

Values of coagulation parameters in hospitalized patients with SARS-CoV-2 infection in the University Clinical Hospital Mostar

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ABSTRACT

Background: The aim of this study was to determine the presence of coagulation parameter disorders in patients hospitalized due to COVID-19 and to investigate the relationship between the abnormalities of coagulation parameters and the final outcome.

Methods: We performed a retrospective cohort study of 81 patients admitted to the University Clinical Hospital Mostar, due to respiratory infection by SARS-CoV-2, in the period from March 15th to May 15th, 2021. Subjects were divided into two groups according to the final outcome. We analyzed age, sex, comorbidity frequency and parameters of coagulation function.

Main findings: Of the 81 patients, 42 died and 72.7% died in the Respiratory Center ($p < 0.001$). Two-thirds of the respondents were male. The mean age of all respondents was 72.88 ± 14.21 years. Non-survivors were significantly older than survivors ($p = 0.002$). Previous chronic disease was confirmed in 84% of the subjects and the most common comorbidity was arterial hypertension. D-dimers were elevated in 95% of the subjects. Non-survivors had a statistically significant prolongation of APTT in seconds ($p = 0.005$) than survivors, while in other coagulation parameters, there was no statistical significance with respect to the severity of the clinical status and the final outcome.

Principal conclusions: SARS-CoV-2 infection is associated with abnormalities in the parameters of coagulation function. Moreover, APTT is an important factor for prognosis assessment in patients with COVID-19.

Key words: COVID-19, SARS-CoV-2, D-dimers, APTT, coagulation parameters, coagulopathy

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INTRODUCTION

Coronavirus disease (COVID-19) is an acute, respiratory, viral, infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); it is characterized by rapid human-to-human transmission and a variable incubation period that lasts from two to 14 days. The first reported cases of atypical pneumonia, caused by this virus, appeared in November 2019 in the Chinese city of Wuhan, from which the virus spread worldwide, causing a pandemic with a considerable impact on the global economy and healthcare systems (1, 2).

After the virus is transmitted through respiratory droplets, it enters the bloodstream of the host and uses the angiotensin-converting enzyme 2 (ACE-2) receptor to enter the target cell. Virus adhesion to ACE-2 receptors and the consequent virus replication cause inflammatory cell infiltration, endothelial cell apoptosis and microvascular thrombosis (3). Patients with SARS-CoV-2 infection mostly present with symptoms such as fever, dry cough, shortness of breath, headache, myalgia, diarrhea and fatigue (4, 5). Although COVID-19 is primarily a disease presenting with respiratory symptoms and atypical pneumonia, patients with a severe form of the disease may develop complications such as acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis and coagulopathy including disseminated intravascular coagulation (6). COVID-19 may be a predisposing factor for thrombosis, due to an excessive inflammatory response and platelet activation, endothelial damage and venous congestion due to the reduced mobility of hospitalized patients (7, 8). The presence of comorbidities such as chronic cardiovascular and pulmonary diseases, diabetes and immunodeficiency has been shown to increase the likelihood of developing severe disease and thromboembolism (9, 10).

Coagulopathy in these patients has been associated with an increased risk of death (6, 11). The most common coagulation disorders

are prolonged prothrombin time, thrombocytopenia and elevated D-dimer values, which are associated with an increased likelihood of intensive care unit treatment and death (6, 9, 12). Disorders of coagulation parameters correlate with an increased incidence of thrombotic complications, the most common of which is pulmonary thromboembolism. According to research conducted by Klok et al. the incidence of thrombotic complications among intensive care patients is 31% (13); this was similarly confirmed by Helms et al. who observed a significantly high number of thrombotic complications in patients with developed COVID-19 ARDS despite anti-coagulant prophylaxis (14).

The main aim of this study was to determine the presence of coagulation parameter disorders in patients hospitalized due to COVID-19 and to investigate the relationship between the values of coagulation parameters and the final outcome.

