MARMARA
MEDICAL JOURNAL

Original Article

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Increased D-dimer is associated with disease progression and increased mortality in Turkish COVID-19 patients

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Submitted: 14.11.2022 **Accepted:** 15.03.2023

ABSTRACT

Objective: Coagulopathy is thought to play an important role in the development of severe COVID-19. High D-dimer levels have been reported in Chinese cohort studies. However, ethnicity has significant implications for thrombotic risk. Our aim in this study is to determine the effect of D-dimer measurements on disease prognosis and mortality in Turkish patients with COVID-19.

Patients and Methods: The study was designed retrospectively. Patients over the age of 18 who were admitted to our hospital were included in the study.

Results: The study included 226 patients. According to the World Health Organization staging, 75(33.2%) patients, according to the staging of Siddiqi et al., 67 (29.7%) patients progressed. In the ROC analysis performed to predict mortality, AUC value for D-dimer was found to be 82.25% (95%CI 74.8%-89.71%). When the cut-off value for D-dimer was accepted as ≥3.25mg/L, specificity was 94.15%, correctly classified rate 88.5%, positive likelihood ratio as (LR):5.69, negative LR:0.71.

Conclusion: As a result, similar to the Chinese cohorts, elevated D-dimer measurements increase disease progression and mortality in Turkish patients with COVID-19. D-dimer levels of 3.25 mg/L and above, strongly determine the risk of increased mortality in the Turkish Caucasian ethnic group.

Keywords: COVID-19, D-dimer, Mortality, Ethnicity

1. INTRODUCTION

At the end of 2019, a new coronavirus was identified as the cause of pneumonia cases in China. World Health Organization (WHO) defined this disease as coronavirus disease 19 (COVID-19) [1]. During the course of COVID-19, coagulation abnormalities are frequently seen that affect the pathogenesis of the disease [2]. Coagulation anomalies do not only increase thrombotic events but also affect mortality. In autopsy studies of individuals who died from COVID-19, diffuse thrombotic microangiopathy limited to the lungs was observed. Similarly, while no embolism was detected in the pulmonary arteries, it was found that the right ventricles of these patients were enlarged [3, 4]. The amount of new vessel growth in the lungs of COVID-19 patients is higher than in the lungs of patients with influenza [5].

D-dimer is a product of cross-linked fibrin showing increased thrombin formation and plasmin and fibrin dissolution. Multivariate regression analysis in COVID-19 cohorts showed that high D-dimer levels are an important risk factor for poor prognosis [6, 7]. Moreover, anticoagulant therapy with low molecular weight heparin (LMWH) appears to be associated with a better prognosis in patients with significantly increased D-dimer [7].

Race and ethnicity have a significant impact on thrombotic risk. Europeans have a significantly higher incidence of venous thromboembolism (VTE) compared to Asian populations [8].

How to cite this article: Mercanci Z, Ilgin C, Yildizeli Olgun S, et al. Increased D-dimer is associated with disease progression and increased mortality in Turkish COVID-19 patients. Marmara Med J 2023: 36(2):175-181. doi: 10.5472/marumj.1302440

ISSN: 1309-9469

http://doi.org/10.5472/marumj.1302440
Marmara Med J 2023;36(2): 175-181

Most of the studies investigating the prognostic importance of D-dimer measurement in COVID-19 patients have been published in China, where the disease originated. In a study conducted with COVID-19 patients of the Caucasian race, a coagulopathy proportional to the severity of the disease was shown. However, this study showed that LMWH did not significantly affect the increase in D-dimer levels observed in patients with severe COVID-19 [9].

To our knowledge, there is no data on D-dimer cut-off level that best predicts mortality in the Turkish population. Our primary goal in this study is; to determine whether high D-dimer levels have an effect on mortality and disease progression in Turkish patients infected with COVID-19. Our second goal; is the determination of the D-dimer cut-off value, which increases the risk of mortality.

