologies for protecting medicines from counterfeiting are used today in various countries of the world [18, 27]. As part of the project Fakeshare, a web platform www.fakeshare.eu was developed, as well as digital cooperation tools. For registered users of this Internet resource, more than 2,000 documents relating to cases of theft and falsification of medicines, analytical results on suspects, samples, scientific articles and special reviews of case studies of professional interest are available [28].

Thus, within the framework of this project, a certain forensic accounting has been created, which helps the authorities responsible for drug quality control in the countries of the European Union to interact. The implementation of the project is aimed at stimulating intersectoral as well as international cooperation to counter pharmaceutical crimes in accordance with Directive № 2011/62/Eu [23] and the MEDICRIME Convention [9]. The project aims to develop coordinated initiatives (such as investigation, information, education) against the illegal distribution of medicines, as well as to optimize the use of resources within the framework of national level activities by: ensuring coordination of investigative activities; collecting information on the illegal distribution of medicines on the Internet; exchange of information between countries [28]. This project has distinguished itself by its efficiency, as well, as its relative ease of implementation, which is the case for the introduction of such forensic accounting in Ukraine.

## CONCLUSIONS

For Ukraine the conduct of electronic trade in medicines is a novelty of the legislation, it has a number of advantages for both consumers and business entities. At the same time, control over the sale of counterfeit medicines by individuals using the Internet remains an urgent problem. This provides them with almost complete anonymity and impunity. Only method that has proven effective in investigating such crimes is to carry out a covert investigative and search action – operational/test purchase, but active digitalization creates more and more new schemes for committing such crimes

with fewer and fewer traces. The undoubted proof of falsified medicines is the chemical-pharmaceutical examination of the medicine, confirming or refuting the fact of its falsification.

An obstacle is also the lack of a specific system that would ensure the examination in court of the original electronic evidence and not its copy or the examination protocol. There is also a direct need to implement the obligations that the MEDICRIME Convention imposes on the signatory states namely: the creation of a universal logo, the creation of information pages in order to inform the public about official web pages where official medicines can be purchased and pay attention to quality control of those medicines that are already licensed on the territory of Ukraine.

Of course, these measures will not make it impossible to sell counterfeit drugs, but the implementation of a project like Fakeshare will help the pre-trial investigation authorities in investigating crimes related to the sale of medicines on the Internet.

## REFERENCES


1. Human Rights Council. Resolution adopted by the Human Rights Council on 1 July 2016. https://documents-dds-ny.un.org/doc/UNDOC/GEN/G16/156/12/PDF/G1615612.pdf?OpenElement. [date access 18.12.2022]
2. Pro zatverdzhennya Litsenziynykh umov provadzhennya hospodars'koyi diyal'nosti z vyrobnytstva likars'kykh zasobiv, optovoyi ta rozdribnoyi torhivli likars'kymy zasobamy, importu likars'kykh zasobiv (krim aktyvnykh farmatsevtychnykh inhrediyentiv): Postanova Kabinetu ministriv Ukrayiny vid 30.11.2016 r. № 929 [On the approval of the Licensing conditions for conducting business activities for the production of medicines, wholesale and retail trade of medicines, import of medicines (except for active pharmaceutical ingredients): Decree of the Cabinet of Ministers of Ukraine dated 30.11.2016 No. 929]. https://zakon.rada.gov.ua/laws/show/929-2016-%D0%BF#Text. [date access 18.12.2022] (in Ukrainian)
3. Pro vnesennya zmin do Litsenziynykh umov provadzhennya hospodars'koyi diyal'nosti z vyrobnytstva likars'kykh zasobiv, optovoyi ta rozdribnoyi torhivli likars'kymy zasobamy, importu likars'kykh zasobiv (krim aktyvnykh farmatsevtychnykh inhrediyentiv): Postanova Kabinetu Ministriv Ukrayiny vid 23.03.2020 № 220 [On making changes to the Licensing conditions for conducting business activities in the production of medicines, wholesale and retail trade of medicines, import of medicines (except for active pharmaceutical ingredients): Decree of the Cabinet of Ministers of Ukraine dated 03.23.2020. No. 220]. https://zakon.rada.gov.ua/laws/show/220-2020-%D0%BF#Text. [date access 18.12.2022] (in Ukrainian)
4. Pro zakhyst naselennya vid infektsiynykh khvorob: Zakon Ukrayiny vid 06.04.2000 r. № 1645-III [On the protection of the population from infectious diseases: Law of Ukraine dated 04.06.2000. No. 1645-III]. https://zakon.rada.gov.ua/laws/show/1645-14#Text. [date access 18.12.2022] (in Ukrainian)
5. Pro pravovyy rezhym nadzvychaynoho stanu: Zakon Ukrayiny vid 16.03.2020 r. №1550-III [On the legal regime of the state of emergency: Law of Ukraine dated 16.03. 2020 No. 1550-III]. https://zakon.rada.gov.ua/laws/show/1550-14#Text. [date access 18.12.2022] (in Ukrainian)
6. Pro vnesennya zmin do statti 19 Zakonu Ukrayiny «Pro likars'ki zasoby» shchodo zdiysnennya elektronnoyi rozdribnoyi torhivli likars'kymy zasobamy: Zakon Ukrayiny vid 17.09.2020 № 904-IX [On amendments to Article 19 of the Law of Ukraine "On Medicines" regarding electronic retail trade of medicines: Law of Ukraine dated 09/17/2020 No. 904-IX]. https://zakon.rada.gov.ua/laws/show/904-20#Text. [date access 18.12.2022] (in Ukrainian)
7. Pro vnesennya zmin do Litsenziynykh umov provadzhennya hospodars'koyi diyal'nosti z vyrobnytstva likars'kykh zasobiv, optovoyi ta rozdribnoyi torhivli likars'kymy zasobamy, importu likars'kykh zasobiv (krim aktyvnykh farmatsevtychnykh inhrediyentiv) ta zatverdzhennya Typovoyi formy dohovoru pro zdiysnennya dostavky likars'kykh zasobiv kintsevomu spozhyvachu): Postanova Kabinetu Ministriv Ukrayiny vid 22.09.2021 № 1002 [On making changes to the Licensing conditions for conducting business activities in the production of medicines, wholesale and retail trade of medicines, import of medicines (except for active pharmaceutical ingredients) and approval of the Standard form of the contract for the delivery of medicines to the consumer: Decree of the Cabinet of Ministers of Ukraine dated 09.22.2021. No. 1002]. https://www.kmu.gov.ua/npas/pro-vnesennya-zmin-do-licenzijnih-u-a1002?fbclid=IwAR2HjZs4nffKxiawTb_EkNkXmbAF0t_kWcs9pZ-EXHAfd3MTrEmJA3U-EIM. [date access 18.12.2022] (in Ukrainian)
8. Pro zvid zakoniv Spivtovarystva shchodo likars'kykh zasobiv dlya lyudyny: Dyrektyva Yevropeys'koho Parlamentu ta Rady YES vid 06.11.2001 №2001/83/ [On the set of laws of the Community regarding medicines for humans: Directive of the European Parliament and the Council of the EU dated 11.06.2001 No. 2001/83/]. https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. [date access 18.12.2022] (in Ukrainian)
9. Council of Europe Convention on the counterfeiting of medical products and similar crimes involving threats to public health. https://rm.coe.int/168008482f [date access 18.12.2022]
10. Kryminal'nyy kodeks Ukrayiny: Zakon Ukrayiny vid 05.04.2001r. № 2341-III [Criminal Code of Ukraine: Law of Ukraine dated 04.05.2001 No. 2341-III]. https://zakon.rada.gov.ua/laws/show/2341-14#Text. [date access 18.12.2022] (in Ukrainian)

11. Pro likars'ki zasoby: Zakon Ukrayiny vid 04.04.1996 r. № 123/96-VR [On medicines: Law of Ukraine dated 04.04.1996 No. 123/96-VR]. https://zakon.rada.gov.ua/laws/show/123/96-%D0%B2%D1%80#Text. [date access 18.12.2022] (in Ukrainian)
12. Huk OH. Fal'syfikatsiya likars'kykh zasobiv ta obih fal'syfikovanykh likars'kykh zasobiv v umovakh yevrointehratsiyi: postanovka problemy [Falsification of medicines and circulation of falsified medicines in the conditions of European integration: statement of the problem]. Journal of the Academy of Advocacy of Ukraine. 2014; 3(24): 44-49. (in Ukrainian).
13. Daraha RD. Vyiavlennia ta fiksatsiia faktiv obihu falsyfikovanoi produktsii, shcho vyhotovliaiut na nelehalnykh vyrobnytstvakh [Detection and recording of facts of circulation of counterfeit products manufactured in illegal industries]. Naukovyi visnyk Natsionalnoi akademii vnutrishnikh sprav. 2013; 2: 222-231 (in Ukrainian).
14. Kovalenko IA. Fal'syfikatsiya ta obih fal'syfikovanykh likars'kykh zasobiv: kryminal'no-pravove doslidzhennya : monohrafiya [Falsification and circulation of falsified medicines: a criminal-legal study: monograph]. Odesa : Vydavnychyy dim «Hel'vetyka». 2018, p.232. (in Ukrainian).
15. Lytvyn AA. Osoblyvosti taktyky ohliadu mistsia podii pid chas rozsliduvannia zlochyniv, uchyniuvanykh u sferi obihu likarskykh zasobiv. [Features of the tactics of inspection of the scene during the investigation of crimes committed in the field of circulation of medicines. Legal scientific electronic journal]. Yurydychnyi naukovyi elektronnyi zhurnal. 2018; 1: 200-203. (in Ukrainian).
16. Tkalich VY. Okremi napryamy protydiyi fal'syfikatsiyi li- kars'kykh zasobiv [Separate directions of combating the counterfeiting of medicines]. Kryminalistychnyy visnyk. 2012; 2: 101-105. (in Ukrainian).
17. Shchur BV, Kamenieva HV. Problemy formuvannia metodyky rozsliduvannia obihu nezakonnykh likarskykh zasobiv [Problems of formation of a technique of investigation of circulation of illegal medicines]. Visnyk Lvivskoho torhovelno-ekonomichnoho universytetu. Yurydychni nauky. 2018; 7: 271-278. (in Ukrainian).
18. Eiben HS. Vykorystannya innovatsiynykh tekhnolohiy zapobihannya fal'syfikatsiyi likars'kykh zasobiv [Use of innovative technologies to prevent falsification of medicines]. Pharmaceutical journal. 2020; 3: 46-52. (in Ukrainian).
19. Kostin I. V Ukrayini vkray skladno dovesty fakty fal'syfikatsiyi likars'kykh zasobiv [In Ukraine, it is extremely difficult to prove the facts of falsification of medicines]. Interfaks-Ukrayina. 18.01.2022. https://interfax.com.ua/news/interview/792354.html. [date access 18.12.2022] (in Ukrainian)
20. Shevchuk VM, Parfylo IV, Sokolenko MO. Falsification of medicines and distribution of falsified medicines in Ukraine: criminalistic means of detection and counteraction. Wiad Lek. 2021;74(11): 2946-2953.
21. Pro chynne zakonodavstvo i proekty zakoniv, shcho dopovnyuyut' rizni pytannya, pov''yazani z kiberzlochynnistyu ta elektronnymy dokazamy ta vnosyat' zminy do nykh [On current legislation and draft laws supplementing and amending various issues related to cybercrime and electronic evidence]. https://rm.coe.int/16806f3743. [date access 18.12.2022] (in Ukrainian)
22. Kryminal'no-protsesual'nyy kodeks Ukrayiny: Zakon Ukrayiny vid 13.04.2012 r. № 4651-VI [Criminal Procedure Code of Ukraine: Law of Ukraine dated 04.13.2012 No. 4651-VI]. https://zakon.rada.gov.ua/laws/show/4651-17#Text. [date access 18.12.2022] (in Ukrainian)
23. Directive 2011/62/eu of the european parliament and of the council «Amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products». https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32011L0062. [date access 18.12.2022] (in Ukrainian)
24. Buying medicines online. European medicines agency. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/falsified-medicines/buying-medicines-online#legal-framework-section. [date access 18.12.2022]
25. International Medical Products Anti-Counterfeiting Taskforce. Anti-counterfeit Technologies for the Protection of Medical Products. http://www.who.int/im-pact/events/IMPACTACTechnologhiesv3LIS.pdf. [date access 18.12.2022]
26. Programme «Prevention of and fight against crime». European Commission. https://ec.europa.eu/home-affairs/sites/default/files/financing/fundings/pdf/isec/call_2012_20111020.pdf. [date access 18.12.2022]
27. Kovacs S, Hawes S, Maley S et al. Technologies for detecting falsified and substandard drugs in low and middle – income countries. PLoS Med. 2014; 9 (3).
28. Yevropeyskiy opyt v bor'be s fal'sifitsirovannymi preparatami [European experience in the fight against counterfeit drugs]. Fakeshare. https://www.apteka.ua/article/461972. [date access 18.12.2022] (in Ukrainian)

