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COAGULOPATHY AND CORONAVIRUS DISEASE 2019

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Interest in coronavirus disease 2019 (COVID-19) in the world of science is constant. Pathogenesis is the subject of many studies, and coagulopathy occupies an important place in research. In our study, blood samples were collected from 131 patients treated for SARS-CoV-2 infection in University Clinical Center Kragujevac. Blood was sampled on the day of admission, and the disease course was monitored. We concluded that our participants do not meet the criteria for disseminated intravascular coagulation (DIC). We showed the statistical significance of platelet count, prothrombin time value and DIC score concerning the form and outcome of the disease. Patients with a critical form of the disease, as well as those who died, had significantly lower values of the number of platelets and significantly higher values of the DIC score.

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Key words: *coronavirus disease, disseminated intravascular coagulation, disease form, disease outcome*

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Introduction

COVID-19 is a pandemic disease caused by the SARS-Cov-2 virus (1). According to the criteria of the World Health Organization from September 2022, the disease is classified into three forms: critical (critical COVID-19), severe (severe COVID-19) and mild (non-severe COVID-19) (2). It was found that the main prognostic factors for a poor outcome were obesity, hypertension, diabetes and older age (3). Further, data from the literature emphasizes the importance of this virus in contributing to hypercoagulability and thrombosis (4). The most common cause of death in COVID-19 is respiratory failure, but also a hemostasis disorder followed by immune and inflammatory reactions (cytokine storm) (5, 6). Thrombosis and coagulopathy significantly contribute to disease progression and mortality (6). This infection is associated with multiple laboratory abnormalities from the onset of the disease (7). In addition to changes in hemostasis, changes in the leukocyte formula (lymphopenia, neutrophilia, changes in the number of monocytes), and other dysregulations in hematopoietic system may occur (8). COVID-19 is associated with a high rate of micro and macrothrombosis. The differences between coagulopathy caused by the SARS-CoV-2 virus and coagulopathy caused by sepsis remain a matter of debate (9). Unlike classic thrombosis, which is based on uncontrolled activation of the hemostasis system, COVID-19 thrombosis is a combination of endothelial dysfunction, increased circulating procoagulant proteins, platelet hyperreactivity, and altered inflammatory cell function, indicating immune-mediated thrombosis in patients with COVID-19 (10). In coagulopathy associated with this virus, initial laboratory tests show high fibrinogen and D-dimer values, decreased platelet count, and non-significantly prolonged prothrombin/activated partial thromboplastin time (PT/aPTT). In conventional DIC, fibrinogen values are reduced, and bleeding times are prolonged (9, 10). Autopsies showed that multiple thrombi, rich in platelets and fibrin, were present in the small blood vessels of the lungs in addition to the large blood vessels, which indicates that the coagulopathy is present at the local level, but there is also diffuse alveolar damage (11, 12). In COVID-19 ARDS, severe damage of vascular endothelium and presence of large thrombi have been demonstrated. The degree of microthrombosis was 9 times higher in COVID-19 than in influenza, and the degree of angiogenesis was 2.7 times higher (6, 13). DIC and increased D-dimer values are prognostic parameter of poor outcome and a frequent finding in non-survivors (14, 15), also changes in platelet-

to-lymphocyte ratio (PLR) during hospitalization, showed a possible correlation with cytokine storm (16). Changes in hemostasis are certainly a bad indicator of coronavirus disease. Most often, an increased value of D-dimer, a decreased level of fibrinogen, a slight decrease in the number of platelets and a prolonged prothrombin time are registered (14). Many retrospective studies highlight the importance of D-dimer and connection of its levels to disease severity in patients with COVID-19 (mild COVID-19 patients exhibited significantly lower levels of D-dimer compared to moderate COVID-19 patients) (17).

Aim

Our study aimed to analyze coagulopathy in patients treated for COVID-19 through the diagnostic algorithm for DIC proposed by the International Society on Thrombosis and Hemostasis (ISTH) (18). We also want to examine whether any of the hemostasis parameters included in this score affect, and to what extent, the clinical outcome of the disease.

