Medicinska istaživanja 2024; 57(3):91-98 | DOI 10.5937/medi57-51924

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

ORIGINAL ARTICLE

Changes in the hemostatic system in severely ill COVID-19 patients

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Recived: 01 July 2024
Revised:18 July 2024
Accepted: 25 July 2024

Check for updates

Funding information:
The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Competing interests:
The authors have declared that no competing interests exist

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Summary

Introduction/research objective: COVID-19 coagulopathy is a disorder of the hemostatic system that occurs in critically ill patients infected with the SARS-CoV 2 virus and it increases the risk of mortality. The goal of the research is to evaluate changes in hemostatic parameters and determine their prognostic significance in patients with a severe form of the COVID-19 disease.

Methods: The study was designed as a retrospective cohort study, which included 146 patients treated from June to September 2020 in the Intensive Care Unit (ICU) of the Clinical Hospital Center "Bežanijska Kosa" in Belgrade, diagnosed with COVID-19 pneumonia. Inclusion criteria were as follows: the age over 18 years, proven current SARS-CoV2 infection, and admission to ICU.

Results: 82 patients (56.2%) died during the treatment, while 64 (43.8%) were discharged. Significantly higher D-dimer values on admission to the ICU were recorded in subjects who died during treatment 888 (1226.5) ng/ml compared to persons who were discharged from treatment 666 (1207.3) ng/ml ($p = 0.03$). Differences were not demonstrated for INR, aPTT and fibrinogen. D-dimer values on admission to the ICU greater than or equal to 760ng/ml are a statistically significant predictor of death during hospitalization ($p = 0.04$).

Conclusion: COVID coagulopathy is a complication that increases the mortality of people infected with the SARS-CoV2 virus. The main feature is a state of hypercoagulability, which is detected by elevated D-dimer values. D-dimer greater than or equal to 760 ng/ml on admission to the ICU may have prognostic significance for survival during hospitalization.

Keywords: COVID-19, coagulopathy, D-dimer, Intensive Care Unit

Cite this article as: Milenković M,Kovač M, Rović I, Šijan Đ, Crnokrak B, Zdravković M. Changes in the hemostatic system in severely ill COVID-19 patients; Medicinska istaživanja 2024; 57(3):91-98 DOI 10.5937/medi57-51924

INTRODUCTION

In May 2023, the COVID-19 pandemic, which lasted approximately three years and two months, was officially declared over (1). According to the latest data, more than 703 million people have fallen ill worldwide, and about 7 million have died, according to https://www.worldometers.info/coronavirus/ 02/18/2024. The pandemic was controlled due to the development of vaccines and antiviral drugs (2).

Most of those infected with the SARS-CoV2 virus developed an asymptomatic or mild form of the COVID-19 disease, while a smaller number of people developed viral pneumonia, which could later be followed by complications and other multisystem disorders, and finally lead to death, especially in the elderly (3). The severe form of the disease is characterized by an immense immune response with the release of many cytokines, with antiviral and anti-inflammatory role, while leading to the death of endothelial and epithelial cells and immunothrombosis (4).

COVID-19 coagulopathy is a disorder of the hemostatic system that occurs in critically ill patients infected with the SARS-CoV-2 virus. The state of hypercoagulability is the main feature of COVID-19 coagulopathy, which can be manifested by thromboembolic complications or even disseminated intravascular coagulation. Since the beginning of the pandemic, a higher frequency of thromboembolic complications, both venous and arterial, has been reported in more severe forms of the disease, despite the use of anticoagulant therapy (5). A meta-analysis that included 47 studies and a total of 6459 patients led to the conclusion that deep vein thrombosis was present in about 30% of cases, that it was more frequent in patients treated in the ICU, and that people with COVID-19 and thrombosis had higher mortality than people without thrombosis (6). Hyperinflammatory response, hypoxia, endothelial damage, as well as comorbidities, immobility, age and history of previous thrombosis are key risk factors for hypercoagulability and subsequent complications (5).