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REVIEW ARTICLE

# ANTI-ALCOHOL EDUCATION OF CHILDREN, YOUTH AND ADULTS AS A FACTOR IN THE FORMATION OF HEALTH-SAVING COMPETENCE THROUGH THE PRISM OF THE HISTORICAL EXPERIENCE OF UKRAINE

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## ABSTRACT

**The aim:** To analyze the leading trends in anti-alcohol education of children, youth and adults in Western Ukraine from the end of the 19th centry till the 1930s and to determine the possibilities of using this historical experience under modern conditions.

**Materials and methods**: A number of scientific methods were used in the research: chronological, historical, specific-search methods that provide selection, analysis of the source base, make it possible to determine general trends, directions, forms, achievements of anti-alcohol education of children, youth and adults in Western Ukraine from the end of the 19th century till the 1930s; extrapolation and actualization i.e. focus on creative understanding, adaptation and use of this historical experience under modern conditions, consideration of anti-alcohol education of children, youth and adults as a factor in the formation of health preservation and in general the Ukrainian gene pool under the modern challenges of the war, which Ukraine faced.

**Conclusions**: Knowledge about a healthy lifestyle became the basis for people's health-preserving behavior, anti-alcohol education acted as a factor in the formation of the health-preserving competence of an individual, which included relevant knowledge, skills and behavior for creating and cultivating a health-preserving environment. This experience now deserves to be used creatively in the process of forming the health-saving competence of the individual throughout his life.

**KEY WORDS:** health care, anti-alcohol education, society"Vidrodzhennia", sobriety movement, children, youth

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## INTRODUCTION

In Ukraine, as well as in the whole world, the problem of alcohol consumption by minors is particularly relevant. Thus, according to the WHO report published in 2020, it is stated that the most alcohol is consumed in Europe (43.8%), followed by the USA (38.2%) and the Western Pacific region (37.9%). World statistics show that more than a quarter (26.5%) of teenagers aged 15-19 regularly drink alcohol [1]. Every year, 1.8 million people in the world die from alcohol [2], 550 thousand men and women become chronic alcoholics, 180 thousand children are born mentally retarded, alcoholization of the population of childbearing age inevitably leads to violations of the genetic code that causes the birth of children with intelligence, physical and mental retardation; to eliminate the consequences of alcohol consumption, it is necessary to spend three times more money than the state receives from the sale of alcoholic beverages [3].

The same acute problem is the problem of alcoholization of the population in Ukraine. Alcoholism is one of the main risk factors for death and disability; in general, alcohol is the cause of almost 60 different diseases and painful conditions, including mental disorders, malignant neoplasms, cardiovascular diseases, various injuries, diseases of the lungs, musculoskeletal system, gastrointestinal tract, immunological disorders, increases the risk of premature birth, causes low birth weight in newborns, leads to shorter life expectancy in Ukraine compared to most countries of the European Union [1].

In Ukraine, alcohol ranks first among the causes of youth mortality. The extent of the spread of alcoholism

among children is of great concern. Thus, according to the results of a 2019 study within the framework of the international project «The European School Survey Project on Alcohol and other Drugs– ESPAD» [4], the vast majority (85.7%) of the surveyed teenagers have experience of drinking alcohol, that is, they drank during their lifetime alcoholic beverages at least once; almost half (46.3%) of the respondents have «significant» experience of alcohol consumption – drank alcoholic beverages ten times or more; in the last year, 74.7% of students drank alcoholic beverages, and 24.4% of respondents drank alcohol quite actively (from 10 times or more); almost half (46.5%) of the interviewed teenagers drank alcohol at least once in the last 30 days; 16.0% of respondents estimated the degree of their intoxication during the last consumption of alcoholic beverages at the level of 5 to 10 points, which can be characterized as «significant» intoxication; at the age of 10 or earlier, 13.4% of respondents tried alcohol for the first time, every fifth respondent experienced a state of significant alcohol intoxication for the first time at the age of 14 or earlier [4].

Therefore, alcoholism is one of the biggest threats to the health and self-realization of children and youth. Addiction to alcohol is one of the main reasons children commit offenses and crimes. There is a tendency to «rejuvenate» the initial age of children's introduction to alcoholic beverages. The social factors of this phenomenon are the negative example of adults, the environment in which children are, the advertising of alcoholic beverages, their availability to minors, the relative cheapness of alcohol, the lack of anti-alcohol education among children and adults, the inadequate level of anti-alcohol education at school, the growing neglect of children, their premature independence, lack of work to involve students in anti-alcohol propaganda, etc.

Despite the acuteness of this problem, Ukraine currently lacks both a reasonable assessment of the consequences of alcoholism among the population, especially among students, and a health care program for children and youth, the adult population, which was especially relevant during the war, when Ukraine faced the threat of losing its gene pool due to the death of Ukrainian soldiers who defend the sovereignty of the state in the fight against the Russian occupier, due to losses among the civilian population, the death of children, the forced deportation of children to Russia, etc. Under such conditions, the experience of the anti-alcohol public movement of Ukrainians, which gained large-scale proportions in Western Ukraine at the end of the 19th century and 1930s, can be usefuland had considerable success in the field of «sobering» society and protecting the health of Ukrainians, it covered various age groups, including children, youth, and adults.

Despite the fact that scientists are actively researching the health care problems of children and youth, the issues of anti-alcohol personality education, with a few exceptions (V. Gerasimchuk [5], L. Slivka [6], etc.), have not been deeply researched. It is worth noting that certain aspects of the problem of anti-alcohol education of children, youth and adults in Western Ukraine in the end of the 19th century and 1930s studied by both Polish and Ukrainian scientists. For example, B. Savchuk analyzed alcohol policy and the sobriety movement in Western Ukraine [7], the anti-alcohol activities of Ukrainian public associations in Galicia during this period were highlighted by I. Bilavych, H. Bilavych, B. Savchuk, L. Slivka, N. Fedchyshyn and others [8], the anti-alcohol movement in Transcarpathia as a factor in the hygienic education of youth in Transcarpathia in the second half of the 19th and early 20th centuries. V. Gerasimchuk [5] investigated the development of the anti-alcohol movement in Bukovina in the second half of the 19th and early 20th centuries. analyzed by B. Savchuk, S. Purych, M. Oliynyk, H. Bilavych [9] and others. Polish scientists J. Biskupski [10], R. Pelczar [11], I. Krasińska [12–13], R. Sławiński [13] consider as general problems the health of young individuals, the issue of prevention of alcoholism in children and adolescents on at the present stage, they also analyze the anti-alcohol movement in Poland at the beginning of the 20th century, highlight the role of abstinent teachers, priests in the fight against alcoholism and anti-alcohol education, highlight the importance of periodicals in the education of a healthy lifestyle for children and youth, etc. However, the scientific problem presented in the title of the article has not been deeply investigated.

## THE AIM

To analyze the leading trends in anti-alcohol education of children, youth and adults in Western Ukraine from the end of the 19th centry till the 1930s and to determine the possibilities of using this historical experience under modern conditions.

## MATERIALS AND METHODS

A number of scientific methods were used in the research: chronological, historical, specific-search methods that provide selection, analysis of the source base, make it possible to determine general trends, directions, forms, achievements of anti-alcohol education of children, youth and adults in Western Ukraine from the end of the 19th century till the 1930s; extrapolation and actualization i.e. focus on creative understanding,

adaptation and use of this historical experience under modern conditions, consideration of anti-alcohol education of children, youth and adults as a factor in the formation of health preservation and in general the Ukrainian gene pool under the modern challenges of the war, which Ukraine faced.

## REVIEW

In the 19th century in the fairway of the anti-alcohol movement in Western Ukraine, Ukrainian and Polish clergy [6, 7, 9, 11-14]. With the birth of the Ukrainian public movement in the second half of the 19th century in Halychyna, the «Prosvita» society (1868), the Russ' Pedagogical Society ((1881), later the Ukrainian Pedagogical Society (UPS) «Native School») entered the arena of the anti-alcohol struggle, numerous student societies, «Silsky Gospodar» (1899), at the beginning 20th century – Ukrainian youth societies («Sokil» (1894), «Sich» (1900), «Plast» (1911)), women's societies (Union of Ukrainian Women (1917), etc.), Ukrainian Medical Society (1910), «Medical Society (1910), the Ukrainian Hygienic Society (1929), numerous sports societies, etc. With the beginning of its existence (1909), the anti-alcohol and anti-nicotine society "Vidrodzhennia"became the leader of the movement for sobriety, the struggle for a healthy lifestyle of the Ukrainians of Halychyna in the first third of the 20th century.

Without resorting to statistics (this is thoroughly covered in B. Savchuk's monograph [7]), we note that, on the one hand, the state had an anti-alcohol law of April 23, 1920, on the other hand, the situation was actually complicated: as the magazine noted, "Vidrodzhennia", «according to the law in Poland, the maximum number of drunks can be 12,000, but in practice 20,000», therefore «they drink with impunity on Sundays and holidays, during trades, fairs, vacations, churches, on railways, etc.», «innkeepers» «sell alcohol to minors, give it as a loan, as collateral or for work, although all this is prohibited by law» [15].

