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Koagulopatija i COVID-19

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Sažetak: Interesovanje za Covid-19 u svetu nauke ne prestaje. Patogeneza je i dalje tema velikog broja studija, a koagulopatija zauzima značajno mesto u istraživanjima. Naš glavni cilj je da ispitamo kakve su karakteristike koagulopatije u Covidu. U našoj studiji prikupljeni su uzorci krvi 131 pacijenta koji se zbog SARS-CoV-2 infekcije prvi put hospitalno leče u Univerzitetskom kliničkom centru Kragujevac. Krv je uzorkovana na dan prijema i praćen je tok bolesti. Zaključili smo da naši ispitanici ne ispunjavaju kriterijume za DIK. Pokazali smo statističku značajnost broja trombocita, vrednosti protrombinskog vremena i DIK skora u odnosu na formu i ishod bolesti. Pacijenti sa kritičnom formom bolesti kao i oni čija se bolest završila letalno imaju značajno niže vrednosti broja trombocita, a značajno veće vrednosti DIK skora.

Ključne reči: Covid 19, DIC, forma bolesti, ishod bolesti

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Coagulopathy and COVID-19

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Abstract: Interest in Covid-19 in the world of science is constant. Pathogenesis is subject of many studies, and coagulopathy occupies important place in research. In our study, blood samples were collected from 131 patients, who due to SARS-CoV-2 infection, are being treated 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 DIC. We showed statistical significance of platelet count, prothrombin time value and DIC score in relation to the form and outcome of the disease. Patients with a critical form of the disease, as well as those whose disease has progressed to death, have significantly lower values of the number of platelets, and significantly higher values of the DIC score.

Key words: Covid 19, DIC, disease form, disease outcome

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 (eng. critical COVID-19), severe (eng. severe COVID-19) and mild (eng. non-severe COVID-19) [2]. It was found that the main prognostic factors for a poor outcome are: obesity, hypertension, diabetes and older age [3], also data from the literature emphasize 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 still remain a matter of debate [9]. Unlike classic thrombosis, which is based on uncontrolled activation of the hemostasis system, Covid-19 thrombosis is 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, 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]. **Objective**: The aim of our study is to analyze coagulopathy in patients treated for Covid-19 through the diagnostic algorithm for DIC proposed by the International Society for Hemostasis and Thrombosis (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.

MATHERIAL AND METHODS:

In this prospective observational study blood samples were collected from 131 patients who, for the first time SARS-CoV-2 infection, were being 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 for SARS-CoV-2 (rapid Ag test or PCR test) and have any of the three forms of the disease defined by WHO criteria. Exclusion criteria: previously treated for Covid-19, pregnant women or have 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 analyzes were performed immediately in the hematology laboratory of the Hematology Clinic of the University clinical center Kragujevac on a standardized machine (ALCTOP^{CTS}300- Instrumentation Laboratory and UniCel DxH 600 Caulter 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 (> 1g/l - 0 point, <1g/l - 1 point). A score of 5 or

more indicates DIC [18]. **Statistical analysis:** 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 in relation to 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 in relation to 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 in relation to 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 in relation to 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 being 62.3±16.3 years. Regarding to 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. In relation to treatment outcome, 111 (84.7%) patients recovered and 20 (15.3%) died. Descriptive statistical analysis of continuous variables is shown in **Table 1**. We determined that prothrombin time (PT), DIC score, and platelet count (PLT) are three parameters that show statistical significance when observed in relation to clinical forms of the disease **(Table 2)**. A total of 48 patients (36.6%) had a ISTH DIC score of 0, score 1 was given to 4 patients (3.1%), the largest 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 is a statistically significant difference in the values of the DIC score and PLT in relation to the treatment outcome **(Table 4)**. From *chart 1 and 2* we can see that the DIC score values are significantly higher in the patients who died, and PLT values are significantly lower. Using the chi-square test for independence, we determined that the clinical course and the outcome of the

treatment do not depend on the sex of the patients. By applying one-factor ANOVA for different groups and Student's t-test for independent samples, we determined that there is a statistically significant difference in the age of the patients in relation to the clinical course and treatment outcome. Patients with critical disease and with fatal outcome are 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 (x10*9/L) I day	27	559	208,98	102,13	150-450

Table 2. Analysis of hemostasis parameters in relation to 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 (x10*9/L)	**3,703**	**2;128**	**0,027**

Table 3. Analysis of the values of PT, DIC score and platelet count in relation to 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 (x10*9/L)		219.931	220.766	159.992	102.1331

Table 4. Analysis of hemostasis parameters in relation to 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 (x10*9/L)	**2,895**	**129**	**0,004**

Chart 1. Analysis of the value of the DIC score in relation to the treatment outcome