D-dimer is mentioned as the most important indicator in the context of COVID-19 coagulopathy. Elevated D-dimer values were recorded in COVID-19 patients with a more severe form of the disease. Also, it was shown that higher D-dimer values correlated with disease severity and mortality. Certain studies (7-9) confirmed that D-dimer values greater than 1 mg/ml, 0.5 mg/ml, or 0.5 mg/l upon admission were associated with an 18-fold, 7.3-fold, or 4-fold increase in mortality risk, respectively. It has also been proven that elevated D-dimer values are associated with a more severe clinical presentation (10). The results of our recently published prospective study showed that elevated levels of D-dimer, as well as coagulation factor VIII (FVIII), in a certain category of patients (elderly, with a more severe presentation of COVID infection) can be maintained even after 6 months of COVID infection. This indicates that the degree of hypercoagulability is maintained in a certain number of patients even after the infection has passed (11). In addition to high D-dimer values, indicators of COVID coagulopathy can be low platelet values, prolonged prothrombin and partial thromboplastin time, as well as fibrinogen, FVIII, von Willebrand factor (vWF), and reduced antithrombin (AT) values as well as ADAMTS13 (7, 11-13).

This research aims to evaluate changes in hemostatic parameters and to determine their prognostic significance in patients with a severe form of COVID-19 disease.

Material and methods

This study was designed as a retrospective cohort study, which included 146 patients treated from June 2020 to September 2020 in the Intensive Care Unit (ICU) of the Clinical Hospital Center "Bežanijska Kosa" in Belgrade, diagnosed with COVID-19 pneumonia. The inclusion criteria were as follows: the age over 18, proven current SARS-CoV2 infection, and admission to the Intensive Care Unit. Respondents younger than 18 years of age and respondents whose stay in the intensive care unit was not due to a severe form of COVID-19, as well as incomplete data on respondents, were excluded from the research.

Upon admission to the ICU, the usual anamnestic data (hetero-anamnestic data related to the patient's comorbidities and accompanying therapy) and demographic data were collected and entered into the electronic database. All patients, according to the protocol for treatment at the ICU, had blood samples taken for the determination of routine laboratory analyses, such as complete blood count, coagulation profile, biochemical analyses, and markers of inflammation. All these values were recorded in the hospital's electronic database, along with all important patient clinical data.

A computed tomography (CT) score was determined for each patient. The score was graded according to the degree of involvement of the lung tissue by consolidation seen on the CT scan of the chest. Each lung lobe was scored from 1 to 5 depending on the prevalence of consolidation (1. < 5% involvement; 2. 5-25%; 3. 26-49%; 4. 50-75%; 5. > 75%). The values of the total CT score were obtained by adding up the individual score for each lobe, and the score values could range from 0 to 25. The severity of the clinical presentation, as determined by the CT score, was categorized into mild (score <8), moderate (9-15), and severe (>15) (14).

The treatment of patients and the definition of a severe clinical picture were carried out according to the national protocol of the Republic of Serbia for the treatment of COVID-19 (15).

In the statistical analysis, descriptive and analytical statistics methods were used, depending on the type of data distribution. If the distribution was normal, the T-test was used for analysis. For distributions deviating from normality, the Mann-Whitney U test was employed

for non-parametric analysis. The non-parametric tests were the Chi-square ($\chi 2$) test or Fisher's exact probability test. The ROC curve was used to determine the optimal D-dimer cut-off value and its sensitivity (Sn) and specificity (Sp). The Kaplan-Meier method and the log-rank test were used to assess survival. $p < 0.05$ was considered statistically significant. The computer program "R" was used to process statistical data.

Results

The research included 146 respondents, 103 (70.5%) male and 43 (29.5%) female. The average age was 65 years, range from 29 to 89 years. Of the total number of respondents, more than a half died during the treatment, 82 (56.2%), while 64 (43.8%) were discharged after the treatment. Of the 82 patients with a fatal outcome, 58 (70.7%) were male, and 24 (29.3%) were female. The incidence of fatal outcomes matches the representation in relation to sex.