One of the leaders and ideologues of the temperance movement, I. Gerasimovych, in the mass media, analyzing the bill of March 21, 1931, against which, incidentally, all national minorities and representatives of Polish opposition parties voted, noted that this document actually «spread» alcohol policy, «stabilized the number with a cramp and introduced a number of reliefs aimed at increasing alcohol consumption» [16]. Ukrainians sought to spread the «sobriety campaign» in a legal way. The anti-alcohol and anti-nicotine society "Vidrodzhennia", having led the fight against this anti-social phenomenon, continued the traditions of the sobriety mission and brotherhoods in the 19th century. Already on the eve of the First World War, it launched active activities, demonstrating its importance and taking its proper place in the structure of the Ukrainian public movement. A separate page in the history of the sobriety movement of the Ukrainian village was written by the «anti-recruit action» [17], that is, the fight against recursions as centers of the spread of drunkenness. The ideologues of the sobriety movement appealed to the population to replenish the ranks of «abstinents» [12-14, 16-18].

Anti-alcohol and anti-nicotine education of children, youth and adults became an important area of activity of Ukrainian public associations (educational, student, women's, medical, sports, scientific, children's and youth, financial and economic, etc.). The leading center of the Ukrainian sobriety movement was the anti-alcohol circle of the Rohatyn Gymnasium, which was created in 1925 and in 1928, under the guidance of well-known figures M. Tchaikovsky and Yu. Kamenetskyi, grew into the Union of Anti-Alcohol Clubs(hereinafter – UAC) which united 15 organizations of the relevant direction operating in secondary schools with 1,200 people [7, 19, 20]. Among the tasks of the UAC was to provide students of other schools with anti-alcohol literature and provide information on «how to conduct anti-alcohol work» [21].

School «abstinent youth» also created «their own anti-alcohol literature», demonstrated health-preserving behavior, etc. They planned to organize an anti-alcohol course for young people [22]. Thanks to the Rohatyn center, the anti-alcohol movement covered not only educational institutions, but also the entire county, that is, it spread to the adult population as well. The story of the «sobering» of the village of Dibryniv can serve as an example.In the fall of 1929, by the actions of the head of the local reading room «Enlightenment» Pasnak and the priest Fr. Skaskova «anti-alcohol circle» "Vidrodzhennia", which was joined by 150 people. The magazine "Vidrodzhennia" (1930, part 3) informed about the radical changes that took place as a result of the activities of the «anti-alcohol circle»: the inn, which was always crowded, was now empty, the Christmas holidays were free of fights and conflicts, dances and evening parties in the reading room take place without vodka and beer, christenings, weddings – also without alcohol [22].

Thanks to the supporters of the sobriety movement, in particular, «the work of Prof. Yu. Kamenetskyi and Prof. Gr. Zamoroki» similar changes took place in other villages of Rohatyn region: Babukhov, Babintsy, Pukov, Fraza, Stratyn, Vyspa, Hryhorov, Zalanov, Yavch. And in the village On March 2, 1930, 120 men and women «took a festive oath in the church not to drink and not to smoke» [22].

The example of the Rohatyn high school students was supported by the Ukrainian high school in Kolomyia, where the anti-alcohol and anti-nicotine circle «Health» was established; on February 23, 1930, the "Vidrodzhennia" anti-alcohol circle was created in the Ukrainian women's gymnasium of the «Ukrainian Institute in Przemyśl» Society (the leader of the club is student Iryna Stakhiv, the guardian is prof. S. Fedevycheva), which «enrolled 146 students who were obliged to tried to lead a healthy lifestyle and actively promote it [23].Thus, an «anti-alcohol oasis in Rohatyn» arose not in Lviv, but in the county town, when students and teachers of the «Native School» UAC led the sobriety movement. In our opinion, such success of Rohatyn Oblast was caused by the close cooperation of two prominent Ukrainian public associations – UPA «Native School» and the anti-alcohol and anti-nicotine association "Vidrodzhennia", which was manifested primarily in the affiliation of educators to the association "Vidrodzhennia", whose task, according to the charter, consisted in conducting anti-alcohol propaganda and creating for this purpose an extensive organizational network in all Ukrainian lands under Poland [24].

The March issue of the magazine "Vidrodzhennia"for 1930 reflects the success in the field of spreading abstinence among the population in the «most backward county» – Sambirsk, where as a result of the «plebiscite action» (a local referendum for the abolition of kromech) in the village of There was not a single inn in Shlyakhotsky Kulcchytsia (there were more than 14), in the village of Horodyshchi «liquidated three inns» [25]. These and other examples testify to an «unprecedented act» when, in a short period of time, the Ukrainian public, led by «good leaders», managed to organize and direct its «constitutional voice» to solve extremely important social problems i.e. the fight against drunkenness. In addition, the level of social consciousness of Ukrainians was high enough to understand that it is not enough to «drive out the innkeeper» and «abolish inns», it is necessary for every Ukrainian to lead a sober lifestyle, to create a «sober environment» that will become a significant «educational factor».

This is evidenced by the adopted «Resolution of the delegates of the reading rooms «Enlighten»» in the city of Horodenka, which decreed: all «entertainments, evening parties, which take place in the reading room, must take place without alcohol... All cultural institutions, both in Horodenka and in the county, call for alcohol all measures» [25]. The activities of the priests of the Ukrainian Greek-Catholic Church of the Horoden region, who actively carried out the «struggle for the sobriety of their parishioners», in particular V. Hordynskyi from Chernelitsa, Fr. N. Korbutyak from Torgovytsa, Fr. I. Labach from Oliyev-Korolyvka [25].The sobriety movement spread to the central and western voivodships, where there were also Ukrainian communities. Thus, in the article «How is the situation in reality?» published in the magazine "Vidrodzhennia" (1930. Part 3) [26], it was noted: «On February 27, 1930, a general vote was passed to ban the sale and consumption of alcoholic beverages and there inns were liquidated in 208 communities» [26].Therefore, the mass anti-alcohol education of the population of the region, the movement for a healthy lifestyle gave positive results: knowledge about a healthy lifestyle became the basis for people's health-preserving behavior, anti-alcohol education acted as a factor in the formation of the health-preserving competence of an individual, which included relevant knowledge, skills and behavior on the creation and cultivation of a health-preserving environment.

## DISCUSSION

At the origins of the anti-alcohol school movement, there were a number of educators, among whom Y. Kamenetskyi played a key role, he can rightly be considered the «father» of the school sobriety movement, a theoretician and practitioner of health care for children and youth, and other teachers. The support of the anti-alcohol policy of the association from among the Ukrainian people of Halychyna is evidenced by the organizational development of "Vidrodzhennia": under the leadership of the doctor and teacher, public figure S. Parfanovych, then M. Tsennk, as of 1934 there were 27 branches and 135 centers out of 6,400 persons. Subsequently, as a result of the implementation of the course on «eradication of formalism», the number decreased somewhat [7]. Almost half of the society's members were peasants, every tenth was a student, and the rest were townspeople, teachers, priests, and employees. The movement for health preservation became massive in the youth environment as well, this direction of education became «important» in educational work in educational institutions, the age range of the participants of the sobriety movement was from 7 to 20-30 years old, it included children of primary school age, teenagers and youth (we also mean students of elementary schools and gymnasiums and lyceums, professional schools, teacher and theological seminaries, university students, as well as conscious young «progressive peasants» i.e. members of the Khliborob youth academy, which as of 1938 counted among its in the ranks of about 14,000 people [27].Thanks to the activity of public institutions in Western Ukraine from the end of the 19th century till in 1939, a whole system of public anti-alcohol education and upbringing was

developed, in structural and ideological terms it was not integral, but consisted of components based on various organizational and ideological foundations, forms and means of activity, in particular «youth» (it gathered approximately 20,000 young men and women); youth organizations, primarily «Plast» (less than 8,000 people), Catholic Action of Ukrainian Youth (CAUY) «Orly» (about 4,979 children), Mary wives (22,000 people) and others, which solved the educational tasks of anti-alcohol education in terms of their worldview postulates.This gradation primarily concerns Galicia and has its own regional features in relation to Volhynia, Bukovyna, Transcarpathia [5; 7; 9]. So, we assume that young men and women, members of Ukrainian public associations, did not drink alcohol and showed their health-preserving behavior. The leaders of these societies took care of the physical, moral, mental and social health (according to today's terminology) of children and youth, gave it a social direction (a healthy person is a healthy nation), which became a determining factor in the harmonious development of the personality of the period under study [8].The ideologues of the "Vidrodzhennia" society became public figures, doctors, educators (I. Gerasimovych, Yu. Kamenetskyi, S. Parfanovych, I. Rakovsky and others), they substantiated the principles of an uncompromising fight against the use of alcohol, the demand for «complete refusal» from its consumption was motivated the fact that drunkenness is an «anti-national», «anti-patriotic» phenomenon, which is perhaps the most important obstacle on the way to achieving the well-being of the nation, preserving its gene pool.

The fight against drunkenness was actively supported by numerous public organizations, which even created separate structural units at their centers. The most common were the so-called circles of abstinence (lat. «abstinence»), which were most active in student and sometimes teacher organizations, as well as in «Prosvita» reading rooms, branches and circles of UPA «Native School», etc. Abstaining from alcohol consumption was one of the mandatory requirements for membership in the «Sich» and «Lug» societies, and an uncompromising attitude towards it was cultivated in the «Sokil» society. And the use of alcoholic beverages in «Plast» was especially severely punished, even up to expulsion from the organization [7].

Short-term anti-alcohol courses have become an effective means of anti-alcohol education and upbringing. This form of anti-alcohol and anti-nicotine struggle usually began in February, which was declared the «month of sobriety», and lasted the whole year. Anti-alcohol courses were mostly combined with anti-alcohol exhibitions aimed at health education.Thus, only during four months of 1930 (February-May), anti-alcohol training was organized in a number of settlements of the region: on February 21-23, an anti-alcohol course was held in Lviv, in which «many students of craft schools, high school students» took part, «villages arranged a series of thematic lectures» [28]; lectures on anti-alcohol topics, anti-alcohol exhibitions were organized by members of the "Vidrodzhennia"group at the Lviv State Women's Teacher's Seminary, the Men's Gymnasium, the Craft Exchange, etc. [29]; On March 7–9, the Circle of Ideological Citizens held an anti-alcohol course in Przemyśl, where the participants listened to the following «expositions»: «Dr. R. Nesterovych «Effect of alcohol on the body»; Prof. Polikha «What is alcohol»; Dr. Figlyus «Effect of alcohol on the central nervous system»; O. Bilinsky «Alcohol and ethics»; Dir. Zubrey «Methods of combating alcoholism»; delegate of the main section S. Parfanovych «Social harms of alcoholism» [30]; On April 6 and 7, 1930, anti-alcohol courses were held for the peasantry in the Horoden region, 250 participants on the first day listened to reports by K. Masiyanov «The role of women in the fight against alcoholism», Yu. Kamenetskyi «The social significance of alcoholism», «How other peoples fight against disaster» , soon 657 people became members of the «Renaissance» society; in addition, six new communities received permission to organize anti-alcohol groups, thus «there will be 12 groups with more than 1,200 people» [31], etc.The given examples of the development of public anti-alcohol education and enlightenment testify to the interest of children, youth and adults in the idea of sobriety, their participation in the spread of the anti-alcohol movement. As can be seen from the reports, in 1930–1938 the «Renaissance» society, together with «Prosvita» and other national institutions, conducted about 140 «anti-alcohol» events, which had 25-75 participants each [32]. In addition, thematic lectures were arranged on the basis of branches and circles. The statement that after such events about 2/3 of the listeners quit smoking is probably an exaggeration, but it is an indisputable fact that the awareness of the harmfulness of alcohol and tobacco use has been formed in the minds of broad segments of the population [7].

