ORIGINAL ARTICLE

FEATURES OF COVID-19 PNEUMONIA DIAGNOSIS

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ABSTRACT

The aim: The purpose of the study is to evaluate the clinical and laboratory features of COVID-19 pneumonia course, the diagnostic significance of laboratory methods for detecting the SARS-CoV-2 virus based on a retrospective analysis.

Materials and methods: We studied the case histories of 96 patients who were treated at the Municipal Non-Profit Enterprise "Lviv Clinical Emergency Care Hospital" for the period from 01/07/2020 to 31/07/2020 with a diagnosis of pneumonia, which corresponded to 5 points on the CO -RADS scale. We analyzed the clinical and laboratory signs of COVID-19 pneumonia depending on the results of the Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) tests to the SARS-CoV-2 infection (positive result of RT-qPCR was observed in the first group and negative – in the second group).

Results: In both groups, no clinical differences in the course of the disease were found. The most common symptoms of coronavirus pneumonia were found with the same frequency in both patients with a laboratory-confirmed diagnosis and without it. A positive PCR test in nasopharyngeal and oropharyngeal swabs was more often detected during testing up to 10 days, in patients over 60 years of age and in severe COVID-19.

Conclusions: The COVID-19 pneumonia diagnosis should be based on a combination of clinical, laboratory, and radiological signs of this disease. A negative PCR test result does not exclude the diagnosis of coronavirus disease. The test results are influenced by the timing of the sampling, the severity of the disease and the age of the patients.

KEY WORDS: COVID-19 pneumonia, Quantitative Reverse Transcription Polymerase Chain Reaction, computed tomography scan, CO-RADS scale

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INTRODUCTION

The COVID-19 pandemic is a new disease that has engulfed humanity and fostered the efforts of the entire global health community to solve a monumental challenge – to establish mechanisms for the diagnosis, treatment and prevention of this disease. According to the recommendations of the World Health Organization (WHO), the European Centre for Disease Prevention and Control (ECDC), the Agency for Health Technology Assessment and Tariff System (AOTMiT) and other leading health organizations, the main methodology used to diagnose SARS-CoV-2 infection is molecular technique that reveals the genetic material of the virus in the exudates and secretions of the patient, especially from the mucous membranes of the throat and nose [1, 2]. Taking into account the speed of testing and availability of equipment, one of the best methods for detecting viral RNA is the Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) [1].

At the same time, the results of recent studies indicate that the sensitivity of the RT-qPCR method for confirming COVID-19 is 60-71% [3-7], and therefore some patients with symptoms of the disease remain without an established etiological diagnosis. The underlying causes of such sensitivity of the polymerase chain reaction (PCR) may be associated with the insensitivity of test systems to the detection of nucleic acids due to virus mutations, low initial viral load in various body environments, or improper clinical sampling [8]. At a certain stage of the disease, samples from the lower respiratory tract (LRT) can be better diagnostic material than samples from the upper respiratory tract (URT), as is the case with MERS-CoV [8-10].

The detection of specific antibodies complements the PCR method for diagnosing the SARS-CoV-2 virus. Acute IgM antibodies appear only on the seventh day after contact with the pathogen. According to the available data, testing of specific antibodies against SARS-CoV-2 allows to achieve sensitivity at a level similar to that of RT-qPCR only 2-3 weeks after infection, i.e. when in some patients viral RNA is no longer detected, which is equivalent to the absence of infection [1].