PARTICIPANTS AND METHODS

Participants

This retrospective cohort study included 81 patients who were hospitalized in the COVID department of the Internal Medicine Clinic or in the Respiratory Center of the University Clinical Hospital Mostar, due to SARS-CoV-2 infection from March 15th to May 15th, 2021. The main criteria for the inclusion of subjects in the study are a positive polymerase chain reaction (PCR) identified from nasopharyngeal or oropharyngeal swab samples. The study did not include SARS-CoV-2 positive patients with mild symptoms, those with chronic liver disease and previous use of anticoagulant drugs, such as warfarin or new anticoagulant drugs (NOAC). The subjects were divided into two groups according to the final outcome of treatment: a group of 42 patients who died during hospitalization due to COVID-19 (non-survivors) and a group of 39 patients who were cured and discharged from hospital after recovering from COVID-19 (survivors).

Methods

The data required for the implementation of this research were obtained by reviewing the medical records at the Internal Medicine Clinic in the University Clinical Hospital Mostar. All data of interest were collected retrospectively, by reviewing medical history, discharge letters and microbiological and laboratory tests. The parameters that were monitored include demographic data (age and gender) and previous comorbid conditions, such as arterial hypertension, diabetes, chronic cardiovascular disease, chronic kidney disease, chronic lung disease and malignancy. Subjects were monitored for the following laboratory parameters in relation to blood count: platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT). In addition, coagulation parameters were analyzed: prothrombin time (PT), international normalizing ratio (INR), activated partial thromboplastin time (APTT) and D-dimers. Samples of peripheral blood were collected at the time of admission and during hospitalization in citrate-coated tubes and then analyzed in the central laboratory of the University Clinical Hospital Mostar, using a rapid latex immunoassay on a BCS System instrument manufactured by Siemens.

Statistical analysis

The parameters were processed using Microsoft Excel (version 10, Microsoft Corporation, Redmond, WA, USA) and SPSS for Windows

(version 23.0, SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Student t-test and Z-score were used to test the differences between continuous variables; the differences in categorical variables were tested using the chi-square test (χ^2) and Fisher's exact test. The probability level of $p < 0.05$ was taken as statistically significant.

RESULTS

The study included 81 subjects, of which 37 (45.7%) were hospitalized with a moderate clinical picture in the COVID department and 44 (54.3%) were placed in the Respiratory Center as severe cases. A total of 42 subjects died during hospitalization and 39 subjects survived. A statistically significant difference was found in the final outcome of the subjects compared to the severity of the clinical picture, as shown in Table 1.

There was no significant difference between male and female respondents in relation to the final treatment outcome. Of the 44 patients in the Respiratory Center, 41 (93.2%) required oxygen therapy, while none of the patients in the COVID department were treated with oxygen. None of the patients were vaccinated. The demographic characteristics of the patients are shown in Table 2. Of the 81 subjects included in the study, 68 (84%) had some previous chronic disease. The most common comorbidity was arterial hypertension, which was previously diagnosed in 47 (58%) subjects.

Table 1. Differences in treatment outcome relative to the severity of the clinical picture

	Severity of the clinical picture				χ^2	p
	Moderate		Severe			
	n	%	n	%		
Final outcome					15.033	<0.001
Survivors	27	73.0	12	27.3		
Non-survivors	10	27.0	32	72.7		

Diabetes was present in 33 patients (40.7%), chronic cardiovascular disease in 27 patients (33.3%), chronic kidney disease in 10 patients (12.4%), chronic lung disease in seven patients

(8.6%) and malignancy in seven patients (8.6%). No statistically significant difference was found in the incidence of comorbidities between the examined groups (Table 3).

