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The effectiveness of coagulation parameters in classifying patients and predicting mortality in Covid-19

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Abstract

Covid-19 is a viral infection have a high pathogencitity and contagiousness that primarily targets the human respiratory system and leading to a global pandemic. Abnormal coagulation parameters are quite common in Covid-19 patients. In our study, we aimed to evaluate the relationship between coagulation function with disease severity and survival status in Covid-19 patients and the prognostic, predictive value of these parameters. Results of prothrombin time (PT), activated partial thromboplastin time (aPTT), Fibrinogen, and D-Dimer parameters at admission time of 76 Covid-19 negative healthy control with 188 confirmed Covid-19 patients, as well as death events were retrospectively analyzed. Compared with the healthy control group, higher levels of D-Dimer, PT, aPTT, fibrinogen, and CRP ($p < 0.001$ for each) were present during admission in Covid-19 patients. The non-survivor group had higher levels of PT, D-Dimer, and CRP ($p < 0.001$ for each) and aPTT ($p = 0.004$), fibrinogen ($p = 0.019$) compared to the survivor group. 28 (14.89%) of 188 Covid-19 patients lost their lives. Analysis of the ROC curve revealed that D-Dimer, Fibrinogen, PT, aPTT, and CRP had high diagnostic value in distinguishing Covid-19 patients from healthy control group, the critical group from the severe group, and non-survivors from survivors. This study shows that coagulation function is significantly impaired in patients with Covid-19 infection compared to normal patients, and as particularly marked high levels of D-Dimer, PT, aPTT, fibrinogen, and CRP are common. This condition is associated with disease severity and increased mortality. Coagulation parameters are an effective and useful marker for assessing prognosis and for the management of Covid-19 patients.

Keywords: coagulation parameters, prothrombin time, D-dimer, fibrinogen, Covid-19 severity

1. Introduction

Covid-19 is a viral infection have a high pathogencitity and contagiousness that primarily targets the human respiratory system and leading to a global pandemic (1). The World Health Organization declared the epidemic as an International Public Health Emergency of concern on January 30 th, 2020, and recognized it as a pandemic on March 11 th, 2020 (2). While the mild infection is observed 81% of symptomatic patients infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), occurs severe disease in 14% and critical disease 5% of patients (3).

The SARS-CoV-2 virus has been shown to cause a high expression of ACE2, which can cause alveolar damage by migrating from nasopharyngeal mucosa cells to the alveolar endothelium of the lungs. Virus taken from organs with ACE-2 receptor causes local infections in various organs, leading to multiple and fatal organ failure (4). In general, mortality occurs as a result of bilateral pneumonia that can progress to acute respiratory distress syndrome. Despite pulmonary pathophysiology is not yet fully known, severe COVID-19 is associated with a pronounced alveolar inflammatory cell infiltration, systemic cytokine storm response, and as a result of elevated inflammatory cytokines (5). The microvascular system is damaged by the occurrence of inflammatory reactions. As a result of abnormal activation of the coagulation system, generalized small vessel vasculitis and diffuse micro thrombosis develop, leading to venous and arterial thromboembolic diseases (6,7). It has been stated that the incidence of fatal pulmonary embolism (PE) in patients may be much higher than reported (8). Therefore, repeated evaluations and correct strategies are imperative to reduce the occurrence of venous thromboembolism (VTE), prevent fatal PE, ensure the safety of patients, and support early recovery. D-dimer results from the formation and degradation of cross-linked fibrin and reflects the activation of coagulation with fibrinolysis (9). Available data show that Covid-19 is associated with hemostatic abnormalities and that high D-dimer levels are associated with mortality, as well as being a common laboratory abnormality, and can be used as an independent biomarker for poor prognosis (10). In studies, patients with D-dimer levels above 3 µg/ml benefit from heparin treatment, and a decrease in mortality in Covid-19 with anticoagulant treatment also confirms these determinations (11).

