https://doi.org/10.46389/rjd-2024-1456
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2024; volume 31, issue 2, pages 184–190

Original Article

Clinical and pathogenetic features of coronavirus disease course in type 2 diabetes

Solomiia Mahiiovych [1]*, Tetiana Maksymets [1], Viorika Akimova [2], Eugen Sklyarov [1]

[1] Department of Therapy No.1, Medical Diagnostics, Hematology and Transfusion FPGE, Lviv, Ukraine
[2] Department of Clinical Laboratory Diagnostic, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine

* Correspondence to: Solomiia Mahiiovych, Department of Therapy No.1, Medical Diagnostics, Hematology and Transfusion FPGE, Sahaidachny Str 5a, Dubliany, Lviv region, 80381, Ukraine. Phone: +380630605699; E-mail: solka.chekh@gmail.com

Received: 6 November 2023 / Accepted: 12 March 2024

Abstract

A dangerous combination of two diseases that have reached pandemic proportions, COVID-19 and type 2 diabetes, have unique features of the comorbid course. Intense inflammation, hypercoagulation, dysglycemia, and immune and renal dysfunction are underlying processes in the pathogenesis of the combination of these diseases. Our study aimed to compare groups of hospitalized patients with moderate to severe coronavirus disease with and without diabetes, paying particular attention to renal function and examining the relationships between markers of renal dysfunction, inflammation, and thrombosis in these patient groups. In total, 79 patients aged 24 to 73 with moderate to severe coronavirus disease were examined. Patients were divided into 2 groups: 1st – without diabetes; 2nd – with diabetes. The clinical picture, laboratory results (additionally determined cystatin C level) and instrumental studies were compared. Correlation analysis was conducted in groups. The group of patients with type 2 diabetes mellitus had significantly lower oxygen saturation upon admission to the hospital. A significantly higher concentration of glucose in blood serum (11.3 (8.1; 16.5) mmol/l 5.2 (4.4; 6.6) mmol/l, P<0.01) and a lower creatinine level (106.0 (87.3; 123.0) mcmol/l *vs.* 129.5 (104.8; 167.3) mcmol/l, P<0.05) were observed in the 2nd group while there were no differences in urea and cystatin C levels. By means of correlation matrices, it was established that inflammation, hypercoagulation, dysglycemia, and impaired kidney function are underlying causes of the coronavirus disease pathogenesis in group 1 of patients. At the same time, inflammation and hypercoagulation are the causes in the group of patients with a combined course of type 2 diabetes mellitus. Although the combined course of coronavirus disease and type 2 diabetes mellitus is prognostically more severe, we found a significantly lower creatinine level in the group of patients with type 2 diabetes.

Keywords: COVID-19, creatinine, dysglycemia, cystatin C.

Introduction

COVID-19 has a wide spectrum of manifestations, from asymptomatic infection to critical pneumonia with acute respiratory distress syndrome (ARDS) [1]. Thus, multiple organ dysfunction and mortality are very high, especially in adults with comorbidities [2, 3]. A cytokine storm can make the situation with COVID-19 dangerous due to an overactive inflammation and immune response [4]. In addition to impairing respiratory function and the immune system, COVID-19 can affect kidney function, ranging from increased levels of urea or creatinine in the blood to acute kidney injury and kidney failure [5].

Currently, the data of many studies have already been published, which allows a better understanding of the impact of two serious diseases that have reached the scale of a pandemic – COVID-19 and type 2 diabetes mellitus (T2DM). Complications of diabetes and comorbid conditions – diabetic nephropathy, obesity, coronary heart disease, hypertension – further worsen the situation for individuals with T2DM by increasing the severity of the course of COVID-19 [6]. Results were also obtained that evaluated the relationships between

chronic cardiovascular disease, prognosis, and death associated with COVID-19 [7]. There are very few similar studies studying the effects of kidney diseases.