During the interwar twentieth anniversary of the 20th century. on the field of the sobriety movement, there was cooperation between Ukrainian and individual progressive Polish doctors, public activists who understood that the common enemy of the two peoples is the «innkeeper, brewer», the fight against drunkenness is necessary for the preservation of humanity, regardless of nationality, religion, etc.Thanks to such cases of cooperation (participation in 1931 of Ukrainian doctors, public figures, «delegates from the "Vidrodzhennia"» in anti-alcohol courses in Krakow [33], in the Polish

anti-alcohol congress [34], in an anti-alcohol course at the state school of hygiene from November 30 to 5 December 1931, at the VI «alcohololology» in Warsaw (1932) [35], as well as the subscription by the "Vidrodzhennia" centers of Polish-language medical and «anti-alcohol» magazines, etc.), the movement of «doctors without borders» was launched, which through their work proved that there there are a number of points of contact between the two Slavic peoples, there are a number of social problems that must be solved jointly.

According to the results of our analysis, Ukrainian periodicals became an important factor in anti-alcohol education during the studied period in Western Ukraine. There were about fifty Ukrainian public periodicals published in the region raised issues of personal health protection: («Revival», «We are young», «Ukrainian Youth» , «Native School», «Ukrainian School», «Path of Education and Learning», calendars «Enlightenment», «People's Affairs», «Business», «New Time», «Women's Destiny», «World of Youth», «The Farmer «, GKCH, «Cooperative Republic», «Public Voice», «Nove Selo», «Ukrainian Voice», «Nova Zorya», «Pravda», «Beskid», «Rada», «Labour», «Svoboda», « Sokil News», «News from the Meadow», «Uchitelske Slovo», «Our Friend», «Sunday», etc.).Popular means of anti-alcohol education among Ukrainians were «anti-alcohol literature»: reading books, poetry collections, and dramatic works of the appropriate content. The bibliography of "Vidrodzhennia" publications was quite numerous. In total, according to our data, by 1939 the society had published about 1,070,000 copies of various anti-alcohol literature [7]. The magazine "Vidrodzhennia" claimed that in the 1930s, Halychyna rose to one of the first places in Eastern Europe in terms of anti-alcohol propaganda. The reasons for this were given by the fact that in 1931–1937 Ukrainian magazines published more than 2,000 articles of the relevant content [7]. Many of them had thematic «anti-alcohol» pages.

An unprecedented phenomenon in the history of the development of the movement for health care was the making of public oaths by Ukrainians to refrain from drinking alcohol, which was a revival of the traditions of the sobriety brotherhoods of the 19th century. The magazine "Vidrodzhennia"presented dozens of similar facts, including cases when such acts were carried out by entire communities with the participation of several hundred people. So, for example, the New Year of 1930 for the village. Saranchuky (Berezhan Oblast) became iconic; it entered the history of the sobriety movement (and the history of Ukraine in general) as a village where «750 people swore to the local parish priest Omelyan Korduba that they would not drink alcohol». Ukrainian magazines actively popularized this experience [36]. There were cases when people after such «emotional euphoria» «returned to drinking again».

## CONCLUSIONS

According to the level of anti-alcohol propaganda, Halychyna in the 1930s took one of the first places in Eastern Europe. Ukrainian youth stood in the fairway of the youth branch of the sobriety movement. An unprecedented phenomenon in the history of the development of the movement for health care was the drafting of public oaths by Ukrainians to refuse alcohol consumption, anti-tavern plebiscites. Knowledge about a healthy lifestyle became the basis for people's health-preserving behavior, anti-alcohol education was a factor in the formation of the health-preserving competence of an individual, which included relevant knowledge, skills and behavior for creating and cultivating a health-preserving environment.This testifies to the effectiveness of the activities of Ukrainian public associations in the formation of health-saving competence of the individual, this experience needs active popularization today in Ukraine, especially it is actualized under the conditions of Russian aggression, when Ukraine faced the threat of losing its gene pool.

## REFERENCES


1. Towards a healthier Ukraine. Progress on the health-related Sustainable Development Goals 2020. Copenhagen: WHO Regional Office for Europe; 2020. file:///C:/Users/user/Downloads/WHO-EURO-2020-1523-41273-5617-eng.pdf [date access 23.01.2023]
2. Boisvert I, Boislard M, Poulin F. Early sexual onset and alcohol use and misuse from adolescence into young adulthood. J. Adolesc. Health. 2017; 61:514–520. doi: 10.1016/j.jadohealth.2017.04.013
3. European Monitoring Centre for Drugs and Drug Addiction [EMCDDA]. 2021. Policy and Practice Briefings: schools and Colleges. http: // www.emcdda.europa.eu/bestpractice/briefings/schools-and-colleges_en [date access 23.02.2023]
4. ESPAD Group (2020), ESPAD Report 2019: Results from the European School Survey Project on Alcohol and Other Drugs, EMCDDA Joint Publications, Publications Office of the European Union, Luxembourg. 2020, 136 p. https://www.emcdda.europa.eu/system/files/publications/13398/2020.3878_EN_04.pdf[date access 13.01.2023]
5. Herasymchuk V. Antyalkoholna propahanda yak vazhlyvyi faktor hihiienichnoho vykhovannia molodi na Zakarpatti (druha polovyna XIX – pochatok XX st.) [Antialcoholic propaganda as an important factor of hygienic education of youth in the Transcarpathian region (the second half of XIXth – the beginning of XXth century)].Molod i rynok. 2017;4:174-177. (in Ukrainian).

6. Slyvka L. Pytannia antyalkoholnoho vykhovannia ditei i molodi u diialnosti ukrainskykh hromadskykh tovarystv Zakhidnoi Ukrainy (1919–1939 rr.) [The issue of anti-alcohol education of children and youth in the activities of Ukrainian public associations of Western Ukraine (1919–1939)]. Pedahohichnyi almanakh. 2010;5: 278-283. (in Ukrainian).
7. Savchuk B. Korchma: alkoholna polityka i rukh tverezosti v Zakhidnii Ukraini u XIX – 30-kh rokakh XX st. [Inn: alcohol policy and the sobriety movement in Western Ukraine in the 19th and 30s of the 20th century]. Ivano-Frankivsk: Lileia-NV, 2001. 248 p. (in Ukrainian).
8. Bilavych N, Bilawicz J, Slyvka L, et al. Sanitary and hygienic education of children and adults under the conditions of the covid-19 pandemic in measurement of the achievements of public medicine of Galicia (end of the XIX – 30s of the XX century). Wiad. Lek. 2021; LXXIV: 9(1): 2222–2228. doi: 10.36740/WLek202109135
9. Savchuk B, Oliynyk M, Purici S, Bilavych H. Alcohol Consumption and the Soberness Movement of Ruthenians of Bukovina in their Polyethnic Environment in the Second Half of the 19th – Early 20th Centuries. Codrul Cosminului. 2021;27(1):105-129. doi:10.4316/CC.2021.01.006
10. Biskupski J. Zapobieganie alkoholizmowi wśród dzieci i młodzieży [Preventing alcoholism among children and adolescents]. R. Matusiak, K. Sigda, K. Kozioł (red.), Zachowania ryzykowne dzieci i młodzieży. Problemy wychowawcze, uzależnienia, Lublin–Tarnów–Łapczyca: Wydawnictwo Regis.2016:16-32. (in Polish).
11. Pelczar R. Ruch trzezwosci w łacinskiej diecezji przemyskiej w czasach galicyjskich [The sobriety movement in the Latin diocese of Przemysl in Galician times]. Nasza Przeszłość. 2010;113:107-133. (in Polish).
12. Krasińska I. Działalność Związku Nauczycieli Abstynentów w latach 1924–1929 [Activity of the Association of Abstinent Teachers in the years 1924–1929]. K. Dormus, R. Ślęczka (red.), W kręgu dawnych i współczesnych teorii wychowania. Uczeń – szkoła – nauczyciel. Kraków: Wydział Pedagogiczny Uniwersytetu Pedagogicznego im. Komisji Edukacji Narodowej. 2012:492-506. https://rep.up.krakow.pl/xmlui/bitstream/handle/11716/106/20150212_mu_rm_w_kregu_dawnych_T1.pdf?sequence=1&isAllowed=y (in Polish).
13. Krasińska I. Ruch abstynencki w Wielkopolsce w latach 1840–1902 [Absenteeism movement in Greater Poland in 1840–1902]. Folia historica cracoviensia. 2013;XIX:247-278. (in Polish).
14. Krasińska I, Sławiński R. Prasa abstynencka w Polsce (1918–1939) źródłem informacji na temat wychowania do życia w trzeźwości wśród dzieci i młodzieży [The abstinent press in Poland (1918–1939) as a source of information on the upbringing to live in sobriety among children and youth]. [w:] Czasopiśmiennictwo XIX i początków XX wieku jako źródło do historii edukacji, red. I. Michalska i G. Michalski, Łódź. 2010:91-108. http://dx.doi.org/10.18778/7969-912-4.07 (in Polish).
15. Za lehalizatsiiu bezpravstva Vidrodzhennia [For the legalization of the lawless Vidrodzhennia]. 1930;3:41. (in Ukrainian).
16. Herasymovych I. Protyalkoholnyi zakon zminenyi [The anti-alcohol law has been changed]. Vidrodzhennia. 1931;4:3-4. (in Ukrainian).
17. Herasymovych I. Protyalkoholna borotba [Anti-alcohol struggle]. Hospodarsko-kooperatyvnyi chasopys. 1926;18-19:4-5. (in Ukrainian).
18. Kamenetskyi Yu. Choho khoche protyalkoholne tovarystvo «Vidrodzhennia» [Whatdoestheanti-alcoholsociety «Revival» want]. Vidrodzhennia. 1930;1:9-10. (in Ukrainian).
19. Rakovskyi I. Za tverezist. Korotkyi istorychnyi ohliad Ukrainskoho protyalkoholnoho y protynikotynovoho rukhu [For sobriety. A brief historical overview of the Ukrainian anti-alcohol and anti-nicotine movement]. V 25-littia T-va "Vidrodzhennia". Lviv: Ukrainske protyalkoholne tovarystvo "Vidrodzhennia", 1934. 48 p. (in Ukrainian).
20. Bilavych H, Tkachivska I, Rozman I, et al. Voluteer movement of ukrainian students in the field of medical aid, education, health care for children and adults (end of the XIX – 30s of the XX centure). Wiad. Lek. 2022, LXXV: 11: 2854–2861. doi: 10.36740/WLek202211223
21. Soiuz Protyalkoholnykh hurtkiv molodi v Rohatyni [Union of anti-alcohol groups of youth in Rohatyn]. Vidrodzhennia. 1930;3:51. (in Ukrainian).
22. Protyalkoholni oseredky v rohatynskomu poviti [Anti-alcohol centers in the Rohatyn district]. Vidrodzhennia. 1930;3:51-52. (in Ukrainian).
23. Novi protyalkoholni hurtky pry himnaziiakh [New anti-alcohol circles at gymnasiums]. Vidrodzhennia. 1930;4-6:76. (in Ukrainian).
24. Statut Protyalkoholnoho tovarystva "Vidrodzhennia" [Statute of the Anti-alcohol Society "Vidrodzhennia"]. Lviv, 1929. 12 p. (in Ukrainian).
25. Visti z protyalkoholnoho rukhu [News from the anti-alcohol movement]. Vidrodzhennia. 1930;3:51-54. (in Ukrainian).
26. Yak maietsia sprava v diisnosty? [How is the situation in reality?]. Vidrodzhennia. 1930;3:42-43. (in Ukrainian).
27. Kaplistyi M. Khliborobskyi vyshkil Molodi [Khliborobsky Vyshkyl Young]. Makar Kaplisty. Regional Landlord Society «Rural Landlord» in Lviv 1899-1944]. Kraiove Hospodarske Tovarystvo «Silskyi Hospodar» u Lvovi 1899-1944. Niu-York, 1970:115-125. (in Ukrainian).
28. Visty z antyalkoholnoho rukhu. Protyalkoholnyi kurs [News from the anti-alcohol movement. Anti-alcohol course]. Vidrodzhennia. 1930;3:49-50. (in Ukrainian).
29. Pomitne ozhyvlennia protyalkoholnoho rukhu sered shkilnoi molodi u Lvovi [Noticeable revitalization of the anti-alcohol movement among school youth in Lviv.]. Vidrodzhennia. 1930;3:49. (in Ukrainian).
30. Protyalkoholnyi kurs [Anti-alcohol course]. Vidrodzhennia. 1930;3:50. (in Ukrainian).
31. Protyalkoholnyi kurs [Anti-alcohol course]. Vidrodzhennia. 1930;4-6: 74-75. (in Ukrainian).
32. Protyalkoholnyi dvodennyk i persha ukrainska mandrivna vystavka [Anti-alcohol biennial and the first Ukrainian traveling exhibition]. Vidrodzhennia. 1932;2:26. (in Ukrainian).