One of the most important problems during the epidemic is the high volume of patients admitted to hospitals. Risk classification will be extremely helpful in managing the process, as available human support and mechanical capacities, especially intensive care support, are limited. For this, early and effective markers are needed, and coagulation parameters, which may have prognostic and predictive value, are very important in the course of the disease. Thus, the aim of this study is to investigate coagulation parameters in patients with

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Covid-19 and healthy control groups and to examine their role in predicting disease progression and survival.

2. Methods

2.1. Patients

This study was included 101 severe, 87 critical, a total of 188 adult patients and 76 healthy controls, whose diagnosis was confirmed, admitted to Başakşehir Çam and Sakura City Hospital in İstanbul between 15-30 November 2020. All patients were diagnosed according to the T.C. Ministry Department of Health's Covid-19 (SARS-CoV-2 infection) guidelines (12). Patients were defined and classified according to clinical, laboratory, and radiological parameters as those requiring hospitalization.

Nasal and/or pharyngeal swab samples of the patients were confirmed using the rRT-PCR test. Inpatients were divided into two groups: they were defined as admitted to the ward (Severe) and admitted to the Intensive Care Unit (ICU) (Critical). Inclusion criteria were those aged 18 years and older who had a positive Covid-19 rRT-PCR test were hospitalized for follow-up and treatment. Patients with hematological disease or who had a blood transfusion while hospitalized, data were incomplete, were excluded from the study. Again, 76 adult patients who were admitted to the hospital on the same dates whose clinical examination, CT and RT-PCR tests were found to be negative, were taken as the control group. Inclusion criteria for the control group were determined as rRT-PCR test negativity, and those with the comorbid disease were excluded. The routine parameters of all patients and the control group on the day of admission to the hospital were analyzed. This study was approved by the ethics committee of Başakşehir Çam and Sakura City Hospital (No.2021.04.65) and complies with the principles of the Declaration of Helsinki. Due to the retrospective and observational character of the study design, the requirement for informed consent has been waived.

2.2. Data collection

Epidemiological, demographic, clinical, radiological data of patients, laboratory results were obtained retrospectively from electronic medical records. Laboratory evaluations of the patients consisted of routine laboratory parameters such as coagulation, blood count, and biochemistry tests at the time of admission. The tests consisted of prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimer, platelet (PLT), and CRP tests and were studied in the Laboratory of Başakşehir Çam and Sakura City Hospital. Blood samples of the patients were taken into a citrate tube for coagulation, a gel tube for biochemical parameters, and an EDTA tube for a complete blood count.

Coagulation analysis was performed on an automatic coagulation analyzer (Roche Cobas t 711 America), hematology analysis on (Sysmex XN-900, Japan) device, biochemistry analysis on SF-8200 (Roche Cobas 8000 America) brand device using original reagents. All measurements were made within 2 hours. Coagulation functions were compared between Covid-19 patients and the healthy control group, between the severe and critical patient group, as well as between survivor and non-survivor.

2.3. Statistical Analysis

A one-way ANOVA with Bonferroni multiple comparison tests was used for the quantitative data analysis. Pearson or Likelihood Ratio Chi-Square test was used to analyze the nominal scale data. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of study variables in Covid-19 disease. Youden's index was used as a criterion for choosing an optimal cut-off value. The level of statistically significance was set at $p < 0.050$. The statistical analyses were performed using SPSS v26 (IBM Inc., Chicago, IL, USA) statistical software.

3. Results

3.1. Basic characteristics, chronic diseases and coagulation parameters of control group with severe and critical Covid-19 patient groups

In this study, there were a total of 264 patients, 133 (50.40%) females and 131 (49.6%) males. The critical group was made up of 62.1% men, 37.9% women, and the severe group 47.5% men and 52.5% women ($p = 0.008$). The mean age of the critical group was 62.86±16.25, the mean age of the severe group was 60.22±14.29 and the mean age of the control group was 58.76±13.42. Differences between groups in terms of study variables were investigated with ANOVA (Table 1). Platelet count did not change significantly compared to groups ($p = 0.465$).