Patients with T2DM and cardiovascular disease, as well as the elderly and overweight individuals, are extremely vulnerable to COVID-19. As a result of the combination of these conditions, one patient can belong to several high-risk groups at once. At the same time, T2DM is not a factor that increases the risk of infection with COVID-19. According to a meta-analysis of seven studies involving 1.576 patients with COVID-19, patients with diabetes required hospitalization six times more frequently than individuals without diabetes. Moreover, mortality in patients suffering from COVID-19 with comorbidities was 12 times higher than in individuals without comorbidities [8].

According to CORONADO, a multicenter observational study of phenotypic characteristics and prognosis of hospitalized patients with COVID-19 and DM, every fifth patient with DM required treatment in the intensive care unit (ICU), and mechanical ventilation (MV), and every 10th person with T2DM and COVID-19 died [9].

The use of biomarkers in diagnosis, risk assessment, and medical decision-making is common. Mortality was associated with the markers of organ failure, coagulopathy, and inflammation in hospitalized patients with COVID-19 [10, 11]. Identifying patients with unfavorable outcomes may aid in early intensification of therapy and more careful monitoring. In addition, research on new biomarkers may provide a better understanding of the pathogenesis of COVID-19 and its consequences.

Currently, cystatin C is actively studied as a marker of renal dysfunction. It is synthesized by almost all nuclear cells, is freely filtered through the glomerular membrane due to its low molecular weight, and is completely catabolized by proximal tubular cells. Thus, it is impossible to return it to circulation, ensuring a stable blood serum level. It has been proven that the level of cystatin C is not affected by such factors as age, gender, muscle mass, nutritional characteristics, physical activity, and race. These properties allow it to be considered a more sensitive early renal dysfunction biomarker than classical creatinine and urea [12].

Besides, new studies have convincingly shown that cystatin C is involved in immunomodulatory reactions observed during inflammatory processes and infections. It is able to control the release of a variety of cytokines, including nitric oxide, interleukin-12, interleukin-10, and tumor necrosis factor, under the influence of which intracellular components undergo irreversible changes, resulting in cell apoptosis and organ failure [13].

While elevated cystatin C levels in the blood of patients with COVID-19 likely indicate impaired renal function, they may also indicate other abnormal processes, namely systemic inflammation, oxidative stress, and cytokine storm [14].

The aim of our study was to compare groups of hospitalized patients with moderate to severe coronavirus disease with and without diabetes, a particular focus being on renal function, and to examine the relationships between markers of renal dysfunction, inflammation, and thrombosis in these patient groups.

Material and methods

The clinical trial was conducted in accordance with the Declaration of Helsinki, The Convention for the Protection of Human Rights and Biomedicine, Legislation of Ukraine and agreed by the Commission on Ethics of Research, experimental development and scientific works of Danylo Halytsky Lviv National Medical University: No. 10 of December 20, 2021. All patients signed an informed consent before the study.

Thus, 79 patients with moderate and severe coronavirus disease who were undergoing inpatient treatment at the Clinical Municipal Communal Emergency Hospital in Lviv were examined. The degree of severity was established according to the criteria corresponding to the protocol "Providing medical assistance for the treatment of coronavirus disease (COVID-19)", approved by the order of the Ministry of Health of Ukraine dated 02.04.2022 No. 762. The patients ranged from 24 to 73 years, including 47 males and 32 females. Patients were divided into 2 groups: the 1st – without diabetes and the 2nd – with diabetes. Type 2 diabetes is diagnosed according to the recommendations of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Patients were treated following the protocol and recommendations mentioned above. On admission, the anamnesis of the disease and life was investigated in detail; general clinical examinations, saturation measurements, imaging and laboratory studies were performed. Exclusion criteria were CKD 3–5 stages, decompensated heart failure, liver failure, oncology, and pregnancy.

Laboratory, anthropometric and clinical data collection. The diagnosis of coronavirus disease was verified with a polymerase chain reaction, and lung

damage was confirmed with the help of radiological methods (polypositional radiography or computer tomography of the thoracic organs). Hematological and biochemical blood tests and coagulograms were performed using generally accepted methods. Cystatin C was determined using a biochemical method with the SPINREACT test system (Spain). D-dimer was determined using the chemiluminescence Immunoassay analyzer "Immulite 2000" (Siemens, Germany) using the appropriate reagent (Immulite 2000 D-dimer, USA).