Materials and Methods

In this prospective observational study blood samples were collected from 131 patients who, infected with SARS-CoV-2 virus for the first time, were treated in the University Clinical Center Kragujevac from March to August 2021. Inclusion criteria: patients of both sexes older than 18 years, signed informed consent to participate in the study, positive findings for SARS-CoV-2 (rapid Ag test or PCR test) and presence of any of the three forms of the disease defined by WHO criteria. Exclusion criteria: patients previously treated for COVID-19, pregnant women or patients with conditions or diseases that affect the values of the examined parameters of hemostasis (taking anticoagulant therapy, suffering from chronic inflammatory diseases, hematological diseases or other malignant diseases). Blood was sampled on the day of admission and the course of the disease was monitored. Two tubes of blood (of 3 ml each) were sampled. One tube with EDTA (ethylenediaminetetraacetic acid), the other with citrate, the blood was not frozen. The analyses were performed immediately in the hematology laboratory of the Hematology Clinic of the University Clinical Center Kragujevac on a standardized machine using ALCTOPCTS300 (Instrumentation Laboratory) and UniCel DxH 600 Coulter Cellular Analysis System (Beckman Coulter). To calculate the DIC score, the diagnostic algorithm of the ISTH was used, where scoring was performed as follows: number of platelets (> 100—0 point, < 100—1 point and < 50—2 points), D-dimer value (normal: ≤ 0.5 ng/ml—0 point, moderate increase: 0.5–3 ng/ml—2 points, severe increase: > 3 ng/ml—3 points), PT (extended for < 3 seconds—0 point, prolonged for > 3 seconds < 6 seconds—1 point, > 6 seconds—2 points) and fibrinogen value (> 1 g/l—0 point, < 1 g/l—1 point). A score of 5 or more indicates DIC (18).

Statistical data processing was done using the IBM SPSS Statistics v.21 program. The Kolmogorov–Smirnov normality test was used to check the normality of the data distribution. One-factor analysis of variance (ANOVA) was used for the analysis of the tested values concerning the clinical course for different groups, and the statistically significant results were graphically displayed using a line graph. The Student's t-test for independent samples was used to analyze the tested values concerning the treatment outcome, and the statistically significant results were shown using a bar chart. The chi-square test was used to analyze the clinical course and the outcome of treatment concerning the sex of the patient. One-factor ANOVA for different groups and Student's t-test for independent samples were used to analyze the patient's age concerning the clinical course and treatment outcome, and statistically significant results were shown using line and bar graphs. The results were considered statistically significant if the significance (p-value) was less than or equal to 0.05.

Results

Out of 131 patients, there were 53 women (40.5%) and 78 men (59.5%). The participants were between 19 and 90 years old, with the average age of 62.3 ± 16.3 years. Regarding clinical condition, there were 22.1% of patients with a mild disease, 58.8% of patients with a severe disease and 19.1% of patients with critical disease. Concerning treatment outcome, 111 (84.7%) patients recovered and 20 (15.3%) died. Descriptive statistical analysis of continuous variables is shown in Table 1. Prothrombin time (PT), DIC score, and platelet count (PLT) were the parameters that showed statistical significance when observed concerning clinical forms of the disease (Table 2). A total of 48 patients (36.6%) had an ISTH DIC score of 0, score 1 was given to 4 patients (3.1%), the most significant number of patients had a score of 2 (66 patients, 50.4%), 10 patients (7.6%) had a score of 3, and 2 patients (1.5%) had a score of 4. Finally, 1 patient (0.8%) had a score of 5, which fulfilled the criteria for DIC. From Table 3 it is clearly seen that the patients with critical COVID-19 have significantly higher PT and DIC score values and significantly lower PLT values. Also our research showed that there was a statistically significant difference in the values of the DIC score and PLT concerning the treatment outcome (Table 4). Figure 1 and 2 show that the DIC score values were significantly higher in the patients who died, and PLT values were significantly lower. Using the chi-square test for independence, it was determined that the clinical course and the outcome of the treatment did not depend on the sex of the patients. By applying one-factor ANOVA for different groups

and Student's t-test for independent samples, it was determined that there was a statistically significant difference in the age of the patients concerning the clinical course and treatment outcome. Patients with critical disease and with fatal outcomes were significantly older (Results not shown).

