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Effect of troponin I and coagulation parameters on mortality in COVID-19 patients

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ABSTRACT

Objective: Our aim is to determine the levels of troponin-I and some coagulation markers (D-dimer, fibrinogen and International Normalized Ratio (INR)) in coronavirus disease 2019 (COVID-19) patients and to investigate the effects of these markers on mortality.

Patients and Method: It is planned as a descriptive, cross-sectional and analytical study. The study was conducted by retrospectively scanning the files of COVID-19 patients who applied to Inonu University Turgut Ozal Medical Center between 01.03.2020 and 31.12.2020. Levels of cardiac troponin I markers and coagulation parameters (D-dimer, fibrinogen and INR) were detected.

Results: The results of a total of 1858 patients were obtained. One thousand, three hundred and twenty-six patients with only troponin I and D-dimer results (Group 1), 606 patients with only troponin I and fibrinogen results (Group 2), and 1308 patients with only troponin I and INR results (Group 3) were included. Troponin I levels were significantly higher in all patients who died. 96.6% of the patients with high D-dimer levels died in Group 1, 85.5% of the patients with high fibrinogen levels died in Group 2 and 77.3 % of the patients with high INR levels died in Group 3.

Conclusion: Measurements of troponin-I and coagulation markers such as D-dimer, fibrinogen and INR can help predict clinical severity and mortality in COVID-19 patients.

Keywords: COVID-19, Troponin I, Coagulation markers, D-dimer, Fibrinogen, International Normalized Ratio.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become a serious health problem since it was first detected in Wuhan Province, China in December 2019; caused a global crisis in terms of economic, sociological and psychological aspects. The World Health Organization (WHO) declared this epidemic "an international public health emergency" on January 31, 2020 [1].

Complications, such as septic shock, heart, kidney and liver damage, and clotting disorders are considered to be associated with COVID-19. Clotting abnormalities and prolonged prothrombin time were reported in 6% of the patients admitted to hospital with COVID-19 diagnosis, and kidney function failure was observed in 4%. It was emphasized in previous reports that most of the patients who died because of COVID-19 had cardiovascular disease (CVD), COVID-19 infection triggered myocardial damage and cardiac dysfunction, and increased morbidity and mortality [2]. Troponin I is a sensitive cardiac indicator that can be found in the blood up to 7 days after cardiac injury [3].

Although, there is no published case series until our present time, it was reported that there may be an increased risk for venous thromboembolism in COVID-19 patients, and abnormal clotting parameters are detected in severe COVID-19 cases. It was reported in a multicenter study that was conducted in China that especially elevated D-dimer levels and fibrin destruction products were associated with mortality, and 71.4% of patients who died because of COVID-19 showed common intravenous clotting criteria during the disease [4].

Excessive inflammation, hypoxia, immobilization and widespread intravenous clotting accompany this viral respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can cause pneumonia. These conditions can make a patient become prone to venous and arterial thromboembolism, in this way, complicating the pathological condition further, and increasing the life-threatening risk. Various studies provided evidence that coagulation is a major cause of mortality in severe COVID-19 patients [5].

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In the COVID-19 pandemic, which affected the whole world, coagulation disorders and elevations in troponin I levels were frequently observed in patients. Heart damage in COVID-19 patients is associated with high mortality and can occur at any stage of the disease. These cardiac injury mechanisms in COVID-19 are also diverse, one of which is microvascular injuries [6]. Therefore, in our study, we aimed to investigate the effects of troponin I, a cardiac biomarker, and D-dimer, fibrinogen and international normalized ratio (INR) levels, which are indicators of microvascular damage, on mortality. The reason why we chose troponin I as the cardiac marker in our study is that the detection time in blood is longer than other cardiac markers.