The change of patients' chronic diseases according to the groups was examined with the Chi-square test. It was determined that the frequency distributions of all chronic diseases showed significant changes according to the groups. It was found that Hypertension in 41.4% of the critical group, 27.7% of the severe group; Diabetes Mellitus (DM) in 40.2% of the critical group, 33.7% of the severe group; Chronic Obstructive Pulmonary Disease (COPD) in 12.6% of the critical group, 10.9% of the severe group; coronary artery disease (CAD) in 23% of the critical group, 11.9% of the severe group; chronic renal failure (CRF) in 9.2% of the critical group, 2% of the severe group; cancer in 3.4% of the critical group, 6.9% of the severe group.

3.2. Analysis of diagnostic effectiveness of routine coagulation parameters in determination of Covid-19 severity

The ROC curve was created to analyze the effectiveness of various coagulation parameters in the diagnosis of severe Covid-19 patients during admission (Fig. 1). ROC curve analysis revealed that CRP, fibrinogen, aPTT, PT and D-Dimer had high diagnostic value in distinguishing severe Covid-19 patients from healthy subjects ($p < 0.001$) (Table 2). ROC curve analysis revealed that D-Dimer, CRP, PT, aPTT and fibrinogen had high diagnostic value in distinguishing critical Covid-19 patients from severe Covid-19 patients ($p < 0.001$) (Fig. 2) (Table 3).

Table 1. Comparison of the study variables

Parameters	Control group (n=76)	Severe group (n=101)	Critical group (n=87)	F	p
Age (mean ± SD)	58.43 ± 13.42	60.22 ± 14.29	62.86 ± 16.25	1.880	0.155
Male n (%)	29 (38.2%)	48 (47.5%)	54 (62.1%)	9.565**	**0.008**
PT (sec)	8.93 ± 0.47[b]	9.53 ±1.01[b]	11.0 8± 3.61[a]	2.976	**0.000**
INR	0.99 ± 0.05[b]	1.05 ± 0.08[b]	1.21 ± 0.36[a]	23.097	**0.000**
APTT (sec)	28.92±3.19[c]	33.11±5.36[b]	37.36 ± 11[a]	26.627	**0.000**
D-Dimer (µgFEU/mL)	0.31 ± 0.14[b]	0.83 ± 1.02[b]	3.84 ± 3.85[a]	58.589	**0.000**
Fibrinogen (mg/dL)	353.75 ± 62.99[c]	528.77± 139.54[b]	587.02 ± 154.14[a]	70.886	**0.000**
Platelet (×10^9/L)	267.39 ±76.13	257.25 ± 98.82	249.8 ± 89.53	0.768	0.465
CRP (mg/L)	3.63 ± 2.63[c]	63.07 ± 42.45[b]	132.4 ± 97.1[a]	85.247	**0.000**
ALT (U/L	27.01 ± 12.86[b]	34.62 ± 23.38[b]	43.83 ± 45.98[a]	5.965	**0.003**
AST (U/L)	27.05 ± 11.9[c]	39.04 ± 22.88[b]	54.17 ± 55.29[a]	11.594	**0.000**
GGT (U/L)	23.85 ± 17.30 [b]	57.66 ± 42.20 [a]	60.85 ± 56.03 [a]	16.459	**0.000**
ALP (U/L)	73.67 ± 16.97[b]	75.39 ± 27.43[b]	91.46 ± 54.66[a]	5.311	**0.000**

F: One-way ANOVA, **Chi square test, PT = Prothrombin time; aPTT = Activated Prothrombin Time. Means that do not share a letter are significantly different (p <0.05). ap <0.05, b p <0.01, c p <0.001, (mean ± SD)

Table 2. Diagnostic value of some variables for the distinction between control and severe groups

Test Result Variable(s)	Cut off value	Sensitivity	1-spesifity	p	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
PT (sec)	9.165	.797	.409	.000	.730	.653	.807
APTT (sec)	30.150	.725	.333	.000	.740	.665	.815
D-Dimer (mgFEU/mL)	0.4945	.884	.473	.000	.716	.638	.794
Fibrinogen (mg/dL)	446	.971	.247	.000	.889	.838	.940
CRP (mg/L)	8.85	.971	.043	.000	.990	.979	1.000