Comorbidities were present in 109 (74.7%) subjects. Arterial hypertension was recorded in 99 (67.8%) subjects, diabetes mellitus in 50 (34.2%), coronary disease in 25 patients (17.1%), while other comorbidities were less common (obesity and cardiomyopathy in 8.2%, COPD in 4.8%, and asthma in 2.7% of cases).

In relation to the severity of the clinical picture, the majority of respondents had a CT score of 20, i.e., 14.2%. There were 10.4% of respondents with the maximum score. Upon admission to the ICU, most patients were intubated, with 52.7% receiving invasive mechanical ventilation and 34.2% receiving non-invasive ventilation. The lowest percentage of people was on high-flow oxygen therapy, 3.4%, while 9.6% of patients were on low-flow oxygen therapy through an oxygen mask **(Table 1)**.

The values of the subjects' coagulation parameters were as follows: D-dimer 768 (1066) ng/ml, INR 1.1 (0.3), APTT 24.7 (8.3) and fibrinogen 3.8 (1.5) g/ l. The measured values of D-dimer, INR, APTT and fibrinogen did not differ significantly between men and women (D-dimer p=0.51; INR p=0.409; aPTT p=0.826; fibrinogen p=0.212).

Patients with hypertension had higher D-dimer values, 888 (2715) ng/ml, compared to 554 (705.5) ng/ml in normotensive p=0.002. Differences in D-dimer values were not observed between subjects with and without corresponding comorbidities **(Table 2)**.

INR values recorded upon admission to the ICU were higher in patients with cardiomyopathy 1.3 (1.5) than those without 1.1 (0.2)s p= 0.028. INR values did not differ between patients with and without other comorbidities **(Table 3)**.

Table 1. Clinical characteristics of subjects suffering from COVID-19 admitted to the Intensive Care Unit

Clinical features	
Age	*med (IQR)* 65 (21) years
Sex	*n* % 103/43 70.5/29.5
Comorbidity	*n (%)*
Arterial hypertension	99 (67.8)
Coronary disease	25 (17.1)
Cardiomyopathy	12 (8.2)
Diabetes mellitus	50 (34.2)
Obesity	12 (8.2)
Asthma	4 (2.7)
COPD	7 (4.8)
The severity of the clinical presentation according to the CT score	*n (%)*
Mild	
Moderate	7 (4.8)
Severe	25 (17.1) 114 (78.1)
Type of respiratory support	*n (%)*
Low Flow Oxygen	14 (9.6)
High Flow Oxygen	5 (3.4)
Non-invasive mechanical ventilation	50 (34.2)
Invasive mechanical ventilation	77 (52.7)
Number of days of hospitalization	*med (IQR)* 18 (16)
Treatment outcome	*n (%)*
Discharge	64 Male 45 (70.3) Female 19 (29.7)
Fatal outcome	82 Male 58(70.7); Female 24(29.3)

Table 2. D-dimer values of patients with COVID-19 according to comorbidities (values are shown as median (IQR))

Comorbidity	Presence	D-dimer values (ng/ml)	p value
Arterial hypertension	YES	888 (2715)	0.002*
	NO	554 (705.5)	
Diabetes mellitus	YES	680.5 (746)	0.212
	NO	823.5 (3217.7)	
Obesity	YES	1051 (1000)	0.428
	NO	760 (1286.3)	
COPD	YES	741 (1908.7)	0.865
	NO	775 (1213.8)	
Asthma	YES	873.5 (1005.2)	0.980
	NO	760 (1263.8)	
Coronary disease	YES	740 (2990)	0.719
	NO	768 (1123)	
Cardiomyopathy	YES	752 (1066)	0.967
	NO	768 (1229)	

Note: *-statistically significant difference
COPD - Chronic obstructive pulmonary disease

Table 3. INR values of COVID-19 patients according to comorbidities (values are shown as median (IQR))