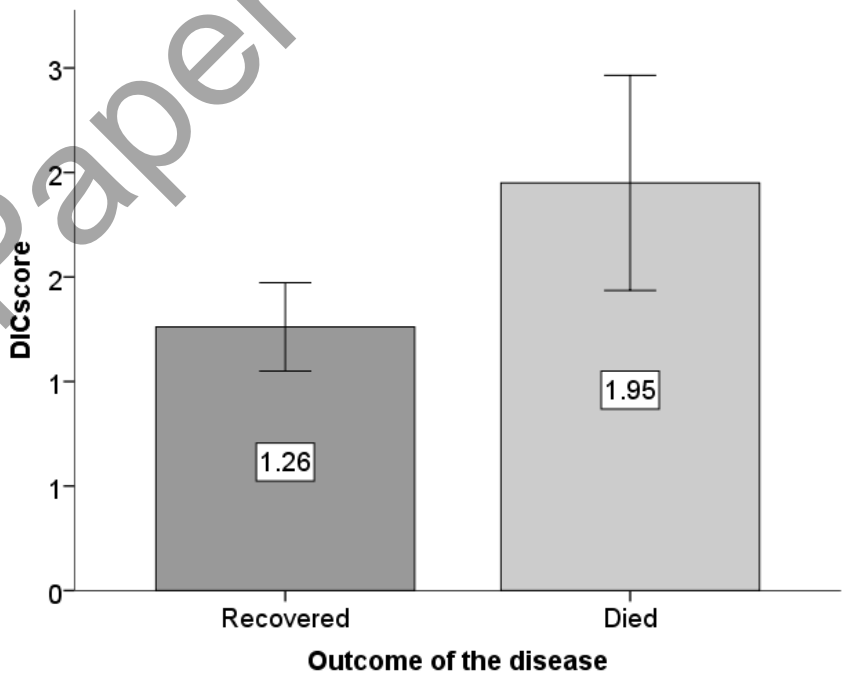
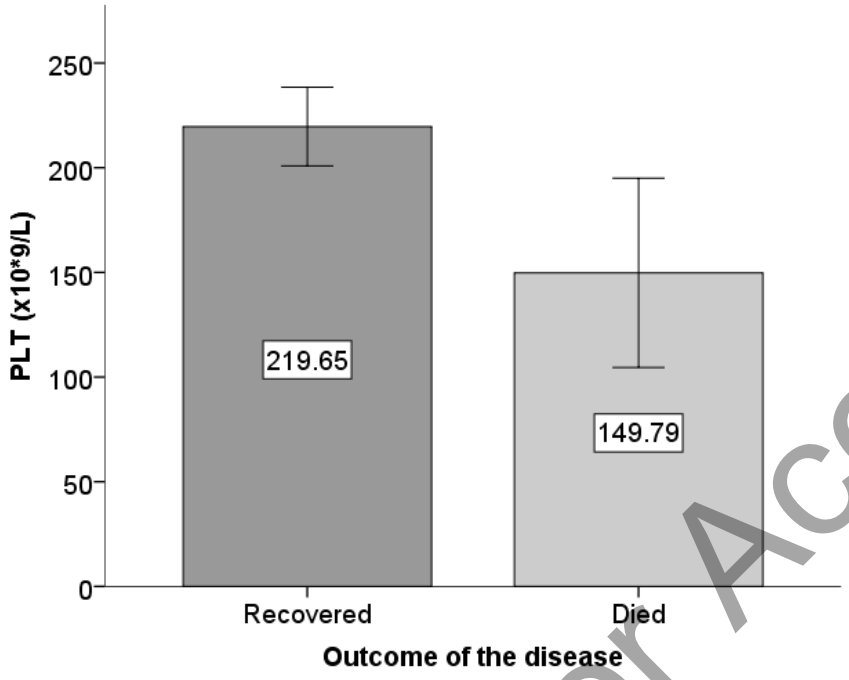


Chart 2. Analysis of the number of platelets in relation to the outcome of the disease



DISCUSSION:

Due to the large amount of research on the topic of coagulopathy and Covid-19, we decided to conduct a study on the frequency of coagulopathy by analyzing it through the DIC score. We also examined the association of other coagulopathy parameters with the clinical course and the outcome of the disease. 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 our study these parameters were not correlated with severe disease or fatal outcome. There are studies that emphasize the great 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]. We

found that there is a statistically significant difference in the value of PT, DIC score and platelet count in relation to the clinical course. We have shown that there is a statistically significant difference in the value of the DIC score and the number of platelets in relation to the outcome of the disease. Other examined parameters had no significant influence on the outcome of the disease. We found that the outcome and form of the disease does not depend on the sex of the patients, but that there is statistical significance in relation to age.

CONCLUSION:

Based on our research, we can conclude that the patients did not meet the criteria for conventional DIC, but that coagulopathy was definitely 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 compared to 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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