Changes in the chest computed tomography (CT) are considered as a very important strategy for additional diagnosis of COVID-19, given the limitations of PCR and IFA methods, in particular, due to cases of false-negative results [11]. Interesting from a scientific and practical point of view are the results of a retrospective analysis, which compared the coefficient of sensitivity to RT-qPCR test and CT scan in 51 patients who had a burdened epidemiological anamnesis and manifestations of acute respiratory syndrome and/or fever. They consistently underwent CT

examination of the chest organs and RT-qPCR test, with an interval of one day – in the case of the first negative result, until a positive test result. The conclusions of this analysis showed that the sensitivity of the RT-qPCR test of the first swab from the oropharynx and nasopharynx was low and amounted to 70%, after the second test it increased by 24% (94%) and by another 3.9% after the third test (98%) while the sensitivity of CT screening in the viral pneumonia diagnosis was 98% [8]. The authors of this study stated that CT is a more sensitive method for diagnosing COVID-19 pneumonia than PCR. In another, more massive, report, the correlation between CT and RT-qPCR COVID-19 testing was carried out taking into account 1014 cases, which were included in the report. According to the data presented, only 59% of the examined patients had positive results of RT-qPCR test, while 88% showed changes on chest CT. In 75% of patients with negative RT-qPCR test results, there were signs of respiratory tract damage on CT; of them – in 48% of patients, the diagnosis of COVID-19 was considered extremely probable, in 33% – probable. Of the 1014 patients, 60% to 93% had initial positive CT scans consistent with COVID-19 before the initial positive RT-PCR results [12].

Overall, a systematic review with meta-analysis of COVID-19 diagnostic tests accuracy showed that CT has a high sensitivity (91.9% [89.8% -93.7%]) [11, 12]. The standardized assessment scheme for patients suspected of being infected with COVID-19 coronaviruses based on CT scans on the CO-RADS scale (COVID-19 Reporting and Data System) proposed by the COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society makes it possible to assess the likelihood of coronavirus disease from very low – CO-RADS 1 to very high – CO-RADS 5 based on a typical X-ray picture – diffuse areas of "ground-glass" opacification and superimposed consolidations [13], which makes it an effective method in the COVID-19 diagnosis.

The object of this paper is to assess the clinical and laboratory features of the COVID 19 pneumonia course, the diagnostic significance of laboratory methods for detecting the SARS-CoV-2 virus based on retrospective analysis.

THE AIM

The purpose of the research is to evaluate the clinical and laboratory features of COVID-19 pneumonia course, the diagnostic significance of laboratory methods for detecting the SARS-CoV-2 virus based on a retrospective analysis.

MATERIALS AND METHODS

We studied the case histories of 96 patients who were treated at the Municipal Non-Profit Enterprise "Lviv Clinical Emergency Care Hospital" for the period from 01/07/2020 to 31/07/2020 with a diagnosis of pneumonia.

The criteria for the inclusion of patients in the retrospective analysis were determined diagnosis of pneumonia verified on the basis of laboratory and instrumental research methods: the detection of the SARS-CoV-2 virus genome in swabs from the nasopharynx and oropharynx by the RT-qPCR method and/or the detection of IgM antibodies to SARS-CoV-2 coronavirus and the level of suspicion of COVID-19 infection on the CO-RADS scale, which corresponds to 5 points; burdened epidemiological anamnesis.

Patients without a confirmed diagnosis of pneumonia, patients with a COVID-19 suspicion level on the CO-RADS scale of 1-4 points, patients with other etiological variants of pneumonia (bacterial, hypostatic) and pulmonary tuberculosis were not included in the analysis.

We assessed the following parameters: age, gender of patients, day of illness at the time of hospitalization, illness symptoms, presence of concomitant diseases. We paid attention to the results of physical examination, indicators of blood oxygen saturation, body temperature (T), blood pressure (BP) and heart rate (HR). We analyzed changes in peripheral blood, glycemic indicators.

In accordance with the order of the Ministry of Healthcare of Ukraine dated 11/11/2020 No. 2583 "On Amendments to the Protocol "Provision of Medical Care for the Treatment of Coronavirus Disease (COVID-19)", we assessed the pneumonia severity according to the following criteria: respiratory rate ≥30 / min (adults), oxygen saturation of blood ≤92%, PaO2 / FiO2 ratio <300, pulmonary infiltrates > 50% of the lung field, according to which one or more of the detected criteria corresponds to the severe disease.

Statistical data processing was carried out using the Statistica 6.0 software package.