Statistical analysis

The results were presented as means with a statistical error. The values with normal distribution are given as confidence interval (95%), and the values where distribution largely deviated from the norm are presented as intervals of 25% and 75% percentiles. A comparison of groups was performed using the Mann – Whitney U-test. Spearman's rank correlation measures were used to denote the associations between variables. Categorical data were presented as proportions and analyzed using the Chi-square test. The results were considered statistically reliable at $p<0.05$.

Results

On admission, patients, regardless of the presence of T2DM, complained of breathlessness, cough, fever, chest pain, hemoptysis, sore throat, nasal congestion, and loss of smell. Some of the patients had gastroen-

Table 1: Basic characteristics and symptoms in patients with coronavirus disease without diabetes mellitus (1st group) and patients with diabetes mellitus (2nd group).

	1st group, n=36	2nd group, n=43	P-value
Male, %	25 (69.4%)	22 (51.2%)	0.09
Age, years	65.5 (55.0; 71.0) [2]	61.8 (58.6; 62.1) [1]	0.45
BMI, kg/m²	26.9 (21.6; 33.8) [2]	31.5 (29.0; 33.9) [1]	0.07
SpO_2,%	91.0 (90.0; 93.3) [2]	90.0 (86.3; 92.0) [2]	<0.05
SBP, mm Hg	141.6 (135.1; 148.2) [1]	143.5 (138.5; 148.4) [1]	0.34
DBP, mm Hg	88.7 (83.2; 90.2) [1]	86.9 (84.3; 89.5) [1]	0.66
HR, bpm	90.0 (81.5; 98.0) [2]	91.3 (88.3; 94.2) [1]	0.71
Dyspnea	28 (77.8%)	39 (90.7%)	0.11
Cough	27 (75.0%)	34 (79.1%)	0.67
Fever	35 (97.2%)	42 (97.7%)	0.89
Hypertension	21 (58.3%)	31 (72.1%)	0.19
Chest pain	21 (58.3%)	32 (74.4%)	0.13
Hemoptysis	5 (13.9%)	7 (16.3%)	0.77
Nausea/vomiting	6 (16.7%)	6 (14.0%)	0.73
Diarrhea	2 (5.6%)	4 (9.3%)	0.53
Myalgia/arthralgia	19 (52.8%)	24 (55.8%)	0.78
Anosmia	17 (47.2%)	14 (32.6%)	0.18
Nazal congestion	8 (22.2%)	11 (25.6%)	0.72
Sore throat	18 (50.0%)	21 (48.8%)	0.62
Lymphadenopathy	3 (8.3%)	4 (9.3%)	0.89
Rash	1 (2.8%)	2 (4.7%)	0.89
Fatigue	32 (88.9%)	39 (90.7%)	0.79

Note: [1] – values with normal distribution, M (M-CI; M+CI); [2] – values, where distribution significantly differs from normal, Me (25%; 75%).

https://doi.org/10.46389/rjd-2024-1456

terological manifestations of the coronavirus disease, namely nausea, vomiting, and diarrhea. Other symptoms were also observed: muscle and joint pain, lymphadenopathy, rash, severe fatigue and weakness. The group of patients with T2DM had significantly lower oxygen saturation upon admission to the hospital (Table 1).

Despite the fact that all patients presented with different blood patterns, no significant difference was found between the groups. The levels of liver parameters and pro-inflammatory markers, such as CRP, fibrinogen, and D-dimer, did not differ either. As expected, a significantly higher concentration of glucose in blood serum was observed in the 2nd group (11.3 (8.1; 16.5) mmol/l 5.2 (4.4; 6.6) mmol/l, P<0.01).

It is noteworthy that the creatinine level was significantly lower in the group of patients with T2DM (106.0 (87.3; 123.0) mcmol/l *vs*. 129.5 (104.8; 167.3) mcmol/l, P<0.05), while no difference was observed in the levels of urea and cystatin C (Table 2).