Comorbidity	Presence	INR values	p value
Arterial hypertension	YES	1.1 (0.3)	0.965
	NO	1.1 (0.3)	
Diabetes mellitus	YES	1.1 (0.2)	0.051
	NO	1.1 (0.3)	
Obesity	YES	1 (0.3)	0.774
	NO	1.1 (0.3)	
COPD	YES	1.2 (0.4)	0.420
	NO	1.1 (0.3)	
Asthma	YES	1 (0.26)	0.135
	NO	1.1 (0.3)	
Coronary disease	YES	1.2 (0.3)	0.562
	NO	1.1 (0.2)	
Cardiomyopathy	YES	1.3 (1.5)	0.028*
	NO	1.1 (0.2)	

Note: *-statistically significant difference
COPD - Chronic obstructive pulmonary disease

Table 4. aPTT values of COVID-19 patients according to comorbidities (values are shown as median (IQR))

Comorbidity	Presence	aPTT (s) values	p value
Arterial hypertension	YES	25.2 (10.3)	0.436
	NO	24.2 (6.5)	
Diabetes mellitus	YES	23.6 (10.5)	0.546
	NO	25.3 (7.4)	
Obesity	YES	21.5 (6.4)	0.257
	NO	25.2 (8.5)	
COPD	YES	30.6 (11.6)	0.916
	NO	24.6 (7.9)	
Asthma	YES	21.7 (13.1)	0.267
	NO	24.6 (8.4)	
Coronary disease	YES	27.6 (10)	0.083
	NO	24.6 (7.5)	
Cardiomyopathy	YES	29.5 (12.8)	0.070
	NO	24.4 (7.3)	

COPD - Chronic obstructive pulmonary disease

Table 5. Values of fibrinogen strains with COVID-19 according to comorbidities (values are shown as median (IQR))

Comorbidity	Presence	Fibrinogen values (g/L)	p value
Arterial hypertension	YES	3.8 (1.65)	0.505
	NO	3.8 (1.15)	
Diabetes melitus	YES	4.2 (2.2)	0.169
	NO	3.7 (1.2)	
Obesity	YES	3.9 (1.3)	0.722
	NO	3.8 (1.5)	
COPD	YES	3.7 (1.8)	0.759
	NO	3.8 (1.5)	
Asthma	YES	5.4 (2.2)	0.047*
	NO	3.8 (1.5)	
Coronary disease	YES	4.1 (1.1)	0.081
	NO	3.8 (1.5)	
Cardiomyopathy	YES	3.4 (1.3)	0.270
	NO	3.8 (1.5)	

Note: *-statistically significant difference
COPD - Chronic obstructive pulmonary disease

The measured values of the partial thromboplastin time did not differ in patients with certain comorbidities and those without, at the admission to the ICU. Detailed values are shown in **Table 4**.

People with asthma had fibrinogen values of 5.4 (2.2) g/l on admission significantly higher than those without asthma 3.8 (1.5) p=0.047. Fibrinogen values in other subjects with and without various comorbidities were not observed. Detailed values are shown in **Table 5**.

Regarding the disease outcome, significantly higher values of D-dimer upon admission to the ICU were recorded in subjects who died during treatment 888 (1226.5) ng/ml compared to patients who were discharged from treatment 666 (1207.3) ng/ml (p = 0.03).

No differences were determined in relation to other parameters of hemostasis **(Table 6)**.

The ROC curve is used to determine the cut-off value of the D-dimer to predict the fatal outcome. The optimal value was 760 mg/ml. Of the total deceased, 51 subjects had D-dimer values greater than or equal to 760 ng/ml, and the remaining deceased (31) had values less than 760 ng/ml. The sensitivity of 60.8% and the specificity of 59.4% of D-dimer was calculated **(Figure 1)**. The Kaplan-Meier survival curve and the log-rank test revealed that D-dimer values of 760 ng/ml or higher are a statistically significant predictor of mortality during hospitalization (p = 0.04) **(Figure 2)**.