RESULTS

According to the results of the analysis, the percentage of patients with SARS-CoV-2 virus detected by RT-qPCR method and serological tests was only 46.9% among patients diagnosed with bilateral pneumonia CO-RADS 5 points.

The average age of the patients was 57.95 ± 1.6 (18-89) years. The percentage of patients over 40 years old was significantly higher – 86.5%. Among the patients, the proportion of women prevailed – 55.2%, men – 44.8%.

The average day of patient hospitalization corresponded to 9.9 ± 0.53 day of illness. The proportion of patients with late admission to hospital exceeded, after 10 days from symptom onset – 51.6%, admissions before 10 days of illness were noted in 43.2% of cases.

In hospitalized patients, the following disorders were noted: in 42.7% – shortness of breath, in 50% – cough, in 17.7% – general weakness, in 10.1% – a loss of smell was documented, in 8.3% – nausea and vomiting, 4.2% of patients complained of chest pain, in 2.1% the leading complaints were diarrhea and decreased appetite.

In 77.1% of patients, the temperature rise was measured from sub-febrile to febrile, in 64.6% – tachycardia was detected. In 55.2% of patients, a decrease in blood oxygen saturation of ≤95% was revealed.

Changes in peripheral blood corresponded to the following picture: the majority of patients (77.6%) demonstrated

Table I. Age, data of physical and laboratory examinations of patients with laboratory-confirmed (first group) and without laboratory-confirmed (second group) diagnosis of coronavirus disease.

Indicators	1 group M±Std.dev	2 group M±Std.dev	P
Age, years	60,63±11,87	61,76±14,26	0,731
Saturation, %	89,33±16,07	90,84±4,52	0,609
SBP, mm Hg	134,60±15,42	135,59±32,01	0,878
Heart rate (HR), bpm	91,56±4,45	89,12±14,54	0,471
Body temperature (T), ^{0}C	37,9±0,74	38,13±0,82	0,298
WBC, 109/L	8,05±3,13	8,95±3,97	0,353
RBC, 1012/L	5,01±0,67	4,71±0,51	0,130
PLT, 109/L	260,78±96,1	304,25±83,1	0,131
ESR, mm/h	22,73±13,95	34,44±19,13	0,02
Total fibrinogen, g/L	5,43±1,92	5,83±0,95	0,749
Blood sugar, mmol/L	6,40±4,66	7,23±5,40	0,576

Table II. Gender, risk factors, clinical features of pneumonia in persons with laboratory-confirmed (first group) and without laboratory-confirmed (second group) diagnosis of coronavirus disease.

Indicators		Frequency, n		Percentage, %		P
		1group	2 group	1 group	2 group	
Gender	Women	24	29	58,5	53,7	0,726
	Men	16	25	39,0	46,3	0,646
Age up to 60 years		14	24	34,1	44,4	0,533
Testing up to the 10th day of illness		25	16	62,5	29,1	0,037
Oxygen-Dependent Patients		10	6	24,4	11,1	0,515
AH		25	16	61,0	29,6	0,05
CAD		22	13	53,7	24,1	0,09
DM		10	4	24,4	7,4	0,469
Loss of smell		2	1	4,9	1,85	0,833
Shortness of breath		21	20	51,2	37,1	0,364
Cough		25	29	61,0	40,7	0,137
Nausea, vomiting		5	2	11,1	3,9	0,764
General weakness		11	7	24,4	13,7	0,582
Diarrhea		2	0	4,4	0	0,805
Chest pain		0	2	0	3,9	0,778

an acceleration of the erythrocyte sedimentation rate (ESR), in almost half of the cases (47.8%) – leukocytosis was diagnosed and 47.8% of patients had a normal level of leukocytes. In 4.5% of patients, leukopenia was noticed. In some cases (9.1%), thrombocytopenia was diagnosed.