Further, we conducted a correlation analysis to find out the relationships between the critical indicators by which the patient's condition was assessed. As can be seen from Figure 1 in the group of patients with COVID-19 without T2DM, there are many direct relationships between the level of glucose and leukocytes with other indicators, while the coagulation component of the inflammatory process is involved only indirectly through D-dimer. The levels of renal markers had strong correlations between themselves and the level of leukocytes, which may indicate the influence of inflammatory activity on kidney function and the immunomodulatory effect of cystatin C. According to the data of the correlation matrix in group 1 of patients, the pathogenesis of COVID-19 is based on inflammation, hypercoagulation, dysglycemia and impairment of kidney function (Figure 1).

In the group of patients with T2DM, associations of D-dimer with SRP, saturation level, leukocytes, glucose and creatinine are observed. There is also a reliable inverse relationship between the level of platelets and leukocytes, between the level of platelets and oxygen saturation, and a direct relationship with the concentration of fibrinogen. These close connections prove the involvement of the coagulation component in the process.

When analyzing the correlation matrix in the 2nd group of patients, it becomes clear that the pathogenesis of the combined course of COVID-19 and T2DM is based on inflammation and hypercoagulation (Figure 2).

Table 2: Hematological and biochemical markers in patients with coronavirus disease without diabetes mellitus (1st group) and patients with diabetes mellitus (2nd group).

	1st group, n=36	2nd group, n=43	P-value
RBC, 10*12/l	4.7 (4.5; 5.0)[2]	4.9 (4.7; 5.1)[1]	0.16
WBC, 10*9/l	9.4 (7.2; 13.4)[2]	8.3 (5.5; 11.7)[2]	0.16
Platelets, 10*9/l	190.0(157.0; 241.0)[2]	218.1 (192.5; 243.6)[1]	0.56
Haemoglobin, g/l	138.0 (130.8; 154.0)[2]	141.5 (136.4; 146.5)[1]	0.86
ESR, mm/h	29.7 (23.3; 36.1)[1]	31.9 (27.4; 36.4)[1]	0.46
Glucose, mmol/l	5.2 (4.4; 6.6)[2]	11.3 (8.1; 16.5)[2]	<0.01
ALT, U/l	38.0 (20.9; 62.3)[2]	26.3 (12.6; 42.5)[2]	0.07
AST, U/l	29.3 (24.7; 46.5)[2]	28.6 (20.3; 38.7)[2]	0.19
Bilirubin, mcmol/l	10.3 (7.0; 14.3)[2]	10.5 (8.3; 14.0)[2]	0.69
Creatinine, mcmol/l	129.5 (104.8; 167.3)[2]	106.0 (87.3; 123.0)[2]	<0.05
Urea, mmol/l	9.4 (7.4; 14.9)[2]	8.1 (5.8; 10.7)[2]	0.07
Cystatine, mg/l	1.36 (0.89; 2.38)[2]	1.15 (0.73; 1.60)[2]	0.45
CRP, mg/l	42.0 (26.3; 97.5)[2]	48.0 (26.0; 95.5)[2]	0.52
Fibrinogen, g/l	5.5 (4.7;6.2)[1]	5.5 (4.9;5.9)[1]	0.82
D-dimer, ng/ml	788.0 (310.7;2025.7)[2]	846.9 (306.5;1615.7)[2]	0.87

Note: [1] – values with normal distribution, M (M-CI; M+CI); [2] – values, where distribution significantly differs from normal, Me (25%; 75%).