Table 6. Values of coagulation parameters of COVID patients measured at admission to the ICU in relation to the outcome of treatment

Variable	Death outcome	Median (IQR)	p value
D-dimer (ng/l)	YES	888 (1226.5)	0.033*
	NO	666 (1207.3)	
INR	YES	1.1 (0.3)	0.437
	NO	1.1 (0.3)	
aPTT (s)	YES	25.9 (10.3)	0.518
	NO	23.9 (6.2)	
Fibrinogen (g/l)	YES	3.8(1.7)	0.157
	NO	3.8 (1.2)	

Note: *-statistically significant difference

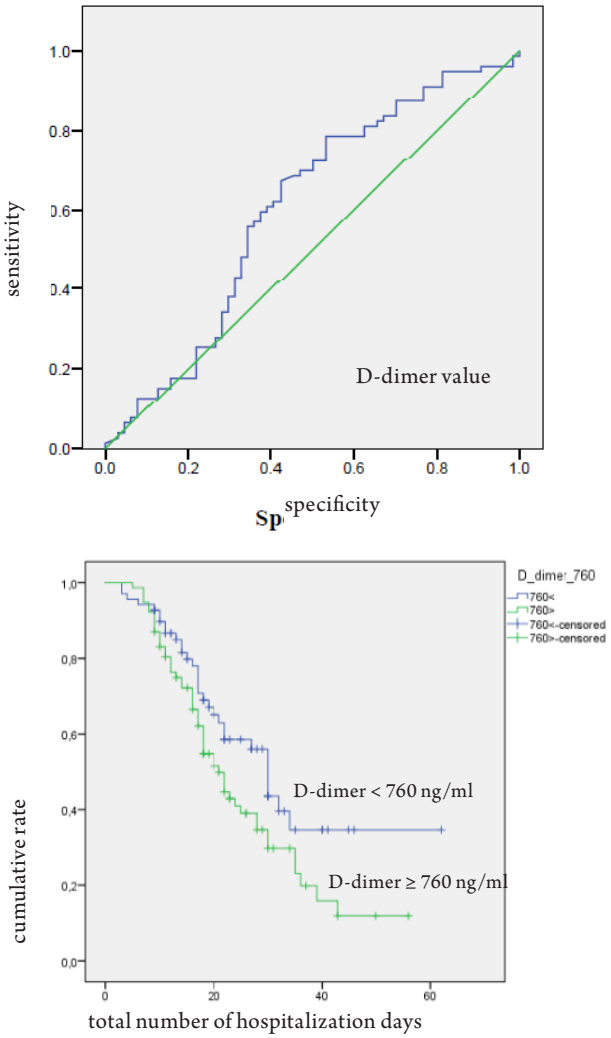

Figure 1. ROC curves of D-dimer values for predicting outcomes of treatment

Thrombosis was detected in 11 patients (7.5%). Among these, 8 had arterial thrombosis (including myocardial infarction in 5 patients and thrombosis of the brachial, radial, and ulnar arteries in 3 patients), while 3 had venous thrombosis, specifically pulmonary thromboembolism. Of the total number of subjects with thrombosis, eight died, while three were discharged after treatment. D-dimer values did not differ significantly between subjects with and without thrombosis (p = 0.46).