33. Protyalkoholnyi kurs u Krakovi [Anti-alcohol course in Krakow]. Vidrodzhennia. 1931;4-6:19. (in Ukrainian).
34. Polskyi protyalkoholnyi kongres [Polish anti-alcohol congress]. Vidrodzhennia. 1931;11:8-10. (in Ukrainian).
35. VI Kurs alkoholohii v Varshavi [VI Course of Alcoholology in Warsaw]. Vidrodzhennia. 1932;1:12. (in Ukrainian).
36. Selo Saranchuky Berezhanskoho povitu [The village of Saranchuka of the Berezhansky District]. Vidrodzhennia. 1930;1:12. (in Ukrainian).

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CASE STUDY

# GASTRIC AND DUODENAL AMYLOIDOSIS IN AN HIV-INFECTED PATIENT: A CASE REPORT AND A LITERATURE REVIEW

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**ABSTRACT**

We report the case of a 38-year-old female with gastrointestinal amyloidosis who presented with acute abdominal pain. The computed tomography scan showed that the patient had generalized lymphadenopathy. This clinical picture with absolute leukocytosis was interpreted as an acute secondary bacterial process of unspecified etiology with generalized lymphadenopathy. The patient was administered a broad-spectrum antibacterial drug and detoxication therapy. The upper endoscopy revealed bleeding of unknown origin. After a 2-day conservative hemostatic therapy, gastric tumor involvement was suggested during control endoscopy. The human immunodeficiency virus (HIV) antibodies were found with the following confirmation of their specificity by immunoblotting. Histopathological study of the biopsy specimens made it possible to diagnose gastrointestinal AA/AL-amyloidosis complicated by gastrointestinal bleeding.

**KEY WORDS:** gastric amyloidosis, gastric tumor, gastrointestinal bleeding, HIV infection, abdominal pain

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## INTRODUCTION

Various causes of acute abdominal pain are known; differential diagnosis usually includes an abdominal aortic aneurysm, appendicitis, cholangitis, cholecystitis, gastric or duodenal ulcer, ectopic pregnancy, heart attack, intestinal obstruction, kidney stones, mesenteric ischemia or mesenteric thrombosis, pancreatitis, peritonitis, viral gastroenteritis. However, we detected a completely another condition that manifested by acute abdominal pain.

## CASE REPORT

A 38-year-old female (patient P.) presented to the clinic with complaints of acute abdominal pain. She had been suffering from discomfort in the anticardium for two days. Afterwards, her condition suddenly deteriorated. She had acute pain in the upper abdomen and severe general weakness.

The patient has a medical history of nodular goiter (grade 2), euthyroidism, and chronic pharyngitis (2015). She had acute bronchitis with nasopharyngeal leakage syndrome (2019). In 2020, cervical lymphadenopathy was revealed during a routine consultation with an endocrinologist. The patient was recommended to undergo additional laboratory and instrumental tests to rule out the human immunodeficiency virus (HIV). The patient flatly refused. She denies infectious jaundice, tuberculosis, venereal diseases, diabetes mellitus, surgeries, blood transfusions, blood substitutes, or bad habits like smoking, alcohol abuse, or drug addiction.

An express test for SARS-CoV-2 antigen is done upon admission; the result is negative. The patient's condition is of moderate severity, consciousness is clear, place- and time-oriented. Weight 60 kg, height 170 cm, body mass index 20.8 kg/m$^2$. The skin is clean and dry, of normal color and turgor. There are no peripheral edemas, and the body temperature is 38.7°C. The anterior and posterior cervical, submandibular, and axillary lymph nodes are palpated as mobile, painless conglomerates that are not soldered to the skin and the subcutaneous tissue, sized 1.5-2 cm. Breathing is spontaneous, deep, and rhythmic; the respiratory rate is 16 per minute. The lungs are clear to percussion and auscultation. Cardiac

activity is rhythmic; the tones are sonorous and clear. The pulse is 70 bpm, regular and satisfactory; the blood pressure is 100/70 mm Hg in each arm. The tongue is moist and covered with a thick white coat. The tonsils and throat are clean. The abdomen is of ordinary shape; symmetrical, not swollen, participates in respiratory movements, is soft upon palpation, and painful in the upper abdomen. Peritoneal signs are negative. The liver is not enlarged; palpation is not available. The spleen is not enlarged; palpation is not available. No costovertebral angle tenderness on both sides. Urination is normal, painless, and unimpeded. According to the patient's self-report, the stool is regular and formed, with no abnormalities.

The patient was hospitalized in a surgical department with suspected acute pancreatitis and a duodenal ulcer.

At the time of hospitalization, the patient's complete blood count (*cito!*) had an absolute leukocytosis ($17.9\times10^9$/L) with neutrophilia ($13.7\times10^9$/L; normal range: 1.8-$7.7\times10^9$/L), light monocytosis ($1.4\times10^9$/L; normal range: 0-$0.8\times10^9$/L), and corresponding changes in the white cell count: stab neutrophils 28%, segmented neutrophils 53%, lymphocytes 8%, monocytes 10%, eosinophils 1%, and erythrocyte sedimentation rate (ESR) 60 mm/h. Erythrocytes of $4.69\times10^{12}$/L and hemoglobin of 133 g/L were within normal ranges, as well as levels of hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count (PLT), and mean platelet volume (MPV). The biochemical tests revealed that the liver panel (total bilirubin, direct and indirect bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, and alkaline phosphatase), nitrogenous wastes (urea and creatinine), lipase, and pancreatic amylase were within normal range. The clinical urine test showed no abnormalities.

Frontal chest radiography showed lung pattern deformation, mainly in the right lower parts, and streaking roots of the lungs. Those changes were not accompanied by alterations in clear lung fields, nodular infiltrative shadows, deformation of the costo-diaphragmatic sinuses, hemidiaphragm, cardiovascular shadow, or mediastinal displacement.

Thyroid ultrasound revealed a node in the isthmus and signs of regional lymphadenopathy: multiple hypoechoic masses with echogenic boundaries and enhanced vascularization were visible on the posterior surface of the neck on the left (sized 27.8×12.5 mm, 19×7 mm, 11×6 mm, 17×8 mm, 15×6 mm) and on the right (sized 20×9 mm, 16×6 mm).

An electrocardiogram showed no pathological abnormalities.

Urgent contrast-enhanced computed tomography (CT) of the chest and abdomen did not reveal focal pulmonary infiltrates, bone-destructive changes or injuries, or fluid in the pleural cavities and pericardium. No signs of obstruction and displacement of the trachea, main, lobar, and segmental bronchi. Mammary glands without pathological findings. Due to enlarged paratracheal (up to 9 mm), subcarinal (up to 9 mm), tracheobronchial (up to 9 mm), para-aortic (up to 8 mm), supraclavicular (up to 15 mm), axillary (3-15 mm), and lower pericardial (9 mm) lymph nodes, generalized lymphadenopathy was detected.

An abdominal CT scan revealed no free fluid or gas. Intestinal obstruction, bone-destructive changes, great vessel thrombosis, and colon neoplasms were ruled out. No abnormalities were found in the liver, intrahepatic bile ducts, portal vein, gallbladder, pancreas, parapancreatic tissue, intrapancreatic part of the common bile duct, major pancreatic duct, spleen, and splenic vein. There was a slight wall thickening of the antrum and duodenum. As in the chest cavity, the lymph nodes in the upper part of the abdominal cavity were enlarged, mostly due to the mesenteric group – up to 10 mm in diameter, hypervascular, and showing symptoms of mesenteric lymphadenitis.

The results obtained were interpreted as acute sepsis with generalized lymphadenopathy. The patient was administered a broad-spectrum antibacterial drug and detoxication therapy.