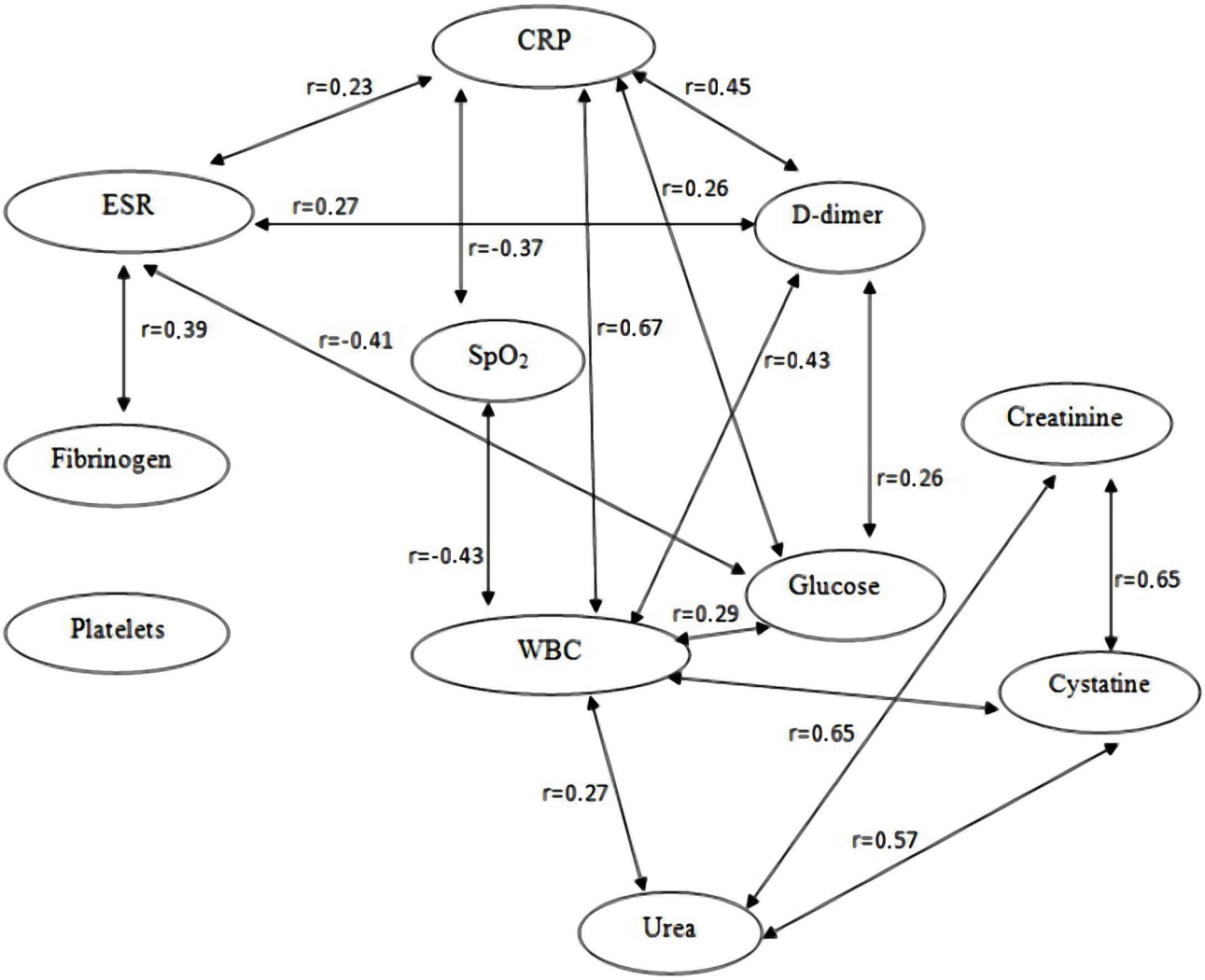

Figure 1: Correlations between saturation, hematological and biochemical indicators, and pro-inflammatory markers in patients of the 1st group ($p<0.05$).

