

Original Article

Coronavirus disease (COVID-19) in patients with type 2 diabetes mellitus: clinical and laboratory peculiarities

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Abstract

This study aims to study the clinical-laboratory peculiarities of the coronavirus disease (COVID-19) course in patients with type 2 diabetes mellitus (DM). There were examined 60 patients with the coronavirus disease COVID-19. Patients were divided into two groups: group I – 30 patients with the coronavirus disease (COVID-19) with concomitant type 2 diabetes mellitus; group II – 30 patients with coronavirus disease (COVID-19) without diabetes mellitus; control group – 20 people. There were studied peculiarities of clinical-laboratory changes in patients with coronavirus disease with type 2 diabetes mellitus. General clinical laboratory tests, determination of biochemical parameters, coagulogram, ferritin, CRP, procalcitonin, D-dimer and endothelin-1 were performed. Blood saturation was measured. Out of the instrumental methods, an ultrasound examination of the lungs and RTG of thoracic organs was performed. Patients were admitted on the 5.46 ± 0.87 day of the disease. The length of the hospital stay for patients of group I was 19.9 ± 1.66 bed days and 14.7 ± 0.91 bed days for the patients of group II. A severe course of the disease was observed in 83.3% of patients of group I and 33.3% of group II; a moderate severity course was observed in 16.7% of patients with concomitant DM and 66.7% of patients without concomitant DM. Respiratory failure (RF) of 1 degree was observed in 30% of patients of group I, RF of the 2 degree – in 16.7% of patients, and RF of the 3 degree – in 10% of patients. In patients without DM, RF of 1 degree – was in 30% of patients, and RF of the 2 degree – was in 13.3% of patients. The laboratory diagnostic methods determined that the levels of leukocytes, D-dimer, endothelin-1, IL-6, procalcitonin, and ferritin were higher in patients with concomitant type 2 DM. In patients with type 2 DM, the course of the coronavirus disease is more severe and longer, with the development of pneumonia and respiratory failure. It is accompanied by leukocytosis, lymphopenia, increased ESR, prothrombin index, IL-6, CRP level, procalcitonin and endothelin-1.

Keywords: coronavirus disease, COVID-19, diabetes mellitus.

Introduction

The coronavirus disease (COVID-19) is an infectious disease that was first identified in human beings in December 2019 in Wuhan, Central China. The disease be-

gan as an outbreak that developed into a pandemic. The cause of the disease is the SARS-CoV-2 coronavirus. This new virus causes respiratory diseases in humans and can be transmitted from person to person [1–4]. The World Health Organization (WHO) recognizes the disease as



an international health emergency. In Ukraine, the first cases of the coronavirus disease COVID-19 were registered in March 2020, and since then, the disease has been spreading among the population of Ukraine and, in particular, in our region. As of 23 August 2022, it is known that during the entire period of the pandemic in Ukraine, 5,044,941 people fell ill; 4,922,125 people recovered, and there were 108,803 deaths. As for the Ivano-Frankivsk region, during the entire period of the disease, 185,573 people fell ill, 181,9754 recovered, and there were 3,591 fatal cases [5].

Predictors of a severe course of the coronavirus disease COVID-19 are considered to be the age of 65 years and over and the presence of severe concomitant pathology – diabetes mellitus, severe chronic pathology of the respiratory and cardiovascular systems, immunosuppressive conditions and kidney failure. In particular, in type 2 diabetes mellitus, there are pathogenetic mechanisms such as metabolic disorders, endothelial dysfunction, impaired kidney, liver and immune system functioning, and cardiovascular pathology, creating prerequisites for a severe course and adverse consequences of COVID-19 [6, 7].

The presence of DM aggravates the course of the disease and doubles the risk of fatal complications development of COVID-19 in patients. The pathophysiological mechanisms underlying type 2 DM and coronavirus disease are based on the development of dysregulation of ACE-2 expression – a key factor in cell penetration and clearance of the virus and disruption of the immunological response, generally leading to greater susceptibility of patients with DM to the development of SARS-CoV-2 infection and a greater risk of the formation of a hyper-inflammatory state and the “cytokine storm” syndrome [6, 8].