Table 1. Descriptive analysis of the examined parameters of hemostasis

	Lowest value	Highest value	Mean value	Standard deviation	Reference values
aPTT (s) I day	21.4	62.1	35.19	7.43	24.0–35.0
PT (s) I day	11.1	55.3	14.85	4.75	11.8–15.3
INR I day	0.89	4.67	1.18	0.41	0.9–1.1
D-dimer (ng/ml) I day	24	11900	872.59	1380.67	0–230
Fibrinogen (g/l) I day	2.52	9.35	4.88	1.22	2.0–4.5
DIC score	0	5	1.37	1.14	< 5
PLT (x 10*9/L) I day	27	559	208.98	102.13	150–450

Table 2. Analysis of hemostasis parameters concerning the form of the disease

	F statistic	Degrees of freedom	Significance
aPTT (s)	2.063	2;128	0.131
PT (s)	**3.178**	**2;128**	**0.045**
INR	2.183	2;128	0.117
D-dimer (ng/ml)	0.118	2;128	0.889
Fibrinogen (g/l)	1.777	2;128	0.173
DIC score	**4.374**	**2;128**	**0.015**
PLT (x 10*9/L)	**3.703**	**2;128**	**0.027**

Table 3. Analysis of the values of PT, DIC score and platelet count concerning the form of the disease

		Mild	Severe	Critical	Standard deviation
PT (s)		15.483	14.042	16.600	4.7454
DIC score		1.21	1.23	1.96	1.145
PLT (x 10*9/L)		219.931	220.766	159.992	102.1331

Table 4. Analysis of hemostasis parameters concerning disease outcome

	F statistic	Degrees of freedom	Significance
aPTT (s)	0.776	129	0.439
PT (s)	1.186	129	0.238
INR	0.820	129	0.414
D-dimer (ng/ml)	0.159	129	0.874
Fibrinogen (g/l)	0.375	129	0.708
DIC score	**2.570**	**129**	**0.016**
PLT (x 10*9/L)	**2.895**	**129**	**0.004**