Discussion

The presence of T2DM in patients is associated with an almost 3-fold increase in the risk of a more severe COVID-19 course, the need for treatment in the ICU, and mortality. Patients with prediabetes were also more likely to have more severe COVID-19 than normoglycemic patients [15]. The reason for the poorer prognosis in people with T2DM is likely to be multifactorial, reflecting the polysyndromic nature of diabetes. Age, sex, ethnicity, comorbidities such as hypertension and cardiovascular disease, obesity, and pro-inflammatory and procoagulant conditions likely contribute to the risk of worse outcomes. Glucose-lowering drugs may modulate the risk, but the limitations of their use and potential interaction with coronavirus disease treatment should be carefully evaluated. In turn, infection with the coronavirus itself can be a worsening factor for people with T2DM, as it can provoke acute metabolic complications due to a direct negative effect on β-cell function. This can cause diabetic ketoacidosis in individuals with T2DM, hyperglycemia on hospitalization in individuals without previously diagnosed T2DM, and precipitate the onset of T2DM [16]. According to Wang S. *et al.*, fasting blood glucose ≥7.0 mmol/L on admission is an independent predictor of 28-day mortality in patients with COVID-19 without a prior diagnosis of T2DM [17, 18].

We obtained data suggesting that inflammation, dysglycemia, and renal dysfunction underlie the pathogenesis of coronary artery disease in patients without previously diagnosed T2DM, whereas inflammation and hypercoagulability play a role in patients with T2DM. Such a difference may be due to the influence of hypoglycemic drugs and hypotensive drugs that have a nephroprotective effect. Likely, patients with previously established T2DM are more compliant and have received basic treatment prior to infection with the coronavirus.