Endothelial dysfunction – is a peculiarity of diabetes mellitus that is driven by a number of processes, including oxidative stress and inflammation. Endothelial dysfunction is thought to be a major cause of accelerated atherogenesis in DM, leading to many secondary conditions, including coronary heart disease, ischemic stroke, peripheral vascular disease, and nephropathy [9]. Oxidative stress induced by hyperglycemia is a likely mechanism underlying the endothelial dysfunction associated with DM.

Taking into account the fact that these processes already compromise the endothelium in diabetic patients, the impact of further endothelial dysfunction caused by COVID-19 may be more profound in this group of patients, especially if it is complicated by the effects of advanced age [9, 10].

Material and methods

In the course of the study, there were examined 60 patients with the coronavirus disease (COVID-19), who were treated at the CNPE (Communal Non-Profit Enterprise) “Ivano-Frankivsk Regional Clinical Infectious Disease Hospital of the Ivano-Frankivsk Regional Council”. Patients were divided into two groups: group I (major one) – 30 patients with coronavirus disease (COVID-19) with concomitant type 2 DM; group II (comparison group) – 30 patients with coronavirus disease (COVID-19) without DM; control group (practically healthy) – 20 people.

Criteria for the inclusion of patients with coronavirus disease (COVID-19) in study group I are the presence of confirmation of coronavirus disease (COVID-19) (RNA SARS-COV-2 smear from the naso- and oropharynx) and concomitant type 2 diabetes mellitus, moderately severe and severe course of the disease, age – older than 60 years, and the presence of signed informed consent.

Exclusion criteria from the study: the presence of other severe chronic diseases in patients: COPD, bronchial asthma, oncological diseases, lymphoproliferative and onco hematological diseases, HIV-infection, immunodeficiency conditions – congenital, acquired, medically induced, severe chronic heart failure.

The data obtained from clinical-laboratory studies were compared in groups of patients with concomitant diabetes mellitus and without it.

General clinical laboratory tests, determination of biochemical indices, coagulogram, ferritin, CRP, procalcitonin and D-dimer were performed for all patients upon admission to inpatient treatment. Quantitative determination of the level of endothelin-1 in blood serum was also carried out using the ELISA method. The ratio of neutrophils and lymphocytes was determined [11]. Blood saturation was measured. Such instrumental methods were used – ultrasound examination of the lungs and RTG of the thoracic organs were used.

The study was performed based on the CNPE “Ivano-Frankivsk Regional Clinical Infection Hospital IF RC”. All studies were conducted with the consent of the patients. Their methodology corresponded to the Helsinki Declaration of 1975 (and its revision in 1983). The performance of the study was approved by the IFNMU bioethics commission (protocol No. 121/21, dated May 13, 2021).

Statistical analysis

Statistical processing of the research results was carried out on a personal computer using the standard

package STATISTICA – 5 and Microsoft Excel. Relative ($P\pm mp$) and average values ($M\pm m$) were calculated with an error.

Results

Patients were admitted on the 5.46 ± 0.87 day of the disease. The average length of stay in the hospital for patients of group I was 19.9 ± 1.66 bed days and 14.7 ± 0.91 bed days ($p<0.01$) – for patients of group II. The gender distribution of patients with concomitant diabetes mellitus was as follows: 13 (43.33%) were male and 17 (56.67%) were female. Among patients without DM, there were: 15 (50%) males and 15 (50%) females. The average age of patients in group I was 66.70 ± 1.47 , and in group II was 60.13 ± 2.21 years. According to the research data, it was determined that the severe course of the disease was observed in 25 (83.3%) patients of group I and in 10 (33.3%) of group II; of moderate severity in 5 (16.7%) patients with concomitant diabetes mellitus and in 20 (66.7%) patients without concomitant DM.

Among the examined patients with type 2 DM, the concomitant pathology was found: hypertension in 17 (56.7%) patients, coronary heart disease in 5 (16.7%) patients, fatty hepatosis – in 9 (30.0%) patients, increased body weight – in 20 (66.7%) patients, varicose veins – in 7 (23.3%) patients. If we talk about concomitant diseases that occurred in the patients of the comparison group, coronary heart disease occurred in 21 (70%) patients,

hypertension – in 9 patients (30.0%), nodular goiter – in 2 (6.7%) patients, autoimmune thyroiditis – in 1 (3.3%) patient; chronic pancreatitis – in 9 (30%) patients.