The level of total fibrinogen (100%) was elevated in all patients who underwent such test. In 38.9% of patients, an increased glycaemia was detected before the initiation of treatment. In every seventh patient (14.8%), a decrease in sugar level below the limit norms was determined.

Most often, patients had concomitant diseases of the cardiovascular system, namely: in 42.7% of patients, arterial hypertension (AH) was diagnosed, in 36.5% – coronary artery disease (CAD), in 29.2% – heart failure (HF), in 3% – there were the heart rhythm disorders in the form of atrial fibrillation, in 1 case – dilatation of the heart chambers.

Table III. Influence of patient age, testing time and illness severity on PCR test assessment using Fisher's exact test with Yates' continuity correction.

Indicators	Testing up to the 10th day of illness	Testing after the 10th day of illness	Age up to 60 years	Age over 60 years	Severe illness	Moderate illness
Positive PCR test	25	15	14	27	26	6
Negative PCR test	16	34	30	24	19	16
Chi-square (df=1)	8,33	p= 0,0039	4,30	p=0,0382	5,51	p= 0,0189
V-square (df=1)	8,24	p= 0,0041	4,25	p=0,0392	5,43	p= 0,0198
Yates corrected Chi-square	7,15	p= 0,0075	3,48	p=0,0622	4,36	p= 0,0369
Phi-square	0,09261		0,04522		0,08225	
Fisher exact p, one-tailed		p= 0,0036		p=0,0307		p= 0,0176
two-tailed		p= 0,0055		p=0,0610		p= 0,0220
McNemar Chi-square (A/D)	0,00	p=1,0000	0,07	p=0,7911	5,76	p= 0,0164
Chi-square (B/C)	1,08	p= 0,2976	2,13	p=0,1443	1,93	p= 0,1649

Type 2 diabetes mellitus (DM) was registered in every fifth patient, in 4.2% of cases – diabetes was revealed for the first time.

4.2% of patients suffered from chronic obstructive pulmonary disease (COPD) and the same number – of urinary system diseases (glomerulonephritis, urolithiasis and pyelonephritis).

Chronic rheumatic heart disease, adrenal adenoma, breast cancer (condition after mastectomy), stomach cancer (gastrectomy according to Billroth 1), colorectal cancer (condition after hemicolectomy), hypothyroidism, acute pancreatitis were verified in every one case.

All patients included in the analysis had radiological signs of pneumonia, which corresponded to 5 points on the CO-RADS scale – a very high degree of suspicion. The patients were divided into two groups. The first group included 45 patients with confirmed laboratory COVID-19 status, the second – 51 patients with pneumonia without laboratory confirmed COVID-19 status. Comparative characteristics of both groups are shown in Tables I and II.

As shown in Table I, age, physical and laboratory findings did not differ significantly in both patient groups. The only exceptions concerned ESR indicators, which were significantly higher in patients of group 2 without laboratory-confirmed COVID 19 status ($p = 0.02$).

In both groups analyzed, the proportion of men and women was de facto equal ($p = 0.726$). The percentage of patients under 60 years old in the 1st and 2nd groups also did not differ significantly ($p = 0.184$). The key difference that, in our opinion, influenced SARS-CoV-2 test results, was a smaller proportion of patients who underwent the test before the 10th day of illness in the second group of patients ($p = 0.037$).

In both groups, no clinical differences in the course of the disease were found. The main symptoms of coronavirus pneumonia were found with the same frequency both in patients with a laboratory-confirmed diagnosis and without it. AH ($p = 0.05$) and unreliable CAD ($p = 0.09$) were detected in patients with a PCR-positive test a little more often. In particular, the presence of a comorbid pathology, according to the treatment protocol, may affect the hospitalization terms of such patients.

For better clarity of the presented findings, we analyzed the dependence of positive PCR test results on patient age, testing time and COVID-19 pneumonia severity using Fisher's exact test with Yates' continuity correction. The results of this analysis are presented in Table III.

DISCUSSION

A positive PCR test in nasopharyngeal and oropharyngeal swabs was more often detected during early testing (up to 10 days), in patients over 60 years of age and in severe COVID-19. Probably in these categories of patients, the virus replication was more active, which influenced the test results.