In the course of the treatment, leukocytosis decreased to $10.5\times10^9$/L, neutrophilia to $8.2\times10^9$/L, and the monocyte levels normalized on day 2 of hospitalization. However, anemia symptoms developed: erythrocytes $3.66\times10^{12}$/L, hemoglobin 105 g/L, and hematocrit 30% with normal MCV, MCH, MCHC, RDW, PLT, and MPV levels; ESR increased to 95 mm/h. The clinical urine test: protein 1.275 g/L; 3-5 leukocytes per field of view (FOV); 8-10 abnormal red blood cells per FOV; 0-1 hyaline casts per FOV. Liver and pancreas function tests, total protein, albumin, glucose, and glycosylated hemoglobin levels remained within normal limits. However, creatinine (0.151 mmol/L; normal range: 0.044-0.080 mmol/L), urea (12.74 mmol/L; normal range: 1.70-8.30 mmol/L), C-reactive protein (43.0 mg/dL; normal range: less than 0.5 mg/dL), procalcitonin (2.39 ng/mL; normal range: less than 0.5 ng/ml), and uric acid (0.430 mmol/L; normal range: 0.142-0.340 mmol/L) levels increased. The blood coagulation test showed a decrease in the prothrombin index to 67.6% (normal range: 70-130%) and an increase in fibrinogen concentration to 4.96 g/L (normal range: 1.8-3.5 g/L), while the values of the international normalized ratio (1.15) and activated partial thromboplastin time (36.5 sec) were

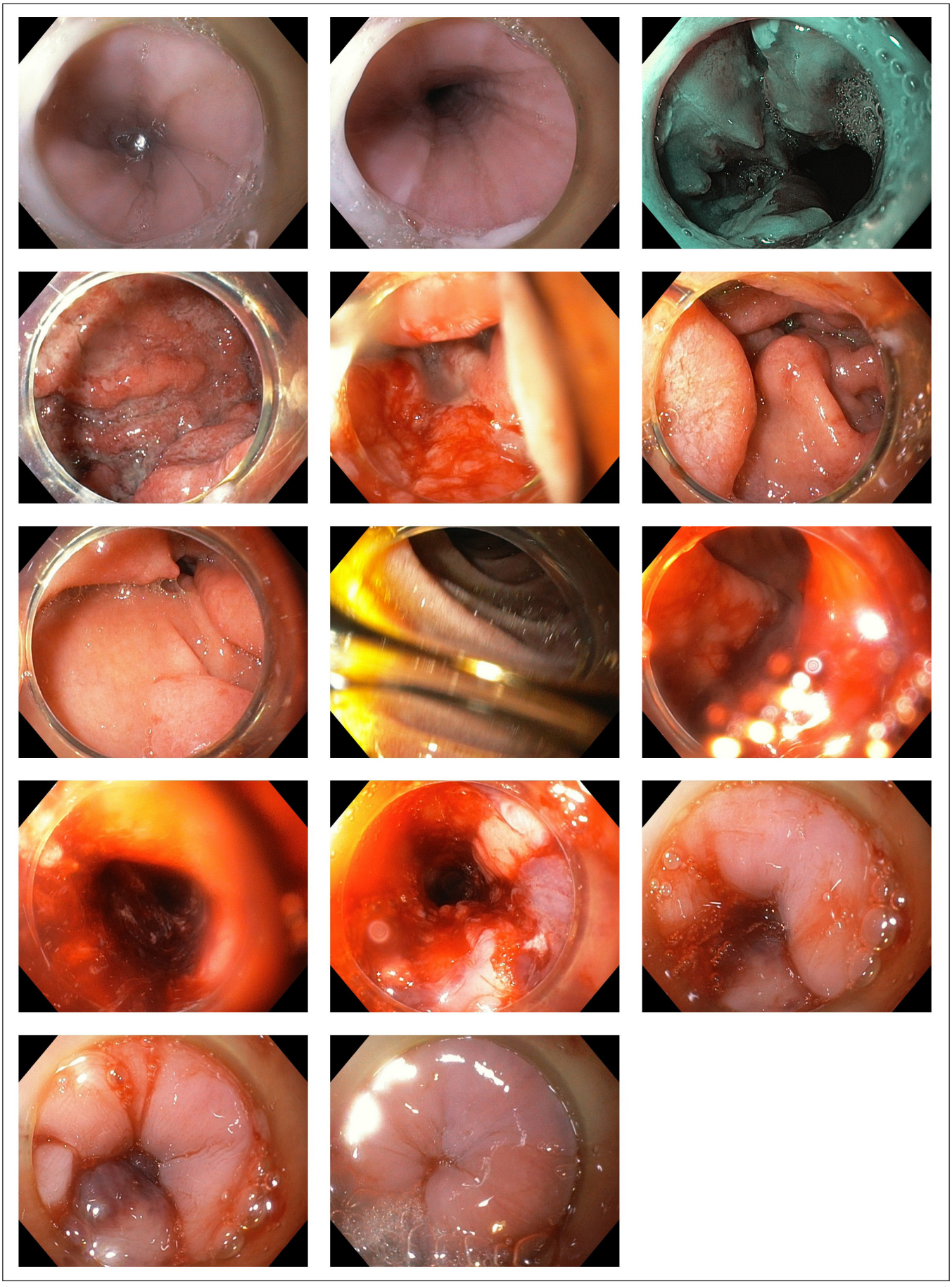

**Fig. 1.** First upper endoscopy of the 38-year-old patient P.

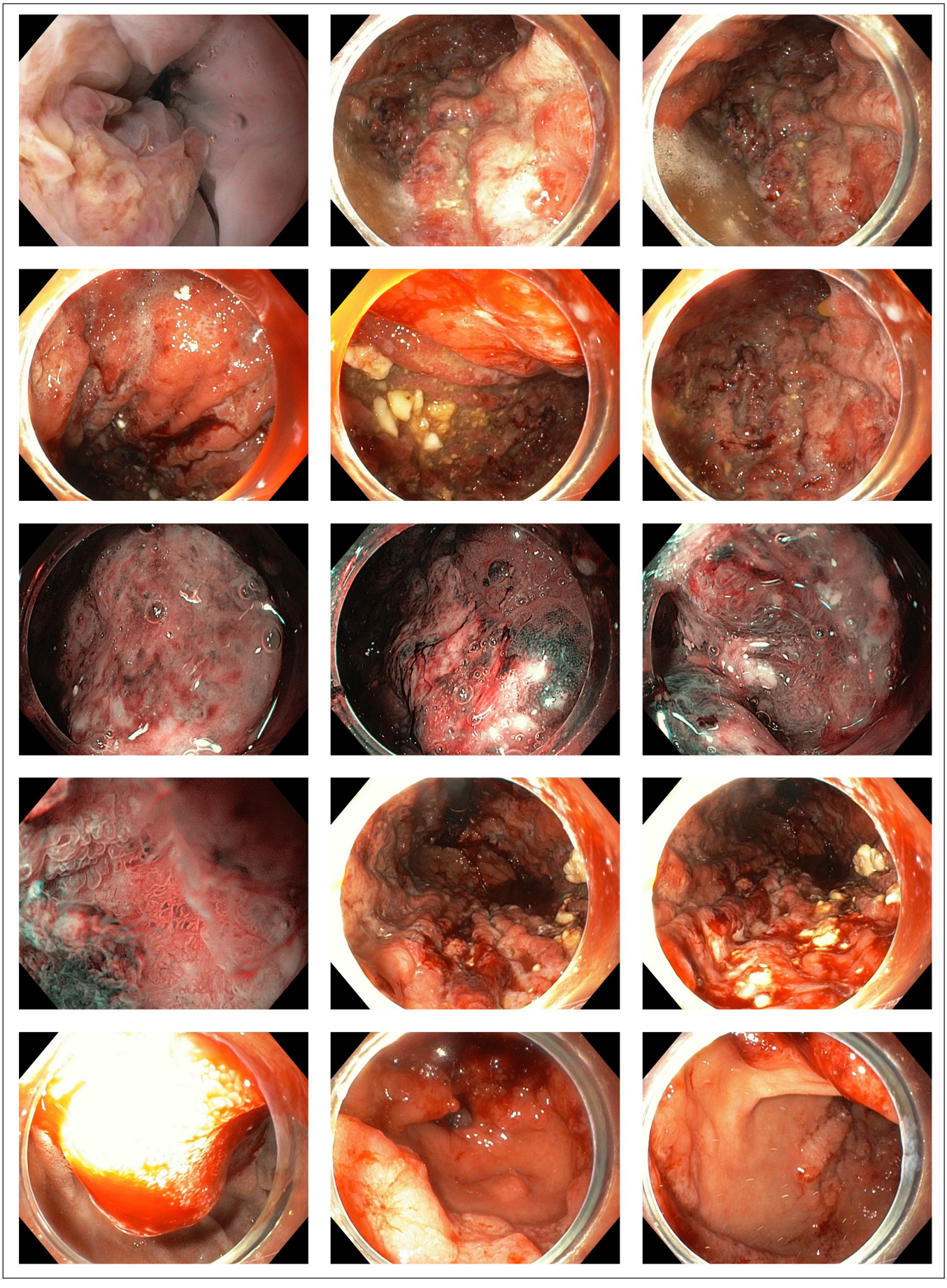

**Fig. 2.** Control upper endoscopy of the 38-year-old patient P.

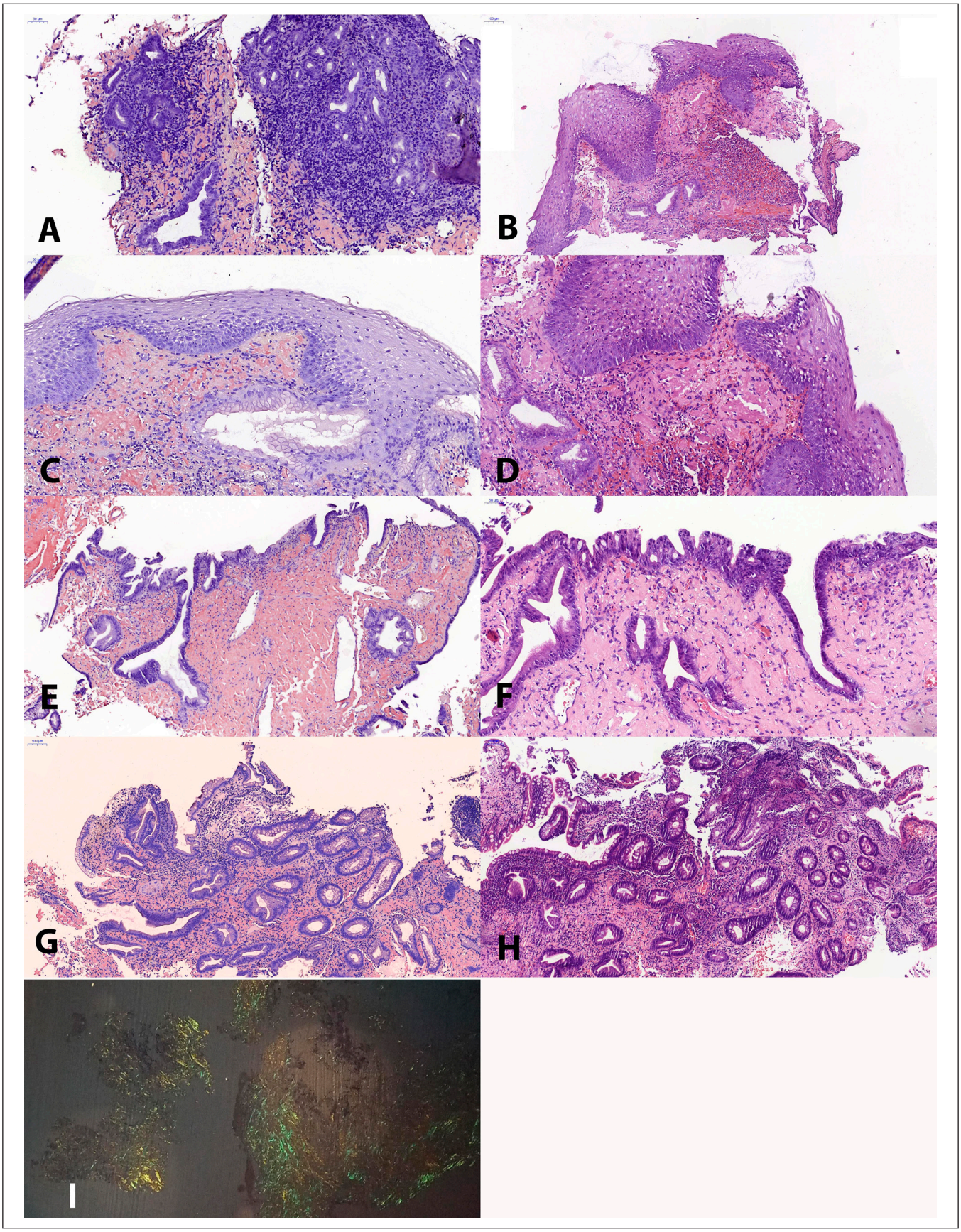


**Fig. 3.** Results of a histopathological study of the 38-year-old patient P. show the signs of gastric amyloidosis.
A – antrum; B, C, D – cardia; E, F, I – major duodenal papilla; G, H – duodenum.
A, C, E, G – Congo red staining; B, D, F, H – hematoxylin-eosin stainig; I – birefringence under polarized light.
B, E, G, H – × 10 magnification; A, C, D, F – × 20 magnification.

within normal range. The levels of sodium (133.8 mmol/L) and potassium (3.81 mmol/L) stayed in the normal range the whole time the patient was in the hospital.