Table 3. Diagnostic value of some variables for the distinction between severe and critical groups

Test Result Variable(s)	Cut off value	Sensitivity	1-spesifity	p	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
PT (sec)	9.78	.797	.607	.000	.763	.692	.834
APTT (sec)	37.05	.806	.733	.007	.619	.533	.704
D-Dimer (mgFEU/mL)	1.15	.884	.587	.000	.862	.808	.916
Fibrinogen (mg/dL)	843	.971	.947	.034	.593	.508	.678
CRP (mg/L)	101.15	.971	.660	.000	.740	.662	.818

Table 4. Comparison of the study variables

Parameters	Severe survivor group (n=101)	Critical group (n=87)		F	p
		Survivor group (n=59)	Non-survivor group (n=28)		
Age	60.22 ± 14.3	61 ± 17.01	66.79 ± 13.97	2.094	0.126
Male n (%)	48(47.5%)	35 (59.3%)	19 (67.9%)	8.596**	0.103
PT (sec)	9.53 ± 1.01 b	11.19 ± 4.2 ab	10.86 ± 1.96 a	8.520	0.000
INR	1.05 ± 0.08 b	1.22±0.41 ab	1.19±0.2 a	9.800	0.000
APTT (sec)	33.11 ± 5.36b	37.36 ±12.8a	37.38 ± 5.77 a	5..816	0.004
D-Dimer (µgFEU/mL)	0.83 ± 1.02 b	3.67 ± 3.76 a	4.2 ± 4.08 a	28.710	0.000
Fibrinogen (mg/dL)	528.77 ± 139.54 b	597.31 ± 159.67 b	564.08 ± 141.27 ab	4.058	0.019
Platelet (×109/L)	257.25 ± 98.82	263.19 ± 94.05	221.61 ± 72.92	2.006	0.137
CRP (mg/L)	63.07 ± 42.45 c	117.79 ± 93.73b	162.67 ± 98.61a	25.101	0.000
ALT (U/L	34.62 ± 23.38 b	35.38 ± 34.97 b	61.26 ± 60.42 a	6.583	0.002
AST (U/L)	39.04 ± 22.88 b	41.39 ± 32.66 b	81.15 ± 79.66 a	12.645	0.000
GGT (U/L)	57.66 ± 42.20	55.45 ± 52.74	72.14 ± 62.20	0.901	0.409
ALP (U/L)	75.39 ± 27.43 b	89.62 ± 50.79 ab	95.29 ± 62.95 a	3.036	0.051

Table 5. DIC in non-survivors with New Coronavirus Pneumonia (N = 28)

Platelet count (× 10^9/ L)	Number of patients (%)
< 50 (2 point); 50-100 (1 point)	0; 1 (3.57)
D-Dimer (µg/mL)	
1.0-3.0 (2 point); > 3.0 (3 point)	13 (46.43); 11 (39.29)
Fibrinojen (g/L)	
<1.0 (1 point)	24 (85.71)
Prolongation of PT (sec)	
3-6 (1 point); > 6 (2 point)	1 (7.14); 2 (3.57)
Meeting the ISTH criteria of DIC (Total points ≥5)	5 (17.86)

Table 6. Diagnostic value of some variables for the distinction between severe and non-survivor groups

Test Result Variable(s)	Cut off value	Sensitivity	1-spesifity	p	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
PT (sec)	9.665	.710	.115	.000	.793	.695	.890
APTT (sec)	37.05	.806	.346	.001	.713	.599	.828
D-Dimer (mgFEU/mL)	1.11	.817	.154	.000	.879	.800	.958
Fibrinogen (mg/dL)	548.5	.624	.423	.252	.574	.448	.699
CRP (mg/L)	94.54	.828	.192	.000	.849	.757	.940

Table 7. Diagnostic value of some variables for the distinction between survivor and non-survivor groups