2. PATIENTS and METHODS

This study was planned as a descriptive, cross-sectional and analytical study. The study includes patients who applied to Inonu University Turgut Ozal Medical Center between 01.03.2020 and 31.12.2020 and were diagnosed with COVID-19 by polymerase chain reaction (PCR) test and treated in the hospital. The cardiac marker troponin I and coagulation parameters D-dimer, fibrinogen and INR levels of these patients were screened retrospectively. When the data of COVID-19 patients whose troponin I, D-dimer, fibrinogen and INR values were examined from the hospital data recording system, a total of 1858 patient results were obtained. Since, relations between troponin I and, respectively, D-dimer, fibrinogen and INR would be examined, the levels of all three categorically were classified based on troponin I. In this classification, patients were evaluated according to their survival status. According to the results obtained from the hospital data recording system; There were 1326 patients with troponin I – D-dimer results (Group 1), 606 patients with troponin I-fibrinogen results (Group 2), and 1308 patients with troponin I-INR results (Group 3). In the data obtained, among 1858 patients with troponin I results; There were 1326 patients with troponin I and D-dimer levels, 606 patients with troponin I and fibrinogen levels, and 1308 patients with troponin I and INR levels. The figure for the categorization of the data is given below (Figure 1).

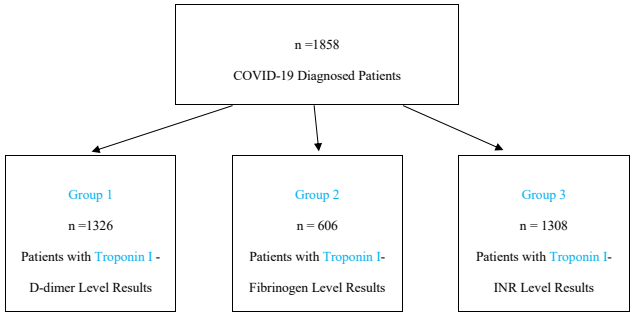

Figure 1. *Distribution of examined patients according to groups*

The test values of the patients with multiple troponin I, D-dimer, fibrinogen and INR results at first admission were included in the study. Troponin I levels were examined in Abbott brand Architect i1000 Autoanalyzer Device (Abbott Laboratories, Wiesbaden, Germany) with chemiluminescence method. The reference range for serum troponin I measurements was within the range of 0-34.2 pg/mL. D-dimer, fibrinogen and INR levels were analyzed with turbidimetric method in Sysmex CS-2500 fully automated device (Sysmex Corporation, Norderstedt, Germany). Reference ranges were accepted to be between 0-0.55 mg/L for serum D-dimer, 150-350 mg/dL for fibrinogen, and 0.8-1.2 for INR.

Statistical Analysis

Statistical Package for Social Sciences for Windows (SPSS) 20.00 (SPSS v. 22.0 software, Chicago, USA) program was used for statistical analysis. The descriptive statistics for continuous variables were summarized as mean and standard deviation values and for categorical data, values were summarized in tables with frequency and percentage values. The Pearson Chi-Square Test was used to compare categorical data. The Bonferroni Correction was made for binary comparisons in case there were differences among groups. The normality of numerical data was tested with the Kolmogorov-Smirnov Test. As not all numerical variables were distributed normally in the study, linear relations between numerical variables were determined by Spearman's rho Correlation Coefficient. The results were evaluated for a significance level of $p < 0.01$.

3. RESULTS

Troponin I – D-dimer Group

When the mortality/survival status was examined, it was determined that 15% (n=208) of 1326 patients evaluated in the 1st group died. Of the 208 patients who died in group 1, 66.8% (n=139) were male and were significantly more than women in terms of gender ($p<0.05$); 71.2% (n=148) were in the group that were aged 65 and over, and were significantly more than the 18-65 age group ($p<0.001$); 72.6% (n=151) had high troponin I levels, and were significantly higher than those with normal troponin I levels ($p<0.001$); and 96.6% (n=201) had high D-dimer levels, and were significantly higher in terms of D-dimer levels compared to those with normal D-dimer levels ($p<0.001$) (Table I).

Table I. *Distributions of Troponin I, D-Dimer Levels, Age and Gender according to Mortality/Survival Status*

	Total	Survivor	Non-Survivor	χ^2	p value
Gender					
Female	523 (39.4%)	454 (40.6%)	69 (33.2%)	4.059	0.044
Male	803 (60.6%)	664 (59.4%)	139 (66.8%)		
Age					
18-65	743 (56.0%)	683 (61.1%)	60 (28.8%)	74.015	<0.001*
≥65	583 (44.0%)	435 (38.9%)	148 (71.2%)		
Troponin I Levels					
Normal	1034 (78.0%)	977 (87.4%)	57 (27.4%)	367.469	<0.001*
High	292 (22.0%)	141 (12.6%)	151 (72.6%)		
D-Dimer Levels					
Normal	418 (31.5%)	411 (36.8%)	7 (3.4%)	90.614	<0.001*
High	908 (68.5%)	707 (63.2%)	201 (96. 6%)		
Total	**1326**	**1118**	**208**		