It should be noted that poly segmental pneumonia was observed in 25 (100%) patients with concomitant diabetes mellitus and a severe course of the disease.

Analyzing the development of respiratory failure, it was determined that RF of the I degree (SpO_2 of blood in the range of 85–94%) was observed in 15 (30%) patients, RF of the II degree (SpO_2 75–85%) – in 5 (16.7%) patients, RF of the III degree ($SpO_2<75-85\%$) – in 3 (10%) patients. In patients without DM, 9 (30%) patients had RF of the I degree, 4 (13.3%) patients had RF of the II degree.

Analyzing the clinical symptoms, we can see that an increase in temperature over $37.5^\circ C$ was observed both in patients of group I (63.3%) and in patients of group II (63.3%). Most patients of both groups complained of cough (80%) and runny nose (60%). In the group of patients with type 2 DM, general weakness was noted in 26 (86.7%) patients *versus* 16 (53.3%) in the group without DM. Crackling rales were heard both in patients of group I – in 93.3% of patients, and in patients of group II (90%). General weakness was observed more often in patients of group I – 86.7% *versus* 53.3% of patients of group II. Symptoms such as loss of smell and taste were also more common in patients of group I (Table 1).

According to the data of laboratory diagnostic methods, it was found that in the group of patients with DM, the level of leukocytes was higher than in patients without DM: $(10.77\pm 0.81)\times 10^9/l$ *vs.* $(7.68\pm 0.57)\times 10^9/l$,

Table 1: Characteristics of the clinical symptoms of the coronavirus disease (COVID-19) in patients with concomitant diabetes mellitus, n=30.

| Symptoms | Group 1, n=30 | | Group 2, n=30 | |
|----------------------------|--------------------|------|--------------------|------|
| | Number of patients | % | Number of patients | % |
| Fever up to $37.5^\circ C$ | 10 | 33.3 | 12 | 40.0 |
| Fever over $37.5^\circ C$ | 19 | 63.3 | 9 | 63.3 |
| Cough | 25 | 83.3 | 24 | 80.0 |
| Runny nose | 18 | 60.0 | 18 | 60.0 |
| Dry wheezing | 8 | 26.7 | 9 | 30.0 |
| Crackling rales | 28 | 93.3 | 27 | 90.0 |
| Headache | 10 | 30 | 6 | 20.0 |
| General weakness | 26 | 86.7 | 16 | 53.3 |
| Muscle pain | 9 | 30 | 7 | 23.3 |
| Loss of smell | 9 | 30 | 5 | 16.7 |
| Loss of taste | 4 | 13.3 | 3 | 10 |
| Mental disorders | 3 | 10 | 2 | 6.7 |

$p < 0.01$. Against the background of leukocytosis, there was lymphopenia, which was found both in patients of group I (1.01 ± 0.10) and in the patients of group II (1.40 ± 0.10), $p < 0.001$. The average value of the level of neutrophils in patients of group I (6.12 ± 0.22) was significantly different from that of patients in group II (4.89 ± 0.54), $p < 0.05$. As a marker of a severe course, the coefficient of the ratio of neutrophils to lymphocytes above 3.13 was registered in 28 (93.3%) patients with DM and was observed only in 16 (53.33%) patients without DM. The level of platelets did not differ significantly in patients of groups I and II. The average values were 239.13 ± 20.77 in patients of group I and $249 \pm 15.84 \times 10^9/l$ in patients of group II, $p > 0.1$. It should be noted that eosinopenia was inherent in both patients with DM 0.01 ± 0.00 and patients without DM 0.04 ± 0.00 , $p < 0.05$. Analyzing ESR indices, we can see that the average value is higher in group I of patients, 31.53 ± 2.38 versus 19.17 ± 2.07 mm/h ($p < 0.001$). Taking into account the level of glucose, we understand that in the group of patients with type 2 DM, this level (15.13 ± 0.64) expectedly significantly exceeded similar indices in the group of patients without DM (4.85 ± 0.12) and in the group of practically healthy people (4.21 ± 0.13), $p < 0.001$. The level of glycosylated hemoglobin was also significantly different in patients of groups I (15.13 ± 0.64) and II (4.85 ± 0.18), $p < 0.001$.