2. PATIENTS and METHODS

The study was designed retrospectively. The data of 543 patients over the age of 18 who applied to our hospital between March and June 2020 were analyzed. Individuals with positive COVID-19 polymerase chain reaction (PCR) tests were included in the study. In addition, pregnant women and patients who did not have laboratory data and lung computed tomography (CT) at the time of application were not included in the study. As a result, data of 226 patients were used. The study was approved by the ethics committee of our hospital (12.06.2020 approval number: 09.2020.697).

Medical treatments related to COVID-19 of the patients were carried out by the recommendations updated by the Turkish Ministry of Health [10].

For hypoxemic patients; Oxygen titration was performed such that the initial target oxygen saturation (SpO2) was ≥94% and for maintenance oxygenation ≥90%. For most critically ill patients, the lowest possible fraction of inspired oxygen (FiO2) required to meet oxygenation targets was preferred, ideally targeting a SpO2 of 90 to 96 percent if possible. Considering this goal, treatment with a nasal cannula, mask, high flow nasal cannula (HFNC), or noninvasive mechanical ventilation (NIMV) was given, and intubation was performed in patients for whom clinical goals could not be achieved [11].

Patients who developed acute respiratory distress syndrome (ARDS) and septic shock were treated by the recommendations in international guidelines [12]. Anticoagulation treatments of the patients were arranged according to the guidelines updated regularly by the Turkish Ministry of Health and the local hospital guides [10]. Since, the recommendations in the guidelines are dynamic recommendations updated with new information, there have been changes in the treatment of patients from time to time.

The patients' symptoms and laboratory values including clinical, radiological, and coagulation tests at the hospital admission, and the worst laboratory values were recorded during the hospitalization. The clinical severity scores of the patients were calculated with two separate scoring systems which are the WHO and Siddiqi et al. and at least 1 step worsening in this scoring system during follow-up was accepted as progression [13, 14].

Siddiqi et al., classified the early infection period as the 1st stage, the lung involvement period as the 2nd stage, and the hyperinflammation period as the 3rd stage [13].

D-dimer measurements were made with the American Beckman Coulter device purchased from TURMED, Istanbul, Turkey. Immuno-turbidometric method was used [15].

In addition, supportive treatments and anticoagulation treatments, initial symptoms, and comorbidities were recorded.

Statistical Analysis

STATA 15.1 software was used for statistical analysis. Since, continuous variables did not show normal distribution, the median and interquartile range (IQR) were reported with minimum and maximum values. Categorical variables were reported with numbers and percentages.

Mann-Whitney U and Kruskal-Wallis tests were used to determine the differences of continuous variables between independent groups, and Chi-square and Fisher's exact tests were used for comparisons between categorical variables.

Odds ratios were given with 95% confidence interval (CI) when necessary. Sensitivity, specificity, correct classification, positive and negative predictive values, positive and negative likelihood values were reported for the cut-off value determined by the non-parametric receiver operating characteristic (ROC) test. A p-value less than 0.05 was considered statistically significant.

3. RESULTS

A total of 226 patients with a mean age of 54 (min-max 20-95) were included in the study (Table-I). All patients were of Turkish Caucasian ethnicity. When the values recorded as the highest values from the laboratory values checked during the first application and follow-up of the patients were examined, the median of the admission D-dimer values was 0.6 Interquartile Range (IQR) 0.67, min-max 0.14-20), and the median of the highest D-dimers in their follow-up was 0.895 (IQR 1.93, min.-max 0.14-20) (Table-II).

In the ROC analysis performed to predict mortality, the area under the curve (AUC) value for D-dimer was found to be 82.25% (95% CI 74.8% – 89.71%). When the cut-off value for D-dimer was accepted as 3.25 mg/L and above, the specificity was calculated as 94.15%, sensitivity 33.33%, correctly classified rate 88.5%, positive likelihood ratio (LR) 5.69, negative LR 0.71. The negative predictive value was 93.24% and the positive predictive value was 36.84% (Figure).