**p < 0.01 was considered significant*

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Since, troponin I and D-dimer values of the patients in group 1 (1326 patients) were not normal according to the Kolmogorov-Smirnov Test (p<0.001), Spearman's RHO Correlation Coefficient was calculated for the linear correlation between the variables (r=0.547; p<0.001). It was detected that there was a strong uphill linear relation between troponin I and D-dimer values (Figures II – V).

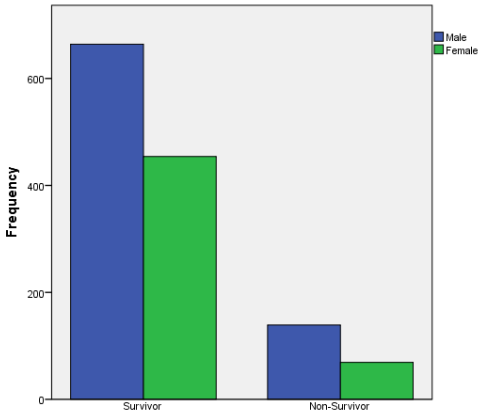

Figure II. *Mortality/Survival by gender in Group 1*

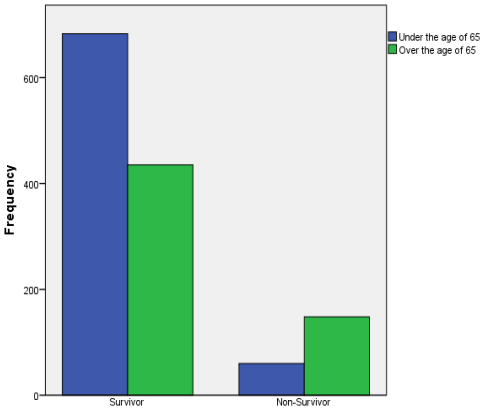

Figure III. *Mortality/Survival by age in Group 1*

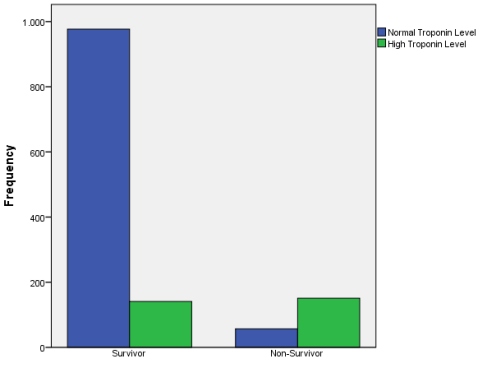

Figure IV. *Mortality/Survival by Troponin I Levels in Group 1*

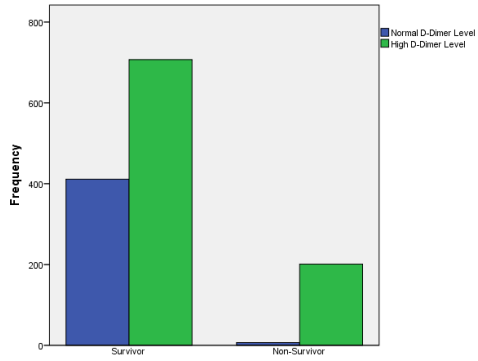

Figure V. *Mortality/Survival by D-dimer Level in Group 1*

Troponin I – Fibrinogen

When the mortality/survival status was examined, it was determined that 32% (n=193) of 606 patients evaluated in the 2st group died. Of the 193 patients who died in this group, 69.9% (n=135) were male and significantly higher than the other gender (p<0.01); 71.5% (n=138) were in the group that was aged 65 and over, and were significantly higher than the 18-65 age group (p<0.01); 73.6% (n=142) had high troponin I levels, and were significantly higher than those with normal troponin I levels (p<.001); and 85.5% (n=165) had high fibrinogen levels and were significantly higher than those with normal fibrinogen levels (p<0.001) (Table II).