Test Result Variable(s)	Cut off value	Sensitivity	1-spesifity	p	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
PT (sec)	9.67	.345	.115	.554	.541	.410	.672
APTT (sec)	32.050	.455	.154	.082	.620	.496	.744
D-Dimer (mgFEU/mL)	1.55	.455	.308	.642	.532	.400	.664
Fibrinogen (mg/dL)	546.5	.491	.423	.624	.466	.334	.598
CRP (mg/L)	73.00	.345	.077	.049	.630	.512	.760

3.3. Basic characteristics, chronic diseases and coagulation parameters of survivor and non-survivor Covid-19 patient groups

111 (59.04%) patients were discharged, 28 (14.89%) patients died, and the remaining 49 (26.06%) patients remained in hospital in stable condition on December 9th, 2020. The non-survivor group was made up of 67.9% men, 32.1% women, and the survivor group 59.3% men and 40.7% women (p =0.103). The mean age of the non-survivor group was 66.79±13.97, the mean age of the survivor group was 61±17.01, and the mean age of the severe group was 60.22±14.3. Differences between groups in terms of study variables were investigated with ANOVA (Table 4). Platelet count did not change significantly compared to groups (p =0.137).

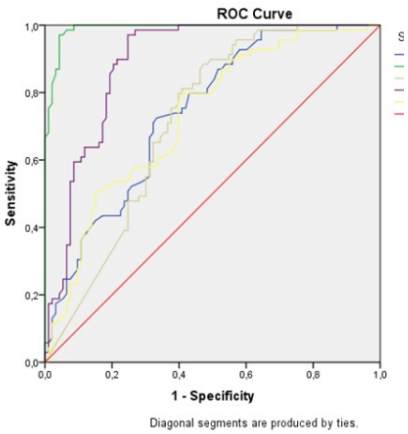

Fig. 1. ROC curve of CRP and coagulation parameters for comparing control and severe groups

It was found that Hypertension in 50% of the non-survivor group, 37.3% of the survivor group; DM in 50% of the non-survivor group, 35.6% of the survivor group; COPD in 7.1% of the non-survivor group, 15.3% of the survivor group; CAD in 14.3% of the non-survivor group, 27.1% of the survivor group; CRF in 3.6% of the non-survivor group, 11.9% of the survivor group; cancer in 5.1% of the survivor group.

In five of the patients who died from Covid-19 on admission, significant DIC was present according to the International Society for Thrombosis and Hemostasis (ISTH) criteria for disseminated intravascular coagulation (DIC) (Table 5) (10).

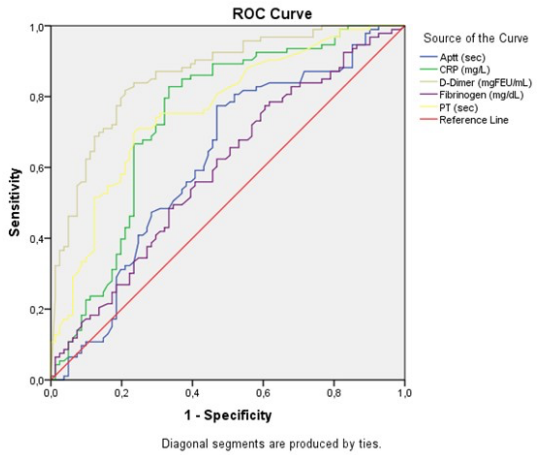

Fig. 2. ROC curve of CRP and coagulation parameters for comparing severe and critical groups

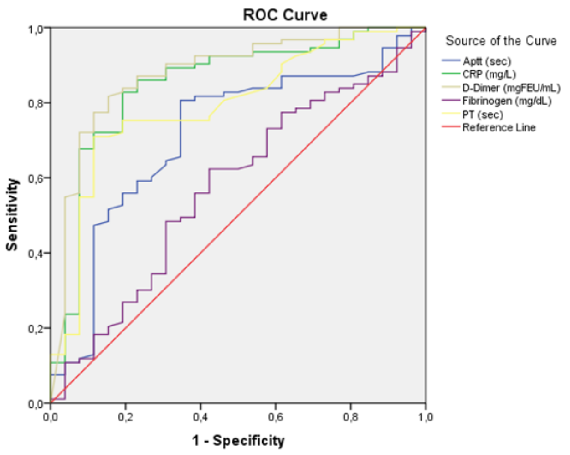

Fig. 3. ROC curve of CRP and coagulation parameters for comparing severe and non-survivor groups