https://doi.org/10.46389/rjd-2024-1456

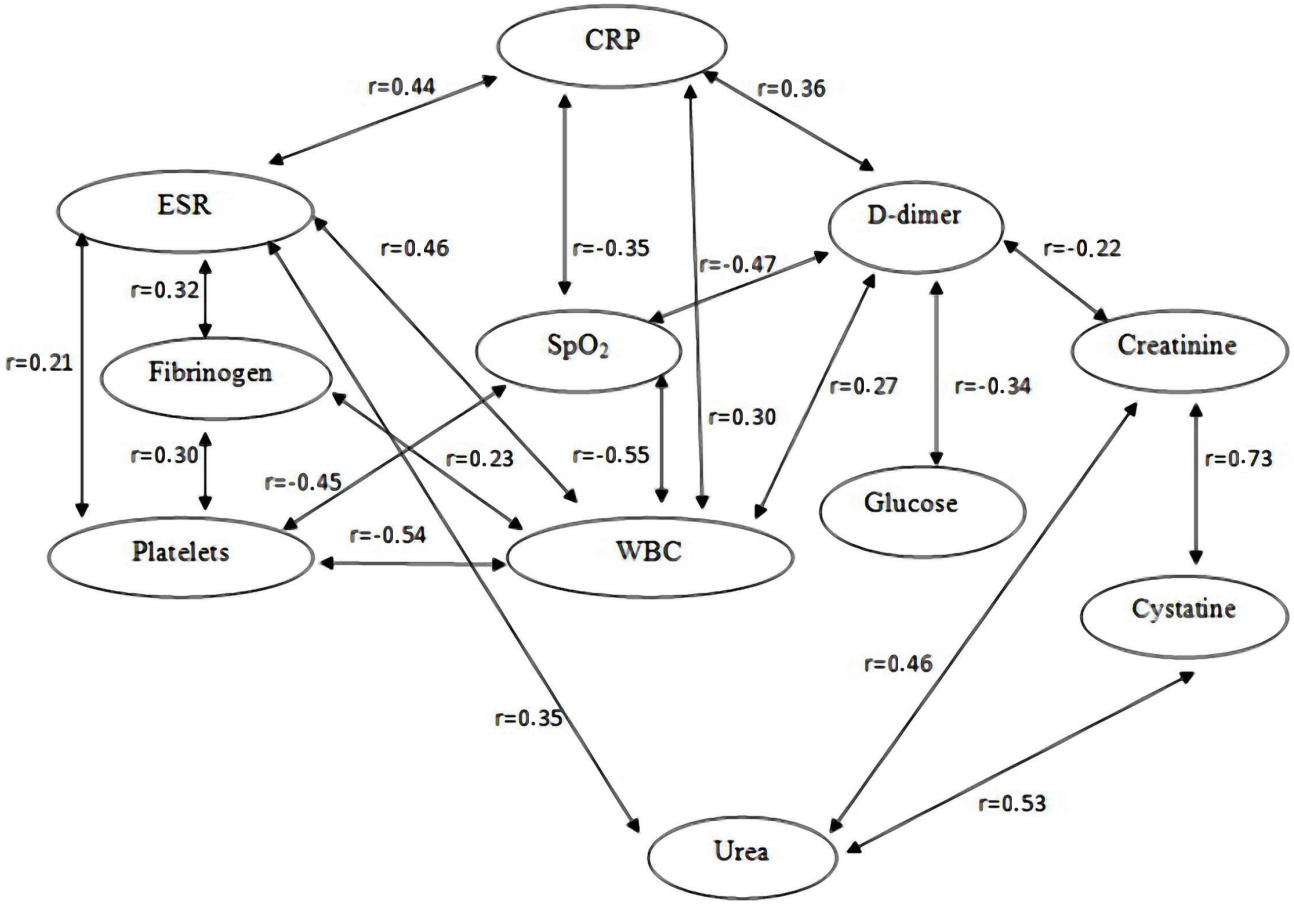

Figure 2: Correlations between saturation, hematological and biochemical indicators, and pro-inflammatory markers in patients of the 2nd group (p<0.05).

Almost all patients from group 2 received metformin or a combination of SGLT-2 inhibitors and metformin, and in case of worsening conditions, they were switched to insulin during inpatient treatment. Metformin is associated with a reduction in cardiovascular risk indirectly through suppressive effects on insulin resistance, systemic inflammation, and hypercoagulation [19, 20]. The pleiotropic effects of metformin can explain our observations.

In the CORONADO study, patients with newly diagnosed T2DM were most likely to be admitted to the ICU and required mechanical ventilation, presumably due to prolonged undiagnosed conditions without glycemic control [9].

It is important to remember that hyperglycemia can be not only a manifestation of diabetes but also the so-called "stress" phenomenon or a side effect of drugs, in particular steroids, which were prescribed at the pre-hospital stage.

It should also be emphasized that controlling the blood glucose level in patients with diabetes can mitigate the consequences of COVID-19. This was shown, for example, in a large retrospective multicenter study conducted in China involving 7.337 patients with COVID-19 with and without T2DM. Compensation for diabetes facilitates the overcoming of the coronavirus disease for such patients, and *vice versa* – poor control of T2DM significantly increases the risk of mortality from COVID-19. Today, we can only speculate that long-term suboptimal glycemic control may impair certain aspects of the immune response to viral infection and potential secondary bacterial infectious processes in the lungs. It is the phenomenon of glucose toxicity, endothelial dysfunction, and oxidative stress that leads to extensive changes and worse consequences [21].

Conclusions

On admission, the patient's symptoms, regardless of T2DM presence, actually did not differ. The group of patients with T2DM had significantly lower oxygen saturation, higher concentration of glucose in blood serum (11.3 (8.1; 16.5) mmol/l 5.2 (4.4; 6.6) mmol/l, P<0.01) and significantly lower creatinine level (106.0 (87.3; 123.0) mcmol/l *vs*. 129.5 (104.8; 167.3) mcmol/l, P<0.05).

According to the correlation matrix data, the pathogenesis of COVID-19 in patients is based on inflammation, hypercoagulation, dysglycemia, and impaired kidney function, whereas with the combined course of COVID-19 and T2DM, it is due to inflammation and hypercoagulation. Such differences may be ascribed to the pleiotropic effects of hypoglycemic drugs that the patients received at the pre-hospital stage.

Conflict of interest

The authors declare no conflict of interest.