Table II. *Distributions of Troponin I, Fibrinogen Levels, Age and Gender according to Mortality/Survival Status*

	Total	Survivor	Non-Survivor	χ^2	p value
Gender					
Female	224 (37.0%)	166 (40.2%)	58 (30.1%)	5.806	0.016
Male	382 (63.0%)	247 (59.8%)	135 (69.9%)		
Age					
18-65	282 (46.5%)	227 (55.0%)	55 (28.5%)	37.032	<0.001*
≥65	324 (53.5%)	186 (45.0%)	138 (71.5%)		
Troponin I Levels					
Normal	377 (62.2%)	326 (78.9%)	51 (26.4%)	154.271	<0.001*
High	229 (37.8%)	87 (21.1%)	142 (73.6%)		
Fibrinogen Levels					
Low	21 (3.5%)	10 (2.4%)	11 (5.7%)	9.882	<0.01*
Normal	85 (14. 0%)	68 (16.5%)	17 (8.8%)		
High	500 (82.5%)	335 (81.1%)	165 (85.5%)		
Total	**606**	**413**	**193**		

**p < 0.01 was considered significant*

Since, troponin I and fibrinogen values of the patients in group 2 (606 patients) were not normal distribution according to the Kolmogorov-Smirnov Test (p<0.001), Spearman's rho Correlation Coefficient was calculated for the linear relations between the variables (r=0.195; p<0.001). It was detected that there was a weak uphill linear relation between troponin I and fibrinogen values (Figures VI – IX).

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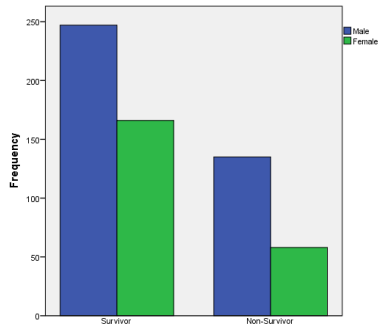

Figure VI. *Mortality/Survival by gender in Group 2*

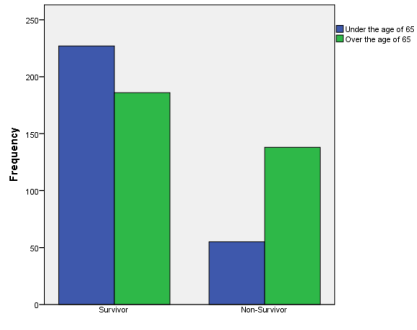

Figure VII. *Mortality/Survival by age in Group 2*

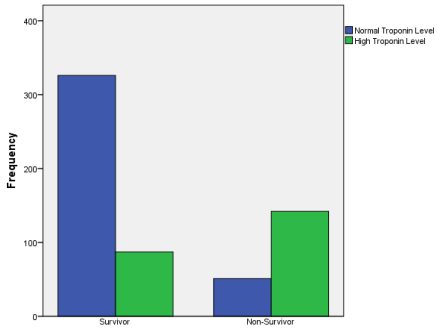

Figure VIII. *Mortality/Survival by Troponin I Levels in Group 2*

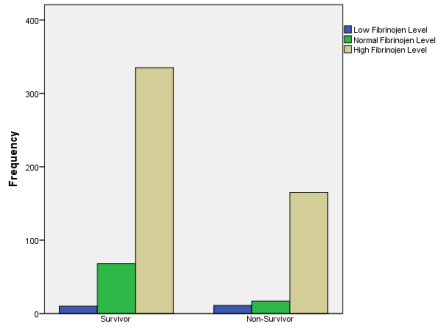

Figure IX. *Mortality/Survival by Fibrinogen Levels in Group 2*

Troponin I – INR

When the mortality/survival status was examined, it was found that 17% (n=220) of 1308 patients in the 3rd group died. Of the 220 patients who died in this group, 68.6% (n=151) were male and significantly more than the other gender (p<0.01); 71.4% (n=157) were in the group that was aged 65 and over, and were significantly more than the 18-65 age group (p<0.001); 70.5% (n=155) had high troponin I levels, and were significantly higher than those with normal troponin I levels (n=155) p<0.001); and 77.3% (n=170) had high INR levels, and were significantly higher than those with normal INR levels (p<0.001) (Table III).