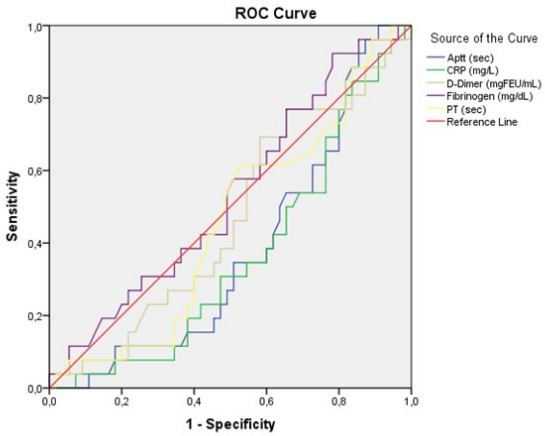

Fig. 4. ROC curve of CRP and coagulation parameters for comparing survivor and non-survivor groups

3.4. Analysis of diagnostic effectiveness of routine coagulation parameters in survival of Covid-19 patients

The ROC curve was created to analyze the effectiveness of coagulation parameters in comparing severe patients with non-survivor patients (Fig. 3). ROC curve analysis revealed that D-Dimer, CRP, PT, aPTT had high diagnostic value in distinguishing severe Covid-19 patients from non-survivor patients ($p < 0.001$) (Table 6). ROC curve analysis showed that parameters other than aPTT and CRP were not effective in determining the survival of critical Covid-19 patients ($p < 0.05$) (Fig. 4) (Table 7).

4. Discussion

Covid-19 is a viral infection with highly complex pathophysiology, leading to a pandemic starting from Wuhan, China in December 2019 (1). While mild infection is observed in the majority of symptomatic patients infected with SARS-CoV-2, severe and critical illness occurs in 19% of patients (3). Risk classification will be extremely helpful in managing the process due to the limitation of human support and mechanical capacities, support as well as tendency of SARS-CoV-2 to cause venous and arterial thrombosis, and the lack of an effective treatment. Early and effective markers are needed for diagnosis and follow-up, and coagulation parameters, which may have prognostic and predictive value in the course of the disease, are very important.

Consistent with previous studies in our study, hospitalized Covid-19 patients had abnormal coagulation parameters on admission compared to the healthy control group (10,13). Tang et al. reported that when coagulation parameters are abnormal, Covid-19 patients have a worse prognosis (10). The overactivation of immune cells and overproduction of proinflammatory cytokines during Covid-19 is called cytokine storms (14). It has been stated that the mechanism of inflammatory damage can develop as a result of T cell activation, increased granulocyte-macrophage colony-stimulating factor, and IL-6 production (15). As a result of the developing hyperinflammatory condition affecting the immune system, the microvascular system is damaged. The link between inflammation and hemostasis, defined as immunothrombosis, leads to abnormal activation of the coagulation system, thrombin formation, and inhibition of fibrinolytic reaction. These events that increase the likelihood of thrombosis are associated with increased production of proinflammatory cytokines (16).

Critical cases were older and had more underlying diseases compared to severe cases. similar to other studies (15,17). Covid-19 patients with major underlying conditions are at high risk of coagulation dysfunction. Our study showed that the incidence of abnormalities in parameters of coagulation function on admission was significantly higher in critical cases than in severe cases, that is, it was associated with disease severity (15,17). D-dimer elevation has been reported to be one of the most common laboratory findings recorded in Covid-19 patients requiring hospitalization (18). In our study, especially D-dimer levels were significantly higher in critical patients. D-dimer is a fibrin degradation product that is a reliable indicator of the activation of the hemostatic system and the activity of the fibrinolysis system. An analysis showed that D-dimer values were three times higher in severe Covid-19 patients than in those with milder forms (19). In a study of 138 patients, D-dimer levels were found to be significantly higher in patients who need ICU than in patients who do not (20). Huang et al. stated that patients with high D-dimer levels on admission need more ICU support (21). Since a marked increase in D-dimer is thought to be associated with the formation of multiple microthrombi, it has been stated that hospitalization of these patients should be considered even in the absence of other serious symptoms (22). In some studies, critical or non-survivor patients have been reported to have statistically significantly higher levels of D-dimer than non-critical or survivor patients (23).