It is worth noting that the results of our analysis are consistent with data from cohort studies conducted and published earlier. In particular, the highest percentage (100%) of positive results of RT-qPCR test for the SARS-CoV-2 virus, according to the results of one of the original studies of 56 hospitalized patients with confirmed SARS-CoV-2 infection in hospital departments in Wuhan (China), was obtained only in the first week of illness. Accordingly, at 2, 3, 4, 5 and 6 weeks the frequency of positive tests was lower and corresponded to 89.3%, 66.1%, 32.1%, 5.4% and 0%. [3]. The findings of a retrospective cohort study of viral load dynamics assessment in 96 patients infected with SARS-CoV-2 in the Chinese province of Zhejiang in January-March 2020, published by authoritative British Medical Journal, are similar to those previously published, in particular, the SARS-CoV-2 detection frequency in the obtained samples from the respiratory tract decreases over time: from 95% at the 1st week from the onset of symptoms to 54% at the 4th week of illness with subsequent negative results [6].

In another leading study in the UK, in the first week after coronavirus disease symptom onset, the semi-quantitative viral load – geometric mean (GM) of the RT-PCR cycle threshold (Ct) was 28.18 (95% confidence interval (CI): 27.76–28.61); in the second week GM Ct was 30.65 (95% CI: 29.82–31.52; $p < 0.001$ compared with week 1) and after 14 days, GM Ct was 31.60 (95% CI: 31.60–34.49; $p = 0.01$ compared with week 1). RT-qPCR cycle threshold (Ct) values correlate strongly with cultivable virus. Thus, the ability to cultivate SARS-CoV-2 in patients with mild to moderate disease was highest in the first week and decreased significantly by day 10 after the onset of symptoms [14]. The strengths of this study include a relatively large number of analyzed patients – 754 persons that tested positive for SARS-CoV-2 by RT-PCR targeting the RNA-dependent RNA polymerase (RdRp) gene, inclusion of a large proportion (> 50%) of samples taken more than 7 days after symptom onset and that all analysis was performed in a single laboratory. Persistent SARS-CoV-2 replication was demonstrated in severe COVID-19 cases during longer period of time – up to 32 days after the onset of symptoms and even at high Ct values [14].

A meta-analysis of data from seven previously published studies providing results on RT-qPCR testing for SARS-CoV-2 (total n = 1330) showed: within 4 days – between infection (day 1) and the typical time of onset of symptoms (day 5), the probability of a false-negative result in an infected person decreases from 100% (95% CI, 100% to 100%) on day 1 to 67% (CI, 27% to 94%) on day 4. On the day of symptom onset (day 5), the median false-negative rate was 38% (CI, 18% to 65%). This decreased to 20% (CI, 12% to 30%) on day 8 and then began to increase again, from 21% (CI, 13% to 31%) on day 9 to 66% (CI, 54% to 77%) on day 21. Overall, in this pooled analysis, the rate of false-negative RT-qPCR tests was highest on the day of infection, and lowest at 8 days after infection, and then increased again [15].

The problem of diagnosing COVID-19 pneumonia we met, in our opinion, was primarily due to the untimely recourse of patients for medical help (more than 10 days) and late PCR testing, which significantly influenced the results of molecular laboratory diagnostics of the SARS-CoV-2 virus.

CONCLUSIONS

The COVID-19 pneumonia diagnosis should be based on a combination of clinical, laboratory, and radiological signs of this disease. A negative PCR test result does not exclude the diagnosis of coronavirus disease, and in the presence of other signs of this disease, the approaches to treatment and prevention of Covid-19 should be identical as in patients with a positive PCR test. The test results are influenced by the timing of the sampling, the severity of the disease and the age of the patients, which must be taken into account when planning the sampling of nasopharyngeal and oropharyngeal specimens to verify the diagnosis of coronavirus disease.

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