Table III. *Distributions of Troponin I, INR Levels, Age, and Gender according to Mortality/Survival Status*

	Total	Survivor	Non-Survivor	χ^2	p value
Gender					
Female	511 (39.1%)	442 (40.6%)	69 (31.4%)	6.594	<0.01*
Male	797 (60.9%)	646 (59.4%)	151 (68.6%)		
Age					
18-65	725 (55.4%)	662 (60.8%)	63 (28.6%)	76.845	<0.001*
≥65	583 (44.6%)	426 (39.2%)	157 (71.4%)		
Troponin I Levels					
Normal	995 (76.1%)	930 (85.5%)	65 (29.5%)	314.500	<0.001*
High	313 (23. %9)	158 (14.5%)	155 (70.5%)		
INR Levels					
Normal	884 (67.6%)	834 (76.7%)	50 (22.7%)	242.939	<0.01*
High	424 (32.4%)	254 (23.3%)	170 (77.3%)		
Total	**1308**	**1088**	**220**		

INR: International Normalized Ratio
**p < 0.01 was considered significant*

Since, troponin I and INR values of the patients in group 3 (1308 patients) were not normally distributed according to the Kolmogorov-Smirnov Test (p<0.001), Spearman's rho Correlation Coefficient was calculated for the linear correlation between the variables (r=0.467; p<0.001). It was detected that there was a moderate uphill linear relation between troponin I and INR values (Figure X – XIII).

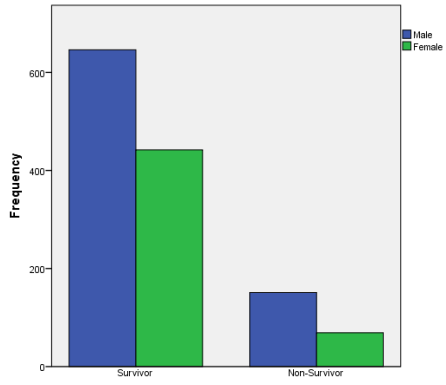

Figure X. *Mortality/Survival by gender in Group 3*

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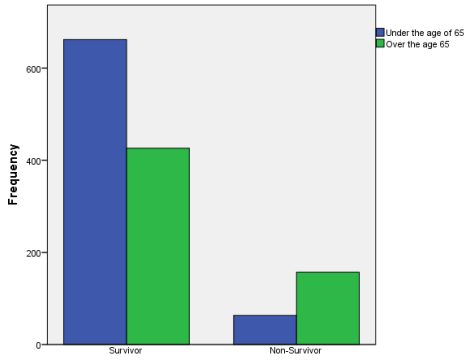