Advanced age and chronic diseases in severe Covid-19 patients; hypercytokinemia, endothelial dysfunction, and inflammation are known risk factors for sepsis characterized by excessive, resulting in hipercoagulability (23,24). The cytopathic effect caused by the virus may lead to platelet activation and excessive thrombin formation as a result of widespread endotheliitis and inflammatory cell death (18). Hypoxia caused by respiratory failure in severe Covid-19 can not only increase blood viscosity, but also stimulate thrombosis through signaling (25). Refractory hypoxemia can lead to vasoconstriction, which reduces blood flow and increases vascular obstruction (23,24). Another risk factor is the aggressive proinflammatory response and insufficient control of the anti-inflammatory response. Stasis due to prolonged immobilization and invasive treatment, especially in severe Covid-19 patients, are risk factors for hypercoagulability or thrombosis (18). Some patients may develop sepsis-induced DIC (10,18). In the epidemiological analysis of 72,314 Covid-19 cases, most of the deaths were seen in people over 60 years of age with comorbidities (26,27). In our study, high levels of D-dimer and other coagulation parameters are associated with mortality in elderly and comorbidity patients. Individuals with

older, comorbidities and hypercytokinemia are known to be more likely to die from Covid-19 infection are known to be more likely to die from Covid-19 infection (7,26). The association between an increase in D-dimer levels and the deaths of patients infected with Covid-19 was also observed by Zhou and colleagues in a multicenter cohort study in China. It has also proven that high D-Dimer is an independent risk factor for mortality in Covid-19 patients (16,28).

Increased fibrin and conversion of and plasminogen to plasmine at the site of inflammation leads to a division of fibrin protofibrils and cumulative release of D-dimer, a known marker of Covid-19-associated thrombosis (16). In a logistic regression model, advanced age and D-dimer higher than 1 µg/mL during hospitalization was associated with an increased likelihood of death (19,29). When the increase in D-dimer levels reaches above 3 µg/mL, the mortality rate was determined to increases threefold (30). We found significantly higher D-dimer levels on admission in non-survivor. In a study Guan et al. analyzed with Covid-19 patients, they observed non-survivors had significantly higher D-dimer than survivors (31). In 183 patients at Wuhan Tongji Hospital, PT, fibrinogen, D-dimer, and fibrinogen degradation products (FDP) were shown to be significantly increased in Covid-19-related deaths. This condition suggested that coagulopathy is associated with prognosis and therefore these parameters may guide treatment (10). Since increased D-dimer levels in critical patients may be associated with a higher likelihood of developing DIC, these patients should be evaluated for DIC (15). Tang in the study found that 71.4% of non-survivors and 0.6% of survivors met criteria for DIC with high D-Dimer during their hospital stay and had a worse prognosis, increased risk of death (25). PT and APTT were significantly prolonged in non-survivors (10). Zhou et al found that 50% of non-survivors and only 7% of survivors met the DIC criteria (28). Hemostasis disorder may develop in patients with Covid-19, but excessive consumption of coagulation factors leads to the development of DIC. Development of DIC that adversely affects prognosis in Covid-19 is not uncommon (13). In five cases of death in our study, DIC was detected according to the ISTH SSC DIC score. DIC diagnostic scoring system parameters included PT, PLT, fibrinogen, and D-dimer. A score of >=5 is considered open DIC. DIC is a syndrome characterized by intravascular coagulation and causes the development of multiple organ failure (MOF) (26). Our data show that development of DIC in Covid-19 patients is not rare and caution should be exercised in critical patients due to its negative effect on the course of the due to disease. As a result of cytokine release syndrome affecting the immune system, the microvascular system is damaged and leads to abnormal activation of the coagulation system (15). This condition manifests itself as generalized small vessel vasculitis and diffuse microthrombosis (6). Cytokine storming interacts with coagulopathies and leading to vicious cycle associated with poor prognosis (32).