The same day, the patient underwent an upper endoscopy (Figure 1). The esophageal patency is normal, an ulceration in the lower third of esophageal mucous is found, and the palisade vessels are not visible. The Z-line is 38 cm away from the incisors, at the level of the diaphragm and the tops of the gastric folds. Cardia closure is complete. The stomach is of ordinary shape. It contains up to 15 mL of hemorrhagic fluid in a fasting state; its thickened folds straighten freely upon air insufflation; motility is increased. The gastric mucosa is diffusely hyperemic and swollen (mainly in the fundus and body). There is a mucosal friability throughout the stomach body that starts from the esophageal Z-line, except in the antrum. The bleeding spontaneously stopped; its source was not detected. Pathological changes in the pylorus, bulb, and retrobulbar part of the duodenum are not detected. The major duodenal papilla is not visible. Due to the high risk of bleeding, a biopsy is not performed.

Conservative hemostatic therapy was added to the antibacterial and detoxication treatment. The patient's state improved starting from day 3 of hospitalization. Such clinical test results as total leukocyte count ($7.2\times10^9$/L), neutrophils ($5.4\times10^9$/L), monocytes ($0.6\times10^9$/L), erythrocytes ($3.61\times10^{12}$/L), hemoglobin (102 g/L), and hematocrit (29.7%) were stable. MCV, MCH, MCHC, RDW, PLT, and MPV levels were still within normal range, while ESR slightly decreased (62 mm/h). In the clinical urine test, the severity of proteinuria decreased to 0.266 g/L; there was no leukocyturia and hematuria; cylinders, bacteria, fungi, and *Candida* were not detected.

After two days of drug hemostatic therapy, the levels of leukocytes ($5.3\times10^9$/L), white cell count (neutrophils $3.2\times10^9$/L; lymphocytes $1.4\times10^9$/L; monocytes $0.6\times10^9$/L), erythrocytes ($3.73\times10^{12}$/L), hemoglobin (105 g/L), hematocrit (30.7%) preserved positive dynamics in control complete blood count, but ESR levels were significantly elevated again (97 mm/h). The results of the clinical urine test showed that urea and creatinine levels normalized. On day 4 of inpatient treatment, positive results of the HIV test were obtained – the patient had antibodies to HIV, and their specificity was confirmed by immunoblotting.

The same day, a control endoscopy was performed (Fig. 2), suggesting gastric neoplasia.

The esophageal patency is normal, the mucous membrane is pale pink and smooth, and the palisade vessels are visible. Distal to the Z-line, the esophageal mucosa is cyanotic. On the posterior surface of the esophagus, the mucous membrane is ulcerated and covered with fibrin at 38-39 cm from the incisors. The stomach contains up to 500 mL of food debris and hematin in a fasting state. Gastric folds are thickened. In the stomach's fornix, the mucous membrane is thick and swollen. The pylorus is of normal size and shape. There is a circular infiltration, submucosal eminence lesions, and purple-blue swollen mucous membrane in the body of the stomach. The ulcerations are partly covered with fibrin. In the antrum, where the mucosa is still intact, there are multiple mucosal polyps with unstructured superficial and vascular patterns. Mucosal friability and spontaneous bleeding were detected in all stomach parts. The duodenal bulb is of ordinary shape; its mucous membrane is covered with a small whitish plaque. The main duodenal papilla is enlarged and characterized by mucosal friability and lymphangiectasis.

At the patient's request, she was discharged from the hospital on day 5. Diagnosis: HIV infection, stage 2 with secondary diseases (4A/4B), the phase of disease progression in the absence of antiretroviral therapy; malignant gastric neoplasm is complicated by gastrointestinal bleeding. The patient is recommended to turn to the Center for AIDS Prevention and Control, oncologist, and gastroenterologist to select a treatment strategy and get the specific therapy.

However, the data of further histopathological study did not confirm the gastric tumor (Figure 3). Severe diffuse lymphohistoplasmacytic and moderate neutrophilic infiltrate of the stroma, superficial mucosal erosion, as well as amorphous deposits of an eosinophilic substance were found in the antrum mucosa, which stained positive with Congo red. Amorphous eosinophilic deposits were also present in the cardia in addition to moderate diffuse lymphohistoplasmacytic and light neutrophilic infiltrate, superficial mucosal erosions, and fragments of necrotic detritus (obtained from erosions or ulcers). The amorphous deposits stained positive with Congo red. A similar pattern was observed in the major duodenal papilla mucosa. *Helicobacter pylori* bacteria were not found. Additional examination showed birefringence under polarized light after pre-staining with Congo red and discoloration of the masses from red to apple green. Conclusion: the morphological pattern corresponds to gastric amyloidosis (cardia, antrum, body), duodenal and major duodenal papilla amyloidosis with symptoms of active mucosal inflammation and erosion lesions or ulcers.

The blocks and slides were consulted in a leading German pathologie laboratory (OptiPath, Frankfurt/Main), the German specialists confirmed the extensive intestinal amyloidosis as well as mild chronic gastritis without signs of malignacy, lymphoma or multiple myeloma.

The obtained results were the reason for the change in the diagnosis: HIV infection, stage 2 with secondary diseases (4A/4B), the phase of disease progression in the

absence of antiretroviral therapy. Gastric AA (secondary)/AL (immunoglobulin light chain) amyloidosis is complicated by gastrointestinal bleeding.

## DISCUSSION

Gastrointestinal involvement is often present in amyloidosis. In most cases (80%), the pathological process is generalized and manifests as systemic amyloidosis, while local deposition of amyloid in the digestive tract is quite rare [1,2].

One of the most typical forms of gastrointestinal amyloidosis is gastric involvement, when amyloid is deposited in the stomach only, without evidence of multiple myeloma or involvement of other organs, including the heart, liver, kidneys, or nerves [1]. According to a retrospective study of gastrointestinal biopsies (n=542), such types of amyloid as AL, transthyretin (ATTR), and AA are prevalently found in the stomach [3]. Another retrospective review states that in most cases, the amyloid found in the stomach was derived from AL (67%), ATTR (18%), AA (9%), and apo-lipoprotein A1 (3%) [4]. AL amyloid is typically deposited in the muscularis mucosa, whereas AA amyloid is deposited in the proper mucous plate [5]. Therefore, it is difficult to diagnose gastric AL amyloidosis by a conventional forceps biopsy during endoscopy. In this case, fine-needle aspiration should be performed [2,6,7].

Localized gastric amyloidosis usually targets elderly and senile patients with no sex differences [4]. Its symptoms frequently lack specificity. The clinical manifestations vary significantly as the disease can be asymptomatic [8], present as severe dysphagia [9] or postprandial pain syndrome [10], or mimic the long-term course of gastric ulcer [8], nodular gastritis [11], gastroparesis [12], tumors [2,9,13-15], submucosal hemorrhages [16], hematemesis [17], massive spontaneous [18,19] or fatal gastrointestinal bleeding [20]. In patients with multiple myeloma, gastric amyloidosis can mimic intestinal obstruction and cause gastric outlet obstruction [21] or show up as recurrent diffuse gastrointestinal bleeding [22]. D. Savant et al. [6] reported a case of isolated gastric amyloidoma in a 64-year-old male with a history of ulcerative colitis and primary sclerosing cholangitis. The diagnosis was confirmed by fine-needle aspiration without curative-intent treatment [6].

Such a diversity of symptoms is associated with the severity of the gastric wall infiltration and the localization of amyloid deposits, but no correlation between gastrointestinal symptoms and amyloid types has been confirmed [1].

During the initial endoscopic examination, gastric amyloidosis is described as a single or multiple lesions mimicking tumor [5,9,13-15], erythema and erosion [4], ulcer [8], or submucosal mass [12,16] with distinct or blurred boundaries. Endoscopic ultrasound-guided fine-needle aspiration is sometimes used [5,6,7] to confirm a diagnosis when a traditional light endoscopy with a forceps biopsy is not enough.

According to the Guidelines on the diagnosis and investigation of AL amyloidosis [23], the disease can be verified by histological examination of biopsy specimens. Congo red staining remains the "gold standard" for detecting amyloid protein. Stained amyloid deposits turn brick red and produce pathognomonic apple green birefringence when viewed under cross-polarized light [23].

Generally, the aim of treatment for localized amyloidosis is to eliminate extracellular amyloid deposits and restore the normal function of the involved organs. Treatment options include surgery, radiotherapy, and chemotherapy [1]. Observation is not always justified in localized gastric amyloidosis: one case of multiple malignant gastric hyperplastic polyps in *Helicobacter pylori*-negative patient has been reported, which required endoscopic submucosal dissection [24].

There is a point of view that localized amyloidosis has a good prognosis and minimally affects the survival of patients, unlike systemic amyloidosis [1]. However, some experts mention a possible poor prognosis of localized gastric amyloidosis. The amyloid deposits induce the impairment of gastric motility and cause gastroparesis, erosions, and ulcers, including the esophageal ones [17]. Patients' survival at 3 years after confirming the diagnosis of gastric amyloidosis is 60% and does not depend on the type of amyloid [4].

A few clinical cases of amyloidosis in HIV-infected people are available in the literature. One of them reports systemic AL amyloidosis with cardiac involvement [25]. Others present primary localized AA amyloidosis of the oral cavity [26], rectum [27], small intestine [28], kidneys [29,30], and combined involvement of the stomach and duodenum [31]. There is a case of sepsis and acute renal failure in an HIV-infected patient with systemic AA amyloidosis [31].

It is important to consider gastric amyloidosis during the differential diagnosis if the endoscopic signs of gastric cancer and diffuse gastric bleeding are detected. Guidelines for management of localized gastric amyloidosis have not been created yet. The treatment strategy is determined by the clinical setting and may range from active follow-up and chemotherapy to surgery if the complications are observed.

## CONCLUSIONS

Gastric amyloidosis is a relatively rare pathology that can cause acute abdominal pain syndrome, mimic a neoplasm, and be complicated by gastrointestinal bleeding. Concomitant HIV infection can make differential diagnosis more complex.