The average values of creatinine in patients with DM did not differ significantly from those in patients without DM ($p > 0.1$), and their values were 121.78 ± 11.42 $\mu\text{mol/l}$ and

102.18 ± 4.0 $\mu\text{mol/l}$. Regarding the level of urea, it was 8.66 ± 1.10 mmol/l in group I of patients and 6.24 ± 0.44 mmol/l in the second group ($p < 0.05$). The average values of ALT and AST in patients with DM did not differ significantly from those in the group without DM, and their values were: ALT – 32.22 ± 5.97 U/l and 30.87 ± 3.57 U/l ($p > 0.1$), AST – 28.56 ± 6.10 U/l and 26.93 ± 2.58 U/l ($p > 0.1$) (Table 2).

It should be noted that the prothrombin index was increased in patients with DM (109.90 ± 2.62), $p < 0.01$. The average values of the activated thromboplastin time (ATPT) do not differ significantly in patients of group I and II. Their values are 38.60 ± 0.90 in patients of group I and 40.27 ± 1.35 in patients of group II ($p > 0.1$) (Table 3).

When determining the endothelin level, it was found that in the group of patients with diabetes mellitus 67.19 ± 0.06 , it is significantly higher than in patients without diabetes mellitus 12.69 ± 1.13 and significantly exceeds the average value in the group of practically healthy individuals 1.17 ± 0.06 , $p < 0.01$. It should be noted that D-dimer levels were elevated in patients of both groups. However, the average values in group I patients significantly exceeded those in group II patients, 1543.20 ± 254.01 and 522.74 ± 39.45 ($p < 0.001$), respectively (Table 3).

The level of interleukin-6 in patients of group I was 55.92 ± 6.88 pg/ml, which was more than twice as high as that of patients in group II 23.80 ± 3.70 ($p < 0.01$). According to the data received as a result of the study, we

Table 2: Results of hemogram and biochemical indices in patients with coronavirus disease (COVID-19) and in patients with coronavirus disease (COVID-19) with concomitant type 2 diabetes mellitus.

| Indicators | Control group (n=20) | Group I (n=30) | Group II (n=30) | P ₁ | P ₂ | P ₃ |
|-----------------------------------|----------------------|--------------------|------------------|----------------|----------------|----------------|
| Leukocyte count, $\times 10^9/L$ | 5.75 ± 0.20 | 10.77 ± 0.81 | 7.68 ± 0.57 | < 0.01 | < 0.001 | < 0.01 |
| Neutrophil count, $\times 10^9/L$ | 2.40 ± 0.13 | 6.12 ± 0.22 | 4.89 ± 0.54 | < 0.001 | < 0.001 | < 0.05 |
| Eosinophil count, $\times 10^9/L$ | 0.23 ± 0.02 | 0.01 ± 0.00 | 0.04 ± 0.00 | < 0.001 | < 0.001 | < 0.001 |
| Platelet count, $\times 10^9/L$ | 127.45 ± 6.46 | 239.13 ± 20.77 | 249 ± 15.84 | < 0.001 | < 0.001 | > 0.1 |
| ESR, mm/h | 6.30 ± 0.49 | 31.53 ± 2.38 | 19.17 ± 2.07 | < 0.001 | < 0.001 | < 0.001 |
| Urea, mmol/L | 4.83 ± 0.24 | 8.66 ± 1.10 | 6.24 ± 0.44 | < 0.002 | < 0.01 | < 0.005 |
| Creatinine, $\mu\text{mol/L}$ | 73.77 ± 2.0 | 121.78 ± 11.42 | 102.18 ± 4.0 | < 0.001 | < 0.001 | > 0.1 |
| Alanine aminotransferase, U/L | 13.02 ± 0.68 | 32.22 ± 5.97 | 30.87 ± 3.57 | < 0.001 | < 0.01 | > 0.1 |
| Aspartate aminotransferase, U/L | 11.54 ± 0.80 | 28.56 ± 6.10 | 26.93 ± 2.58 | < 0.001 | < 0.01 | > 0.1 |
| Glucose, mmol/L | 4.21 ± 0.13 | 15.13 ± 0.64 | 4.85 ± 0.18 | < 0.01 | < 0.001 | < 0.001 |
| Glycosylated hemoglobin, % | 5.02 ± 0.17 | 7.33 ± 0.14 | 5.87 ± 0.07 | < 0.001 | < 0.001 | < 0.001 |