When the level of coagulation factors falls below 50%, coagulation tests are prolonged, and an abnormality may develop until the decompensation period of DIC due to the continuous activation and consumption of the exogenous coagulation pathway during DIC progression (23). Parameters PT and APTT that differences most in Covid-19 patients may increase due to coagulation activation or decrease due to consumptive coagulopathy (19). PT and APTT have been found to be longer in severe Covid-19 patients than in non-severe patients in some studies (10,21). We found that initial PT and APTT values were significant for risk classification and prognosis determination in Covid-19 patients. Prolonged PT on admission to the hospital has been shown to increase the risk of morbidity and mortality. The reason is that coagulopathy in Covid-19 is mostly due to sepsis in which the exogenous coagulation pathway is activated (23). One study found higher levels of fibrinogen in severe patients than non-severe patients (33). Fibrinogen, synthesized by the liver as an acutely reactive protein, is a coagulation protein. Fibrinogen promotes platelet aggregation and thrombosis, as well as hyperfibrinogenemia is commonly seen in the early phase of Covid-19 in both survivors and non-survivors. But in non-survivors, levels of fibrinogen may gradually decrease and hypofibrinogenemia may occur in the late stage of consumptive coagulopathy (10). In some studies, elevated fibrin levels have been detected in the lungs of patients with Covid-19 and it has been stated that fibrin accumulation in the alveoli causes acute bilateral pulmonary inflammation and chronic pulmonary fibrosis. The cytokine storm associated with Covid-19 also has a major effect on thrombin production and fibrin deposition in the lung. These data support the hypothesis that coagulopathy associated with Covid-19 contributes to the underlying pulmonary pathogenesis (34). In our study, fibrinogen and CRP levels were high in Covid-19 patients requiring hospitalization. The simultaneous increase in fibrinogen and CRP levels is probably due to an acute phase response (15). Free thrombin not controlled by natural anticoagulants can activate platelets (10). As in various viral infections, thrombocytosis due to platelet activation is common in the acute phase of Covid-19 and thrombocytopenia is common in its late stages (19). Development of thrombocytopenia may include direct or indirect factors such as inappropriate platelet activation and consumption due to DIC, immunological platelet destruction, and impaired megakaryopoiesis. In studies, platelet counts were found to be within the normal range in most COVID-19 patients at the time of admission (20,35), but thrombocytopenia was found in severe patients and non-survivors (10,31). Thrombocytopenia seen in critical patients is considered an indicator of bleeding and sepsis mortality as well as helping to detect the severity of coagulopathy (23).

In our study, in which we analyzed coagulation factors in Covid-19 patients, we found that age, comorbidity, elevated CRP, D-Dimer, fibrinogen, PT, aPTT levels have high

diagnostic value. In addition, we determined that coagulation factors increased more in critical patients than in severe patients. In the non-survivor, we found abnormal coagulation parameters that reflect coagulopathy on admission.

There are several limitations of this study. It was a relatively small, retrospective study. Our findings should be confirmed by a larger, powerful clinical trial. But in our study, we analyzed changes in coagulation biomarkers in hospitalized Covid-19 patients and those who lost their lives. We correlated these parameters with disease severity and survival.

Coagulation disorder is common and negatively affects prognosis in Covid-19. Our findings showed that coagulopathy developed common and that coagulation markers were associated with disease severity and survival in Covid-19, largely determining patients ' clinical outcomes. We found that the presence of DIC significantly increased deaths in critical cases. Our data suggest that monitoring of early coagulation tests can be used as independent, effective, easily accessible markers to evaluate prognosis, prevent disease progression, and guide treatment in the disease process, as well as helping to identify early coagulation disorders.

Conflict of interest

None to declare.

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