## REFERENCES


1. Lin X, Pan D, Sang L et al. Primary localized gastric amyloidosis: A scoping review of the literature from clinical presentations to prognosis. World J. Gastroenterol. 2021;27:1132–1148. doi: 10.3748/wjg.v27.i12.1132.
2. Cowan A, Skinner M, Seldin D et al. Amyloidosis of the gastrointestinal tract: a 13-year, single-center, referral experience. Haematologica 2013;98:141–146. doi: 10.3324/haematol.2012.068155.
3. Freudenthaler S, Hegenbart U, Schönland S et al. Amyloid in biopsies of the gastrointestinal tract-a retrospective observational study on 542 patients. Virchows Arch. 2016;468:569–577. doi: 10.1007/s00428-016-1916-y.
4. Said S, Grogg K, Smyrk T. Gastric amyloidosis: clinicopathological correlations in 79 cases from a single institution. Hum. Pathol. 2015;46:491–498. doi: 10.1016/j.humpath.2014.12.009.
5. Takahashi Y, Hatta W, Koike T et al. Localized Gastric Amyloidosis that Displayed Morphological Changes over 10 Years of Observation. Intern. Med. 2021;60:539–543. doi: 10.2169/internalmedicine.5031-20.
6. Savant D, Adler M, Kahn L et al. Amyloidoma of Stomach: A Case Report. Acta Cytol. 2018;62:231–233. doi: 10.1159/000488133.
7. Hashimoto C, Hikichi T, Hashimoto M et al. Localized gastric amyloidosis diagnosed by endoscopic ultrasound-guided fine-needle aspiration. Clin. J. Gastroenterol. 2021;14:1036–1041. doi: 10.1007/s12328-021-01416-4.
8. Matsueda K, Kawano S, Okada H. Primary localized amyloidosis of the stomach mimicking healing gastric ulcer. Gastrointest. Endosc. 2020;91:947–948. doi: 10.1016/j.gie.2019.12.004.
9. Mathialagan J, Sowmya S. Amyloidosis masquerading as gastric carcinoma – A case report. Indian J. Pathol. Microbiol. 2020;63:119–121. doi: 10.4103/IJPM.IJPM_258_19.
10. Inayat F, Ur Rahman A, Zahid E et al. Symptomatic involvement of the stomach and duodenum as initial presentation of AL amyloidosis. BMJ Case Rep. 2019;12. doi: 10.1136/bcr-2018-227550.
11. Asayama N, Nagata N. Secondary amyloidosis presenting as a unique form of nodular gastritis. Intern. Med. 2012;51:1797–1798. doi:10.2169/internalmedicine.51.7811.
12. Lee A, Lee D, Vasanwala F. Amyloid light-chain amyloidosis presenting as abdominal bloating: a case report. J. Med. Case Rep. 2016;10:68. doi: 10.1186/s13256-016-0857-z.
13. Ding Y, Li Y, Sun L. A Rare Case of Asymptomatic Primary Gastric Localized Amyloidosis. Clin. Gastroenterol. Hepatol. 2019;17:A41–A42. doi: 10.1016/j.cgh.2018.08.014.
14. Kinugasa H, Tanaka T, Okada H. Primary Localized Gastric Amyloidosis Mimicking a Submucosal Tumor-Like Gastrointestinal Tumor. Clin. Gastroenterol. Hepatol. 2020;18:e4. doi: 10.1016/j.cgh.2018.09.023.
15. Xiao H, Qing D, Li C. et al. A case report of gastric amyloidosis due to multiple myeloma mimicking gastric cancer. BMC Gastroenterol. 2020;20:219. doi: 10.1186/s12876-020-01359-z.
16. Fossmark R, Skarsvåg E, Aarset H. et al. Symptomatic primary (Al) amyloidosis of the stomach and duodenum. Case Rep. Gastrointest. Med. 2013;2013:525439. doi: 10.1155/2013/525439.
17. Huang Y, Nasir S, Challa S. et al. Gastric AA amyloidosis secondary to chronic infection presenting with hematemesis: a case report. Clin. J. Gastroenterol. 2020;13:1070–1073. doi: 10.1007/s12328-020-01211-7.
18. Alhazmi L, Nuqali A, Assaly R. Bleeding manifestations in a patient with amyloidosis. BMJ Case Rep. 2016;2016:bcr2016216942. doi:10.1136/bcr-2016-216942.
19. Pak S, Markovic J.T. Gastric submucosal haematoma caused by an amyloidoma in the setting of multiple myeloma. Arab. J. Gastroenterol. 2017;18:238–240. doi: 10.1016/j.ajg.2017.12.002.
20. Baird-Howell M, Wurzel J. Fatal gastrointestinal hemorrhage in a paraplegic man with undiagnosed AA (secondary) amyloidosis. Amyloid 2011;18:245–248. doi: 10.3109/13506129.2011.623738.
21. Cohen J, An J, Brown A et al. Gastric Outlet Obstruction due to Gastrointestinal Amyloidosis. J. Gastrointest. Surg. 2017;21:600–601. doi: 10.1007/s11605-016-3248-2.
22. Franck C, Venerito M, Weigt J et al. Recurrent diffuse gastric bleeding as a leading symptom of gastrointestinal AL amyloidosis. Z. Gastroenterol. 2017;55:1318–1322. doi: 10.1055/s-0043-120924.
23. Gillmore J, Wechalekar A, Bird J et al. BCSH Committee. Guidelines on the diagnosis and investigation of AL amyloidosis. Br. J. Haematol. 2015;168:207–218. doi: 10.1111/bjh.13156.
24. Ciochina M, Lupu A, Hervieu V et al. Endoscopic submucosal dissection of a large malignant gastric hyperplastic polyp, developing on gastric amyloidosis, after endoscopic and echoendoscopic characterization. Endoscopy 2019;51:E352–E353. doi:10.1055/a-0929-5842.
25. Denman J, Manavi K, Cook M. Lenalidomide as a treatment for relapsed AL amyloidosis in an HIV-positive patient. Int. J. STD. AIDS 2017;28:1045–1047. doi: 10.1177/0956462417694561.
26. Anaya-Saavedra G, Ramírez-Amador V, Valencia-Mayoral P. Oral primary localized amyloidosis in HIV-infected patients: the oral face of a described skin lesion. Int. J. STD. AIDS 2015;26:1049–1051. doi:10.1177/0956462414566254.
27. Amarawardena W, Wijesundere A, Manohari HA. Amyloidosis associated with HIV infection. Ceylon Med. J. 2013;58:128–129. doi:10.4038/cmj.v58i3.6107.

28. Segoviano-Mateo R, Rojano-Martín B, Díaz-Ley B et al. Intestinal amyloidosis in a patient with HIV infection. Enferm. Infecc. Microbiol. Clin. 2005;23:633. doi: 10.1016/s0213-005x(05)75046-1.
29. Chan-Tack K, Ahuja N, Weinman E et al. Acute renal failure and nephrotic range proteinuria due to amyloidosis in an HIV-infected patient. Am. J. Med. Sci. 2006;332:364–367. doi:10.1097/00000441-200612000-00012.
30. Jung O, Haack H, Buettner M et al. Renal AA-amyloidosis in intravenous drug users--a role for HIV-infection? BMC Nephrol. 2012;13:151. doi: 10.1186/1471-2369-13-151.
31. Newey C, Odedra B, Standish R. et al. Renal and gastrointestinal amyloidosis in an HIV-infected injection drug user. Int. J. STD. AIDS. 2007;18:357–358. doi: 10.1258/095646207780749691.

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LETTER TO EDITOR

# A NEW OUTLOOK ON PATIENT CARE – MY EXPERIENCE AT MAYO CLINIC AS AN INTERNATIONAL MEDICAL STUDENT

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Providing the best possible patient care should be a doctor's number one priority. However, in a real-world setting, there are certain factors that impede practitioners from realizing this goal. As many countries adopt a different philosophy on healthcare provision, doctors have to maneuver within the boundaries set by their respective governments. Consequently, medical professionals have slightly different limitations, responsibilities and perks depending on their country of practice. As a medical student at the Medical University of Warsaw, Poland, I have been able to observe the inner workings of a socialized healthcare system, both its strengths and weaknesses. I was also able to experience a foreign healthcare system during my medical internship in Mongolia, yet this country's approach was very similar to Poland's. However, in the United States healthcare provision is drastically different, one might even argue it is the polar opposite of socialized healthcare. I was intrigued by these differences and wanted to experience them first-hand. This was my reasoning for participating in an observer-ship program in the Department of Neurology at Mayo Clinic, Jacksonville, Florida.

Upon arrival, I immediately noticed the professional, tranquil atmosphere of the clinic. It provided an ideal environment for both high-quality patient care and medical research advancement. As an observer at Mayo Clinic, I was able to participate in many lectures, access the library and use their state of the art simulation center. However, most of my time was allocated to shadowing neurologists and other medical professionals. It was a pleasure observing their every day practice. I admired how during every patient-doctor interaction they upheld the core values of Mayo Clinic (Respect, Integrity, Compassion, Healing, Teamwork, Innovation, Excellence, Stewardship). At each appointment all of the patient's needs and queries were addressed in a kind, considerate manner. Every diagnosis was simply and clearly explained to the patient, ensuring they fully understood their condition. The dynamic between medical professional and patient could only be described as a mutual partnership. It is important to note, that this excellent patient-doctor relationship could not be achieved without the incredible teamwork between Mayo Clinic staff members. There was swift communication and somewhat fluid exchange of responsibilities, which provided an untroubled patient experience. The genuine respect the Mayo staff had for each other was truly inspirational, but at the same time it seemed like such a simple and achievable step towards better patient care.

I quickly realized that Mayo Clinic provides truly exceptional medical services. I am fully aware that my observer-ship at Mayo Clinic, one of the best health institutions in the nation if not the world, has not given me a realistic view of patient care in the United States. Throughout my stay, I was nevertheless able to get rare glimpses into the shortcomings of a mostly privatized healthcare system, the most apparent being the health insurance gap. The topic of insurance coverage was discussed during many of the appointments I attended, and I would always observe a slight uneasiness in the patient's expression whenever it came up. The uncertainty of an insurance provider financing the patient's critically-needed treatment seemed inhumane, especially when the person was already suffering from a debilitating illness. Although I acknowledge that no system is perfect, I believe it is important to strive for perfection. Hopefully, the future of medicine holds a healthcare system, where patients are able to receive the best possible care, without any income-based restrictions.

My visit to Mayo Clinic as an observer would not be as illuminating as it was without the guidance and support from the professors and doctors from the Department of Neurology at Mayo Clinic, Jacksonville. I am especially grateful to Professor Zbigniew Wszolek, thanks to whom I was accepted into the program, and who mentored me throughout my stay. I am appreciative of the help I received from Doctor Jaroslaw Dulski, whose patient guidance and practical advice provided me with a better understanding of the world of medical research. Finally I would like to thank Professor Andrzej Friedman, who took my career aspirations seriously and thus played an important role in orchestrating this invaluable experience.

I truly believe my observer-ship at Mayo Clinic greatly impacted my outlook on quality patient care and how to provide it. I now understand that at the core of being a good doctor lies a simple message: always prioritize your patient and do the very best you can to assist them. My visit at Mayo also taught me that exposing yourself to different perspectives, even if it means traveling to a different continent, will always in one way or another allow you to grow as a human being. My advice to young doctors or soon-to-be doctors is to gain experience and exposure wherever and whenever you can, I can promise it is absolutely worth it.

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