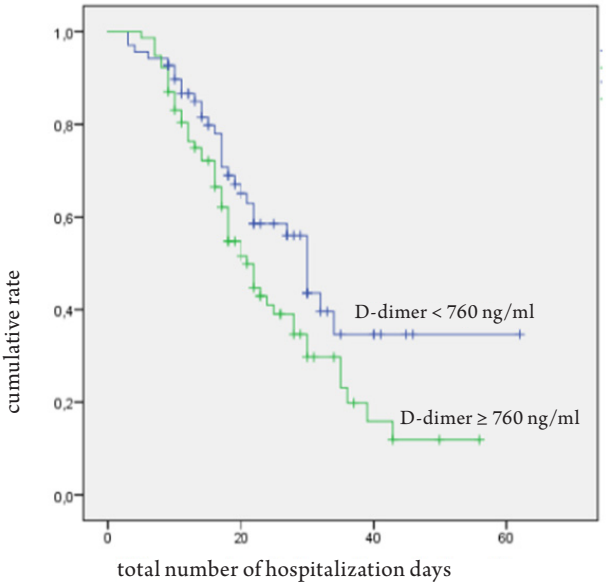

Figure 2. Kaplan-Meier survival curves for D-dimer measured at ICU admision

Discussion

The research revealed distinct patient profiles in terms of age, gender, comorbidities, hemostatic parameters, and elevated D-dimer values among SARS-CoV-2 positive individuals with pneumonia who were treated in Intensive Care Units. The average age of patients who required treatment in the ICU was 65 years. Men had a greater need for treatment in the ICU as well as a higher mortality, while the total mortality was 56.2%. The most common documented chronic disease among the respondents was hypertension (67.8%), followed by diabetes mellitus (34.2%) and coronary disease (17.1%). People with hypertension had higher D-dimer values compared to people without the given comorbidity. Also, people with cardiomyopathy had significantly higher INR values compared to those without it, and higher fibrinogen values were recorded in people with asthma. Significant differences for the remaining parameters of hemostasis were not detected in relation to the present comorbidities. Higher D-dimer values upon admission to the ICU were recorded in persons who died during treatment, while values equal to or greater than 760 ng/ml were associated with a higher risk of in-hospital mortality.

More than 78% of those treated in the ICU had a CT score greater than 15, which speaks in favour of the severe clinical picture of the patients. Patients with a CT score greater than 15 have a high risk of death, followed by a longer stay in the ICU (16). As the CT score increases, the risk of death also rises (17).

Endeshaw et al., in a study conducted on 100 patients, proved that patients with hypertension had significantly higher D-dimer values of 1.1 mg/l, compared to controls of 0.37 mg/l. Additionally, the more severe arterial hy-

pertension was, the higher D-dimer was (18). In addition, the values of D-dimer and fibrinogen are positively related to the duration of hypertension, which suggests that the higher the values the longer the person was hypertensive (19). Hypertension is one of the most common comorbidities in COVID-19 patients (20).

D-dimer represents a significant marker of hemostatic activity and indicates the formation of a fibrin clot, i.e. its breakdown under the action of the fibrinolytic system. Significantly higher D-dimer values were recorded in persons suffering from COVID-19 (21). At the beginning of the pandemic, it was thought that high D-dimer values resulted from an increased frequency of arterial and venous thrombosis, the development of disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), etc. However, the underlying factor is the host's robust inflammatory response to the SARS-CoV-2 virus. The virus induces the synthesis and release of mediators such as IL-6, TNF, G-CSF, etc., leading to mononuclear cell activation. Thus, activated cells express tissue factors that lead to thrombin activation and fibrin conversion. Also, the virus directly causes damage to endothelial cells and the release of cell contents, including plasminogen activator and vWF. Under the influence of plasminogen activators, plasminogen is converted into plasmin, initiating fibrinolysis. The ultimate goal of this process is the breakdown of fibrin into fibrin degradation products. If the fibrin clot is stabilized by coagulation Factor XIII (FXIII), its subsequent breakdown results in the formation of D-dimer (22).

The results of our study showed that D-dimer values of more than 760 mg/ml (measured on admission to the ICU) can represent a great predictor of mortality. Also, numerous studies have reported similar data. A meta-analysis that included 100 studies over 42,000 patients concluded that high D-dimer levels upon admission are associated with the risk of developing a more severe form of the disease, as well as death (23). Popovska Jovičić et al. in their research, where they included 288 patients diagnosed with SARS-CoV2 infection, proved that D-dimer values of 0.82 ug/mL measured upon admission can indicate a potential risk of death during the hospitalization (24). A multicentre study in Spain reported that admission D-dimer values higher than 945 μg/L FEU have a predictive value regarding in-hospital mortality (25). Within the first ten days of hospital treatment, there is a trend of increasing D-dimer, after which the value decreases (26).

It should be noted that the results of our prospective study in which patients were monitored after hospitalization for COVID 19 infection showed that certain categories of patients (the elderly and those with a more severe clinical presentation of COVID infection) can maintain elevated D-dimer and FV III levels, even 6 months after hospitalization. This finding indicates that the degree of hypercoagulability is maintained in a certain number of patients even after the infection has passed, therefore, it represents a risk for thrombosis in the post-Covid period (11).