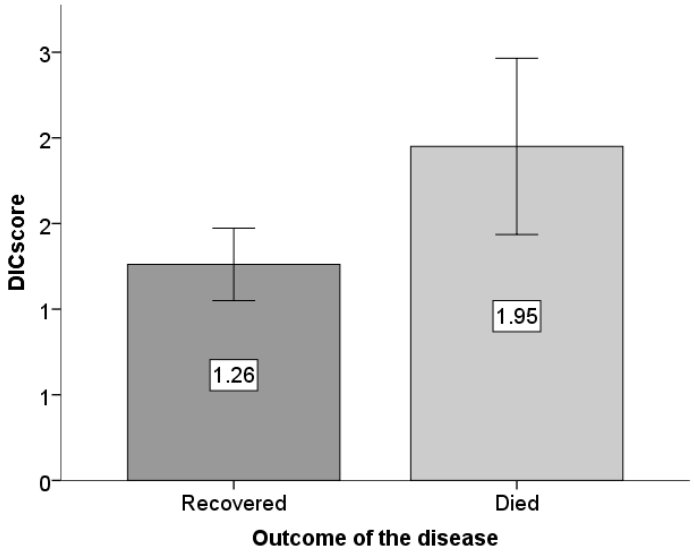

Figure 1. Analysis of the value of DIC score concerning the treatment outcome

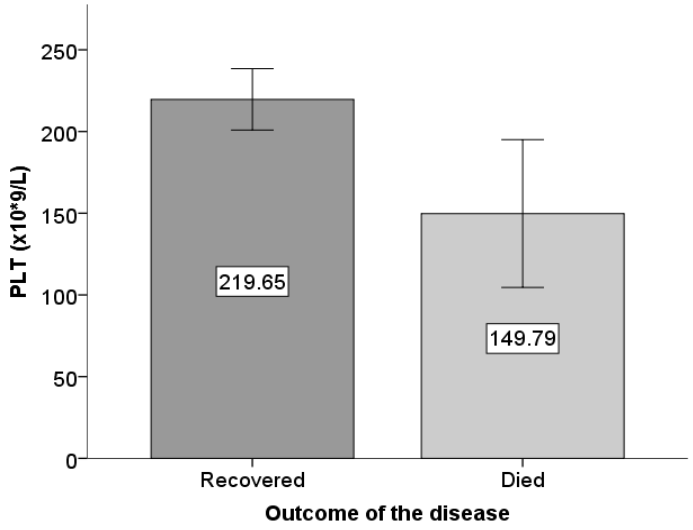

Figure 2. Analysis of the number of platelets concerning the outcome of the disease

Discussion

Due to the large amount of research on coagulopathy and COVID-19, this study aimed to examine the frequency of coagulopathy by analyzing it through the DIC score. In addition, the association of other coagulopathy parameters with the clinical course and the outcome of the disease was examined. In their work, Gerber GF et al. also concluded that average PT/aPTT values were normal or minimally prolonged in COVID-19 (19). In a study that included 183 COVID-19 patients, Arachchillage DR et al. showed that these values were significantly prolonged (20). The increased values of D-dimer and fibrinogen have been described in many studies as indicators of poor outcome (14, 15, 21), but in present study, these parameters were not correlated with severe disease or fatal outcome. Some studies emphasize the significant role of platelets in the pathogenesis of the disease itself, suggesting that platelets abnormalities can be qualitative as well as quantitative ones (22, 23). On the other hand, there are not many studies in the literature investigating the DIC score as a marker of disease severity and prognosis. The question arises whether the existing DIC score can be used in COVID-19 given that the pathogenesis is different compared to sepsis induced DIC (24). In this study, it was found that there was a statistically significant difference in the values of PT, DIC score and platelet count concerning the clinical course. Further, it was shown that there was a statistically significant difference in the value of the DIC score and the number of platelets concerning the outcome of the disease. Other examined parameters had no significant influence on the outcome of the disease. It was found that the outcome and form of the disease did not depend on the sex of the patients, but that there was statistical significance concerning age.

Conclusion

Based on our research, it can be concluded that the patients did not meet the criteria for conventional DIC, but that coagulopathy was registered. Patients with a critical form of the disease, as well as patients who did not survive, had statistically significantly higher values of the DIC score. Patients with a critical form of the disease had significantly higher values of prothrombin time and significantly lower values of the number of platelets than patients with a mild and severe form of the disease. Patients in whom the disease ended fatally had a statistically significantly lower number of platelets compared to patients who recovered.

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KOAGULOPATIJA I KOVID 19

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Interesovanje za kovid 19 u svetu nauke ne prestaje. Patogeneza kovida 19 i dalje je predmet velikog broja studija, a koagulopatija zauzima važno mesto u istraživanjima. Glavni cilj ovog rada bilo je ispitivanje karakteristika koagulopatije izazvane kovidom 19. Za potrebe ove studije prikupljeni su uzorci krvi 131 bolesnika koji se zbog infekcije SARS-CoV-2 prvi put bolnički lečio u Univerzitetskom kliničkom centru u Kragujevcu. Uzorak krvi uzet je na dan prijema, a potom je praćen tok bolesti. Došlo se do zaključka da ovi ispitanici ne ispunjavaju kriterijume za diseminovanu intravaskularnu koagulaciju (DIK). Polazeći od forme i ishoda bolesti, predstavili smo statistički značaj broja trombocita, vrednosti protrombinskog vremena i DIK skora. Pacijenti sa kritičnom formom bolesti, kao i oni kod kojih je ova bolest dovela do smrtnog ishoda, imali su značajno niže vrednosti broja trombocita, a značajno veće vrednosti DIK skora.

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***Ključne reči**: kovid 19, diseminovana intravaskularna koagulacija, forma bolesti, ishod bolesti*