Note: P₁ – the reliability of the difference between indices in patients of group I and the control group; P₂ – the reliability of the difference between indices in patients of group II and the control group; P₃ – the reliability of the difference between indices in patients of the groups I and II.

Table 3: Results of indices of endothelial dysfunction and indices of blood coagulation in patients with coronavirus disease (COVID-19) and in patients with coronavirus disease (COVID-19) with concomitant DM, M±m.

| Indicators | Control group (n=20) | Group I (n=30) | Group II (n=30) | P ₁ | P ₂ | P ₃ |
|----------------------|----------------------|----------------|-----------------|----------------|----------------|----------------|
| Prothrombin index, % | 89.09±1.27 | 109.90±2.62 | 95.68±1.82 | <0.01 | <0.001 | <0.01 |
| Prothrombin time, s | 12.60±0.22 | 14.98±0.26 | 14.40±0.17 | <0.001 | <0.001 | <0.1 |
| ATPT, s | 34.26±1.72 | 38.60±0.90 | 40.27±1.35 | <0.05 | <0.01 | >0.1 |
| Endothelin, ng/ml | 1.17±0.06 | 67.19±0.06 | 12.69±1.13 | <0.01 | <0.01 | <0.01 |
| D-dimer, ng FEU/ml | 270.35±35.66 | 1543.20±254.01 | 522.74±39.45 | <0.001 | <0.001 | <0.001 |

Note: P₁ – the reliability of the difference between indices in patients of group I and the control group; P₂ – the reliability of the difference between indices in patients of group II and the control group; P₃ – the reliability of the difference between indices in patients of the groups I and II.

observe that the level of CRP is elevated in both groups. However, in the group of patients with DM, it is almost twice as high, 33.60±4.62, as in the group without DM, 14.01±4.07. Analyzing the level of procalcitonin in patients of group I (0.78±0.03), we can see that it significantly exceeded the level in patients of group II (0.56±0.05), p<0.001. As for the level of ferritin, it was twice as high in patients of group I (612.50±30.39) as in patients of group II (282.03±22.29), p<0.001 (Table 4)

Discussion

Our study aimed to discover the clinical and laboratory peculiarities of the course of the coronavirus disease in patients with type 2 DM. We have demonstrated that patients with concomitant diabetes mellitus are more prone to a severe course of the coronavirus disease (83%), and the duration of their stay in the hospital is longer (19.9±1.66 vs. 14.7±0.91 bed days). As for the development of respiratory failure, it occurs more often in patients with DM. RF of the I degree was observed in 30% of patients, RF of the II degree – in 16.7%

of patients, and RF of the III degree – in 10% of patients with DM. In patients without diabetes mellitus, 30% of patients had RF of the I degree, and 13.3% had RF of the II degree. This allows us to state that DM is a risk factor for coronavirus disease and aggravates its course, which also corresponds to the literature data [12–16]. According to the results of our study, patients with concomitant type 2 DM had a similar pattern of clinical characteristics to patients without DM: fever, cough, runny nose, headache, general weakness, muscle pain, loss of smell, loss of taste and mental disorders. However, the patients of group I more often complained of general weakness 86.7% against 53.3%, headache 30% against 20% and loss of smell 30% against 16.7%.