http://doi.org/10.5472/marumj.1302440
Marmara Med J 2023;36(2): 175-181

Table I. *Demographics and clinical characteristics of patients*

Demographics and clinical characteristics		Statistics	Total
Count		n (%)	226 (100.0%)
Age		Mean (SD±) Min-Max	54 (15) 20-95
Gender			
Female		n (%)	99 (43.81%)
Male		n (%)	127 (56.19%)
Treatment			
LMWH*	0**	n (%)	69 (30.53%)
	1**	n (%)	97 (42.92%)
	2**	n (%)	60 (26.55%)
Symptoms			
Cough		n (%)	121 (53.54%)
Fever		n (%)	81 (35.84%)
Dyspnea		n (%)	94 (41.59%)
Weakness – Fatigue		n (%)	23 (10.18%)
Diarrhea		n (%)	19 (8.41%)
Nausea – Vomiting		n (%)	24 (10.62%)
Chills		n (%)	35 (15.49%)
Headache		n (%)	23 (10.18%)
Myalgia		n (%)	23 (10.18%)
Comorbidities			
Hypertension		n (%)	83 (36.73%)
Diabetes mellitus		n (%)	64 (28.32%)
Chronic obstructive pulmonary disease		n (%)	16 (7.08%)
Coronary artery disease		n (%)	20 (8.85%)
Chronic renal failure		n (%)	8 (3.54%)
Asthma		n (%)	17 (7.52%)

LMWH: Low molecular weight heparin, 0: LMWH never given, 1**: LMWH given a single dose, 2**: LMWH given a double dose, p<0.05*

http://doi.org/10.5472/marumj.1302440
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Table II. *The effects of laboratory data of patients on both disease staging and mortality*

Laboratory findings		WHO[14] Classification			Siddiqi et al. [13] Classification			Mortality		
	Median(IQR*) Min-Max	0	1	p	0	1	p	Alive	Death	p
D-dimer (at admission)	0.6(0.67) 0.14-20	0.51(0.54) 0.14 – 20	0.81(1.39) 0.19-20	<0.0001	0.52(0.56) 0.14-20	0.78(1.12) 0.19-20	0.0005	0.55(0.53) 0.14-20	1.46(2.59) 0.45-11.27	<0.0001
D-dimer (at peak)	0.895(1.93) 0.14-20	0.62(0.82) 0.14-20	2.54(5.61) 0.25-20	<0.0001	0.66(0.87) 0.14-20	2.42(5.97) 0.25-20	<0.0001	0.73(1.08) 0.14-20	8.61(16.53) 1.49-20	<0.0001

0: no disease progression, 1: there is disease progression, IQR: Interquartile range*

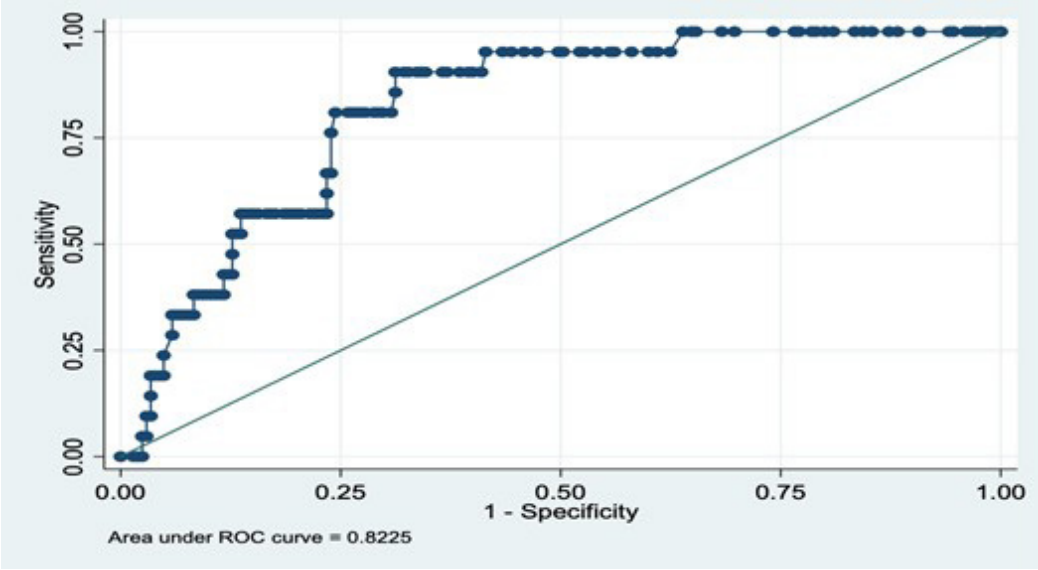

Figure. *Receiver operating characteristic (ROC) analysis for D-dimer in predicting mortality.*