Figure XI. *Mortality/Survival by age in Group 3*

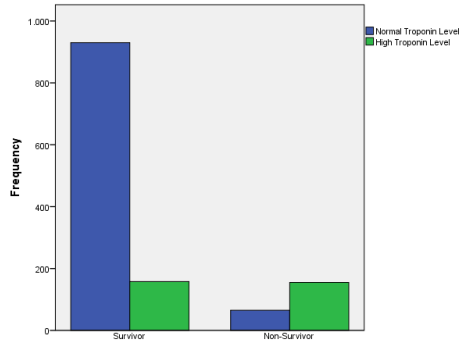

Figure XII. *Mortality/Survival by Troponin I Levels in Group 3*

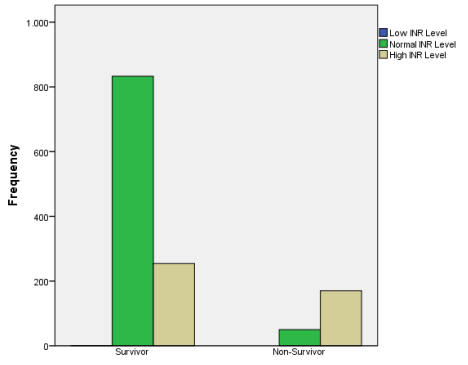

Figure XIII. *Mortality/Survival by INR Levels in Group 3*

4. DISCUSSION

In this study, we analyzed troponin-I and coagulation markers (D-dimer, fibrinogen and INR) levels in COVID-19 patients treated in our hospital. We evaluated the effect of these markers on mortality. Our study has shown that: The levels of troponin-I, D-dimer, fibrinogen and INR of patients who did not survive in all three groups (Group 1-Group 2-Group 3) were significantly higher when compared to the levels of these parameters in survivors. Therefore, elevations in these parameters may be predictive of mortality in COVID-19 patients. When evaluated according to age groups, the majority of patients who died were over 65 years of age in all three groups. This shows that advanced age is a factor that increases the risk of mortality in COVID-19 patients. In addition, there was a significant difference in gender only in the troponin I-INR Group (Group 3) in patients who died, and men had a significantly higher mortality rate than women. There was no relationship between gender and mortality in the troponin I-D-dimer group (Group 1) and troponin I-fibrinogen group (Group 2)

Although, many points about the disease caused by COVID-19 remain unclear, it is reported that the disease caused by this outbreak, which is a viral infection, may have long-term cardiovascular effects [7]. Cardiac damage, which is measured with elevated troponin I levels, was also reported among COVID-19 patients treated in hospital, and it was reported that their high levels indicated poor prognosis. The follow-up of heart damage, inflammation, and clotting markers was evaluated in relation with the severity and outcomes of the disease. Cardiac damage usually appears in critical COVID-19 patients, and elevated troponin I levels following the third day of hospitalization indicate poor prognosis. It was reported several times in previous studies that positive correlation between troponin I, IL-6, and D-dimer during hospitalization may suggest nonspecific cytokine-mediated cardiotoxicity [8].

In studies on COVID-19, high mortality rates have been associated with advanced age and male gender. Singh et al., found that among COVID-19 patients, men had a higher mortality rate than women [9]. Williamson et al., similarly reported that death associated with COVID-19 was associated with male gender and advanced age [10]. In our study, 60.6% of the patients in the group 1, 63% of the patients in group 2, and 60.9% of the patients in the group 3 were male. In our study, it is seen that men are more likely to get the disease than women in terms of being infected with COVID-19 because the percentage of male patients was higher than female patients in all three groups. There were also statistically significant differences in the gender factor among COVID-19 patients who died, and the percentage of male patients who died in all three groups was higher than the percentage of patients who survived.

In the study of Chen et al., with patients infected with COVID-19, it was found that patients aged 65 and over showed more severe symptoms and mortality rates were higher than younger patients [11]. In the study by Li et al., although, overall mortality rates in COVID-19 were low, the mortality rate was much higher in elderly patients [12]. In the cohort study of Singh et al., 93.9% of the total mortality was found in patients aged 50 and over [9]. In our study, the mortality rate of patients aged 65 and over was higher than that of the 18-65 age group in all three groups (Group 1, Group 2, Group 3). The results of our study show that advanced age is a risk factor for death from the disease in COVID-19 patients, similar to the studies in the literature.

Stefanini et al., reported that detecting high troponin I levels earlier would predict mortality in COVID-19 patients, and

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cardiac biomarkers must be evaluated systematically during hospitalization in COVID-19 patients [13]. Qin et al., conducted a retrospective study and evaluated serum cardiac biomarkers of COVID-19 patients. Laboratory results showed that troponin I had a high prognostic value for all-cause mortality [14]. Arcari et al., detected high troponin I levels in 38% of patients hospitalized with COVID-19 pneumonia, reinforcing the assumption that cardiac biomarker assessment may be useful in the follow-up of COVID-19 [15]. In their study, which was aimed at determining the cardiovascular characterization of COVID-19 patients, Rath et al., reported that elevated levels of troponin I were associated with poor prognosis in COVID-19 patients, and it was also found that D-dimer and troponin I levels were significantly higher in the mortality group compared to survivors [16]. These findings suggest that cardiac damage biomarkers are associated with an increased risk of mortality in COVID-19. Similar to previous findings [13-16], we observed that high troponin levels are a risk factor for increased mortality in COVID-19. Troponin I levels were found to be above the normal range in all three groups in patients who did not survive. This is consistent with the literature data that troponin I levels have effects on mortality in COVID-19 patients.