Table 2. Demographic characteristics of the patients

Study population	n (%)	Survivors n (%)	Non-survivors n (%)
Gender			
Female	28 (34.6)	18 (64.3)	10 (35.7)
Male	53 (65.4)	21 (39.6)	32 (60.4)
Age			
<65	21 (25.9)	17 (81)	4 (19)
≥65	60 (74.1)	22 (36.7)	38 (63.3)
Oxygen therapy	41 (50.6)	12 (29.3)	29 (70.7)

Table 3. Differences in the incidence of comorbidities according to the final outcome

	Final outcome				χ^2	p
	Survivors		Non-survivors			
	n	%	n	%		
Comorbidities	30	76.9	38	90.5	1.843	0.175
Arterial hypertension	19	48.7	28	66.7	1.989	0.158
Diabetes mellitus	13	33.3	20	47.6	1.169	0.280
Chronic cardiovascular disease	11	28.2	16	38.1	0.501	0.479
Chronic kidney disease	3	7.7	7	16.7	0.790	0.374*
Chronic lung disease	4	10.3	3	7.1	0.011	0.918*
Malignancy	4	10.3	3	7.1	0.011	0.918*

*Fisher's exact test

Table 4. Differences in values of coagulation parameters in relation to the final outcome

	Final outcome				Z	p
	Survivors		Non-survivors			
	M	IR	M	IR		
Platelets	227.00	110.25	164.00	157.00	-1.290	0.197
MPV	10.30	1.38	11.10	1.40	-1.644	0.100
PDW	12.45	2.80	13.30	2.70	-1.837	0.066
PCT	0.24	0.09	0.18	0.15	-1.422	0.155
PT	1.02	0.13	0.96	0.28	-0.207	0.836
PT-seconds	8.95	0.75	9.20	1.55	-0.174	0.862
INR	1.03	0.13	1.06	0.16	-0.049	0.961
APTT-seconds	29.10	6.82	33.40	9.95	-2.828	0.005
APTT-ratio	1.05	0.30	1.20	0.30	-2.657	0.008
D-dimer	1.13	1.40	1.77	3.11	-1.453	0.146

Table 4 shows the differences in the values of coagulation parameters between survivors and non-survivors. Although there is a disturbance in the values of coagulation parameters with

respect to the reference values in both groups of subjects, a statistical significance was found only for the values of APTT and APTT ratio. Non-survivors had significantly higher levels of

APTT in seconds and APTT ratio than survivors.

The average age of all subjects in the study was 72.88 ± 14.21 (mean $\pm$ standard deviation) years. Non-survivors were significantly older than survivors (Figure 1).

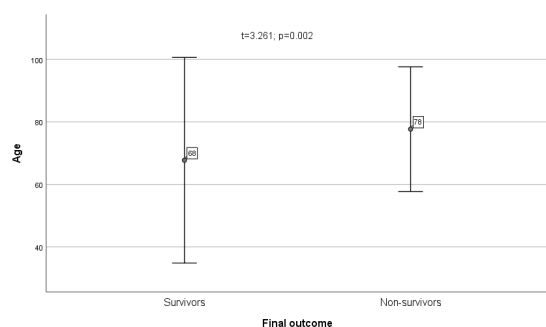


Figure 1. Differences in age (years) of respondents with respect to the final outcome. The arithmetic mean and standard deviation (SD) of age for survivors and non-survivors are presented

DISCUSSION

In this study, a retrospective analysis of coagulation parameter values was performed on 81 patients with a confirmed SARS-CoV-2 infection. The main aim was to investigate the correlation between values of coagulation parameters and the final outcome. Deviations in the values of coagulation parameters with respect to reference intervals at different ratios were observed, but the most common disorder was found in the D-dimer values, which were elevated in almost all patients. We found that APTT is an important factor in prognosis assessment, as APTT values are in seconds and the APTT ratio was significantly higher in non-survivors than in survivors. Other coagulation parameters did not prove to be significant indicators of a poor final outcome and there was no difference between groups.