References

1. Pan Y, Yu X, Du X, *et al*. Epidemiological and Clinical Characteristics of 26 Asymptomatic Severe Acute Respiratory Syndrome Coronavirus 2 Carriers. J Infect Dis. 2020 Jun 11;221(12):1940-1947. doi: 10.1093/infdis/jiaa205.
2. Yang X, Yu Y, Xu J *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475-481. doi: 10.1016/S2213-2600(20)30079-5.
3. Contou D, Claudinon A, Pajot O, *et al*. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care. 2020 Sep 7;10(1):119. doi: 10.1186/s13613-020-00736-x..
4. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020 Jun;8(6):e46-e47. doi: 10.1016/S2213-2600(20)30216-2.
5. Lin L, Chen X, Chen J, *et al*. The predictive value of serum level of cystatin C for COVID-19 severity. Sci Rep. 2021;11(1):21964. doi: 10.1038/s41598-021-01570-2.
6. Landstra CP, de Koning EJP. COVID-19 and Diabetes: Understanding the Interrelationship and Risks for a Severe Course. Front Endocrinol (Lausanne). 2021 Jun 17;12:649525. doi: 10.3389/fendo.2021.649525.
7. CAPACITY-COVID Collaborative Consortium and LEOSS Study Group. Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries. Eur Heart J. 2022 Mar 14;43(11):1104-1120. doi:10.1093/eurheartj/ehab656.
8. Yang J, Zheng Y, Gou X, *et al*. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020 May;94:91-95. doi: 10.1016/j.ijid.2020.03.017.
9. Wargny M, Potier L, Gourdy P, et al; CORONADO investigators. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. Diabetologia. 2021 Apr;64(4):778-794. doi: 10.1007/s00125-020-05351-w.
10. Qiu P, Zhou Y, Wang F, *et al*. Clinical characteristics, laboratory outcome characteristics, comorbidities, and complications of related COVID-19 deceased: a systematic review and meta-analysis. Aging Clin Exp Res. 2020 Sep;32(9):1869-1878. doi: 10.1007/s40520-020-01664-3.
11. Shi C., Wang L., Ye J., *et al*. Predictors of mortality in patients with coronavirus disease A systematic review and meta-analysis. BMC Infect. Dis. 2021;21:663. doi: 10.1186/s12879-021-06369-0.
12. Coll E, Botey A, Alvarez L, *et al*. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. Am J Kidney Dis. 2000 Jul;36(1):29-34. doi: 10.1053/ajkd.2000.8237.
13. Zi M, Xu Y. Involvement of cystatin C in immunity and apoptosis. Immunol Lett. 2018 Apr;196:80-90. doi: 10.1016/j.imlet.2018.01.006.
14. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med. 2020 Dec 3;383(23):2255–2273. doi: 10.1056/NEJMra2026131.
15. Van Baal L, Reinold J, Benson S, *et al*. Implications of an HbA1c-based Diabetes Screening on Prevalence and Effect of Dysglycemia in Patients With COVID-19. J Clin Endocrinol Metab. 2023 Feb 15;108(3):697-705. doi:10.1210/clinem/dgac590.
16. Apicella M, Campopiano MC, Mantuano M, *et al*. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 2020 Sep;8(9):782-792. doi: 10.1016/S2213-8587(20)30238-2.
17. Wang S, Ma P, Zhang S, *et al*. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without a previous diagnosis of diabetes: a multicenter retrospective study. Diabetologia. 2020 Oct;63(10):2102-2111. doi: 10.1007/s00125-020-05209-1.
18. Dennis JM, Mateen BA, Sonabend R, *et al*.. Type 2 Diabetes and COVID-19-Related Mortality in the Critical Care Setting: A National Cohort Study in England, March-July 2020. Diabetes Care. 2021 Jan;44(1):50-57. Doi: 10.2337/dc20-1444.
19. Holman N, Knighton P, Kar P *et al*. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2020 Oct;8(10):823-833. doi: 10.1016/S2213-8587(20)30271-0.
20. Luo P, Qiu L, Liu Y, *et al*. Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. The American Journal of Tropical Medicine and Hygiene. 2020;103(1):69-72. doi:10.4269/ajtmh.20-0375.
21. Zhu L, She ZG, Cheng X, *et al*. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab. 2020 Jun 2;31(6):1068-1077.e3. Doi: 10.1016/j.cmet.2020.04.021.

 https://doi.org/10.46389/rjd-2024-1456