In a literature review of the effects of COVID-19 on coagulation, Li et al, evaluated 2,068 patients diagnosed with COVID-19 and D-dimer, which is high in coagulation markers, was observed in 58.6% of the patients and mortality was observed in 8.8% (n=183). Also, cardiac and clotting markers increased at significant levels in patients who died, except for fibrinogen levels when compared to survivors. Almost all clotting markers, including D-dimer, increased throughout the entire hospitalization of patients who were critically ill and died. D-dimer levels peaked within 1-3 days, and then decreased in survivors and non-survivors; however, median values were significantly higher in those who did not survive at any time point than in those who survived. They also found that there were significant differences between troponin I and D-dimer levels (n= 396, p <0.001) [8]. The most striking result of our work was that 96.6% (n=201) of patients who died in group 1 had elevated D-dimer levels; and there were significant differences between those with normal D-dimer levels (P<0.001). There was also a moderate and statistically significant linear relation between troponin I and D-dimer levels (r=0.547; p<0.001). However, it was reported in different studies that cardiac markers and coagulation (e.g. D-dimer) biomarkers would be useful in identifying patients at high risk of mortality, which is consistent with our results [10,11,16,17]. In the study of Miesbach and Makris, they reported that the most important change in coagulation parameters in severe COVID-19 patients was observed as an increase in D-dimer level. In addition, it was emphasized that increasing D-dimer values during the course of the disease can be used as a prognostic parameter to determine worsening prognosis [18]. Also, it was reported in a multicenter retrospective cohort study that was conducted by Zhou et al., in China that elevated D-dimer levels were significantly associated with in-hospital mortality [19]. Separate studies conducted by Terpos et al., and Wang et al., also indicated that D-dimer levels increased periodically in COVID-19 patients who did not survive compared to survivors [20, 21]. In our study, higher levels were found in the coagulation parameters in non-survivors than in survivors. This suggests that coagulopathy and especially disseminated intravascular coagulation (DIC) may contribute to mortality in COVID-19 patients.

In a protective study that evaluated the clotting profiles of COVID-19 patients, fibrinogen degradation products (FDP) and fibrinogen levels were found to be higher at significant levels among patients compared to healthy controls [22]. In the studies conducted by Connors and Levy and Thachil et al., it was recommended to monitor especially D-dimer, PZ, fibrinogen levels, and platelet counts regarding the severity of COVID-19 patients [23, 24]. In the study conducted by Terpos et al., it was stated that 71.4% of the patients who died met the clinical criteria for DIC. They noted that PT and other coagulation abnormalities, such as aPTT prolongation and fibrin degradation products, increased in patients infected with COVID-19, and severe thrombocytopenia caused life-threatening intravascular conditions. They emphasized that patients infected with COVID-19 are at high risk for venous thromboembolism [20]. It was found that D-dimer and FDP levels were significantly higher, PT(s) values were longer, and coagulation parameters were significantly associated with prognosis in patients who died from COVID-19 [4]. In a study investigating the relationship between coagulation and disease severity in COVID-19 patients, the PT, INR, APTT, and D-dimer levels of deceased patients were found to be significantly higher than those of surviving patients [25]. Li et al., also reported high INR (1.6) and prolonged PT (14.5 sec) levels in COVID-19 patients [26]. In our study, the rate of those who died and who had high D-dimer levels and those who had high INR levels was higher than in patients with normal values. Previous studies [4, 20, 25, 26] support our study results and it was observed that high INR level is associated with mortality in COVID-19 patients.

It is important to detect fatal complications early, improve patient outcomes, and reduce mortality rates in infected patients in COVID-19. The results of our study showed that measurements of troponin-I and coagulation markers such as D-dimer, fibrinogen and INR can help predict clinical severity in COVID-19 patients. These results can guide clinicians in estimating the risk of death in patients and adjusting treatment. Adjusting the treatment according to the changes in these parameters may be beneficial in reducing mortality rates by providing more effective recovery opportunities.

Since, our study was retrospective, we could not focus on patients' comorbidity data, causes of death, and could not conduct research on this subject. However, we think that the causes of death of the patients who lost their lives are COVID-19 and various complications related to it. In addition, the study needs to be confirmed by multicenter prospective studies, as control of variables cannot be achieved in retrospective studies.

Compliance with Ethical Standards

Ethical Approval: The study was approved by the Ministry of Health of the Republic of Türkiye (Reference number: 2020-11-13T11_11_42). In addition, the study was approved by the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (with the number of 2020/1272).

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