Compared with previous findings, the results of this study partially coincide with and confirm the existence of coagulopathy in COVID-19 patients. According to a study conducted by Helms et al. in two French hospitals, D-dimer values were elevated above the reference interval in more than 95% of subjects, which is equal to the results of this study, while

platelet counts, PT and APTT values were normal in most subjects (14). Several studies confirmed that coagulation parameters are important predictors of final outcome (6, 15). A retrospective cohort study conducted in Spain on more than 3,500 subjects with COVID-19 aimed to establish a link between coagulation disorders and disease prognosis. The results showed that non-survivors had 3.5-fold higher D-dimer values compared to survivors (16). Jin and colleagues showed significant differences in coagulation function between survivors and non-survivors. Patients with a fatal outcome had significantly higher values of D-dimer, PT, INR and APTT than survivors as well as decreased platelet counts (17).

The additional objectives of this study were to determine age and sex differences, as well as the frequency of comorbidities between survivors and non-survivors. Comparing these two groups with respect to their age, we found that non-survivors were significantly older than survivors, suggesting that older age is an important predictor of a poor final outcome. This can be explained by the fact that the immune system weakens with age and that the elderly are more susceptible to infections. Observing by gender, two-thirds of respondents were male, but no significant gender difference was found in relation to the final outcome. Most of the subjects in this study had some previous chronic disease and arterial hypertension was most commonly present, followed by diabetes. Furthermore, one-third of the subjects had chronic cardiovascular disease. This study did not establish a correlation between individual comorbidities and the final outcome.

According to current knowledge, risk factors for the development of more severe forms of the disease and death include older age, male gender and the presence of chronic diseases. The results of this research regarding age and frequency of comorbidities coincide with data from the available literature. A study conducted by Zhou et al. proved that older age is an independent predictor of mortality in patients with COVID-19, as our research has

confirmed. Zhou et al. found that chronic diseases were present in half of the subjects, with hypertension as the most common comorbidity, followed by diabetes and cardiovascular disease. However, no statistically significant difference was found between individual comorbidities and mortality, which is consistent with the results of our research (9). Moreover, the distribution of comorbidities and their frequency coincide with the results of similar studies (6, 14).

This study has several limitations. The data were collected retrospectively, and the study was conducted at a single-center hospital with a limited sample size. Since this is a retrospective study, samples for laboratory analysis were not collected according to a standardized schedule, but data were taken from laboratory findings processed within a few days of admission, which is in some ways a limitation of this study. Given that the results obtained by this study differ in part from previous studies, it would be useful to expand this study and further investigate certain parameters. This primarily implies the values of D-dimers, which were confirmed by this study as a parameter the values of which were disturbed in COVID-19. However, the association of elevated D-dimers with a fatal outcome, as in other studies, has not been proven. Furthermore, it would be advisable to perform repeated measurements of laboratory parameters on the subjects in order to monitor the dynamics in the disturbance of their values. It is also possible to divide the subjects into groups according to the severity of symptoms and clinical characteristics, in order to obtain a better assessment of the impact of coagulation parameters on the severity of the clinical picture.

CONCLUSIONS

This study confirmed the hypothesis that coagulation parameters were disturbed and deviated from the reference values in patients with COVID-19. APTT is an important factor in prognosis assessment. Age is a predictor of

mortality in patients with COVID-19, as older patients are more prone to develop a severe clinical picture and a fatal outcome.

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CONFLICT OF INTEREST

The authors of this manuscript declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

IM: acquisition of data, literature review, contribution to study conception and design, supervision, interpretation of data, writing of the paper; DP: contribution to study conception and design, literature review, supervision, interpretation of data, critical revision of the paper; MM: contribution to study conception and design, literature review, interpretation of data.

ETHICAL BACKGROUND

Institutional Review Board Statement The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital Mostar (Mostar, July 7, 2021).

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: We deny any restrictions on the availability of data, materials and associated protocols. Derived data supporting the findings of this study are available from the corresponding author on request.

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