When discussing the risk of thrombosis associated with acute COVID-19 infection, thrombotic events were verified in 11 (7.5%) subjects, of which 8 were arterial and 3 pulmonary embolisms.

The D-dimer values of persons with verified thrombosis were 1260 (31810) ng/ml and did not significantly differ from the D-dimer values of persons without verified thrombosis, which can be explained by the higher frequency of arterial thrombosis. In other studies, the incidence of thrombosis in ICU patients was significantly hihger (27-29). In contrast to our research, in other studies venous compared to arterial thromboses were detected more frequently (30, 31), and D-dimer levels above 3,000 μg/L measured in patients with COVID-19 can be a predictor of pulmonary thromboembolism (32).

Regarding the limitations of the study, it should be emphasized it was a retrospective study that included a relatively small number of respondents. These are the first data on hemostatic changes in critically ill COVID-19 patients in our country who were treated in the ICU. As such, they represent a significant contribution to understanding this issue and highlight the need for prospective studies with larger sample sizes.

CONCLUSION

COVID coagulopathy is a complication that increases the mortality of people infected with the SARS-CoV2 virus. The main feature is the state of hypercoagulability, which is confirmed by elevated D-dimer values. Our research showed that people suffering from COVID-19 had high D-dimer levels upon admission to the ICU and this value was significantly higher in people who died. D-dimer values greater than or equal to 760 ng/ml upon admission to the ICU may have prognostic significance for survival during the hospitalization.

Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Marija Zdravković and Marija Milenković. The first draft of the manuscript was written by Marija Milenković. Mirjana Kovač and Marija Zdravković edited the manuscript. All authors read and approved the final manuscript.

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PROMENE U HEMOSTATSKOM SISTEMU KOD KRITIČNO OBOLELIH OD KOVIDA 19

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Sažetak

Uvod/cilj istraživanja: Koagulopatija usled kovida 19 predstavlja poremećaj sistema hemostaze koji se javlja kod kritično obolelih bolesnika zaraženih SARS-CoV2 virusom i koja povećeva rizik od mortaliteta. Cilj istraživanja je procena promena hemostaznih parametara i određivanje njihovog prognostičkog značaja kod bolesnika sa teškom formom bolesti kovid 19.

Metode: Studija je dizajnirana kao retrospektivna kohortna studija, koja je obuhvatila 146 pacijenta lečenih od juna do septembra 2020. godine u Jedinici intenzivnog lečenja (JIL) Kliničko bolničkog centra „Bežanijska kosa" u Beogradu pod dijagnozom pneumonije izazvane kovidom 19. Uključujući kriterijumi su bili starost iznad 18 godina, dokazana aktuelna SARS-CoV2 infekcija i prijem u JIL.

Rezultati: Tokom lečenja su preminula 82 bolesnika (56.2%), dok je 64 (43.8%) otpušteno nakon sprovedenog lečenja. Značajno više vrednosti D-dimera na prijemu u JIL zabeležene su kod ispitanika koji su preminuli u toku lečenja 888 (1226,5) ng/ml u odnosu na osobe koje su otpuštene sa lečenja 666 (1207,3) ng/ml (p = 0,03). Razlike nisu dokazane za INR, aPTT i fibrinogen. Vrednosti D-dimera na prijemu u JIL više ili jednake 760ng/ml statistički su značajan prediktor smrtnog ishoda u toku hospitalizacije (p = 0,04).

Zaključak: Koagulopatija usled kovida 19 predstavlja komplikaciju koja povećava mortalitet osoba zaraženih SARS-CoV2 virusom. Osnovno obeležje jeste stanje hiperkoagulabilnosti, koje se detektuje povišenim vrednostima D-dimera. Vrednosti D-dimera više ili jednake 760 ng/ml na prijemu u JIL mogu imati prognostički značaj za preživljavanje u toku hospitalizacije.

Ključne reči: kovid 19, koagulopatija, D-dimer, jedinica intenzivnog lečenja

Primljen: 01.07.2024. I **Revizija:** 18.07.2024. I **Prihvaćen:** 25.07.2024.

Medicinska istaživanja 2024; 57(3):91-98