When performing laboratory tests, in the general blood analysis there were observed significantly higher indices of the number of leukocytes ($10.77 \pm 0.81 \times 10^9$), neutrophils ($12 \pm 0.22 \times 10^9$) and increased ESR (31.53±2.38 mm/h) in patients with DM. The obvious laboratory abnormalities we observed in our study were a decrease in lymphocytes and eosinophils in patients with diabetes mellitus compared to patients without DM, which correlates with the literature data [17–21]. This

Table 4: Results of acute-phase indices of the inflammatory response in patients with coronavirus disease (COVID-19) and in patients with coronavirus disease (COVID-19) with concomitant diabetes mellitus, M±m.

| Indicators | Control group (n=20) | Group I (n=30) | Group II (n=30) | P1 | P2 | P3 |
|----------------------|----------------------|----------------|-----------------|--------|--------|--------|
| Interleukin-6, pg/ml | 4.38±0.26 | 55.92±6.88 | 23.80±3.70 | <0.001 | <0.001 | <0.001 |
| CRP, mg/L | 2.5±0.41 | 33.60±4.62 | 14.01±4.07 | <0.001 | <0.01 | <0.01 |
| Procalcitonin, mg/mL | 0.07±0.02 | 0.78±0.03 | 0.56±0.05 | <0.001 | <0.001 | <0.001 |
| Ferritin, µg/L | 167.80±16.78 | 612.50±30.39 | 282.03±22.29 | <0.001 | <0.1 | <0.001 |

Note: P₁ – the reliability of the difference between indices in patients of group I and the control group; P₂ – the reliability of the difference between indices in patients of group II and the control group; P₃ – the reliability of the difference between indices in patients of the groups I and II.

observation suggests that patients with DM were probably prone to a more severe course of the disease with the development of complications. Lymphocytes play a key role in maintaining immune homeostasis and the inflammatory response to protect the body against viral infections.

The presence of lymphopenia could be a diagnostic criterion and occur against the background of exhaustion of the “normal immune reaction” [17, 21–23]. The ratio of neutrophils to lymphocytes above 3.13, as a marker of the severe course of the disease, was observed in 93.3% of patients with diabetes mellitus and was observed only in 53.33% of patients without diabetes mellitus. If we talk about the indices of the glucose level in the blood of patients of group I, they were expected to exceed those of the patients of group II. Higher glucose levels were usually found in patients with a severe course of coronavirus disease. This tendency is also observed in the literature data, where it is described that severe hyperglycemia often occurs in seriously ill patients and is considered a marker of the severity of the disease [24, 25].

Analyzing the average values of the prothrombin index, we can see that in the group of patients with diabetes mellitus, they were $109.90 \pm 2.62\%$ and were significantly different from the results in patients without DM $95.68 \pm 1.82\%$. In addition, the study showed that an increase in the D-dimer level was observed in patients of both groups. However, in patients with diabetes mellitus, we obtained three times higher results than in the group of patients without diabetes mellitus, which probably indicates the excessive activation of the hemostasis system. It should also be noted that high D-dimer levels were accompanied by a severe course of the disease, which correlates with data from the literature [16, 26]. It is also worth mentioning the development of endothelial dysfunction. Endothelin-1 indices were increased in patients of both groups; however, we clearly observe significantly higher results in the representatives of group I, which indicates that concomitant DM is an important factor affecting the development of endothelial dysfunction and the course of the disease [27–29].

High levels of CRP, ferritin and interleukin-6 in blood serum are the key markers of disease progression and a predictor of severity, indicating the development of a cytokine storm in patients [30–31]. CRP, as a rule, significantly increases in the early stage of inflammation [26–36]. Ferritin is an important mediator of immune dysregulation, and its level has been strongly associated with disease severity.

Conclusions

The course of the disease was significantly longer and more severe in patients with coronavirus disease (COVID-19) and concomitant type 2 DM. In patients with type 2 DM, COVID-19 was significantly more often complicated by the development of pneumonia and the phenomena of respiratory failure of the I-III degree. Lymphopenia, increased activity of indices of inflammation, and destabilization of carbohydrate metabolism were recorded in patients with the coronavirus disease COVID-19 with concomitant DM significantly more often than in the comparison group. Levels of endothelin-1 and prothrombin index in patients with COVID-19 with type 2 DM were significantly higher than those without concomitant type 2 DM, indicating a more pronounced endothelial dysfunction in this combined pathology.

Conflict of interest

The authors declare no conflict of interest.

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