4. DISCUSSION

Our study showed that increased D-dimer measurement was associated with disease progression and mortality in Turkish patients of Caucasian origin with COVID-19. A D-dimer level above 3.25 mg/L was most likely associated with mortality. In addition, the mortality-reducing effect of treatment with LMWH could not be demonstrated in patients with increased D-dimer levels.

The distinguishing feature of our study is that it is the first study to investigate the cut-off level of D-dimer, which increases mortality in the Turkish Caucasian race.

High D-dimer levels are known to increase in infections and sepsis. It has been reported that increased D-dimer level is associated with 28-day mortality in patients with infection or sepsis in the emergency department [16]. The most common anomalies in coagulation parameters in patients with COVID-19 infection is high D-dimer. In a study where five hundred and sixty cases were investigated, they found abnormally high D-dimer levels in 260 (46.4%) of the patients, and this rate was 60% in severe patients [14]. In another series, elevated D-dimers were likewise associated with a poor prognosis. In the study conducted by Zhou et al., it was observed that D-dimer higher than 1 μg/ml was associated with the fatal outcome of COVID-19 [6]. In the study conducted by Rodelo et al., it was shown that D-dimer levels above 2.0 mg/L can predict mortality with 92.3% sensitivity and 83.3% specificity [16].

Similarly, in our patient group, it was observed that the increase in D-dimer affected mortality. The same effect has been demonstrated in disease progression. It has been observed that having D-dimer >3.25 μg/mL increases mortality with high reliability.

Therefore, the use of LMWH has been recommended in this patient group since the beginning of the pandemic. It is known that LMWH has anticoagulant activity as well as anti-inflammatory and endothelial protective activity. Thus, in the studies performed by both Tang et al. [7] and Yin et al. [17], it was shown that LMWH treatment reduced mortality in the

http://doi.org/10.5472/marumj.1302440
Marmara Med J 2023;36(2): 175-181

group with D-dimer >3.0 µg/mL. However, the use of LMWH has not been shown to reduce mortality in our patient group. In fact, these patients were more progressive and more mortal. This may be because high levels of D-dimer were seen in the severely ill patient group and the therapeutic dose of LMWH was given. LMWH at therapeutic dose has not yet been shown to reduce mortality in large studies, and its routine use is controversial [18, 19]. In our study, mortality in patients receiving therapeutic dose LMWH, was statistically significantly higher than those who did not receive therapeutic or those who received prophylactic doses. However, in staging according to both disease severity, the progression rate of those who received therapeutic dose LMWH was higher than those who did not receive therapeutic or those who received prophylactic doses. We think that the reason for this result is that the more severe patients in our study received therapeutic dose LMWH.

The elevation of plasma D-dimers was initially considered an indicator of coagulopathy [7] and was postulated as an indicator of diffuse intravascular coagulation (DIC). However, these patients do appear to have a clear DIC according to the International Society for Thrombosis and Hemostasis (ISTH) criteria [20] and fibrinogen levels are very high [7]. Alternatively, the origin of D-dimer is thought to be a direct result of acute lung injury seen in COVID-19 pneumonia by some authors [21]. It is known that the hallmark of acute lung injury is the accumulation of intraalveolar fibrin and that fibrin levels are controlled by alveolar epithelial cells that produce urokinase and regulate extravascular proteolysis. Urokinase then converts plasminogen to plasmin, which breaks down local fibrin. In addition; It has been described that increased macrophages in lung tissue, another marker of COVID-19 pneumonia, also produce fibrinolysis by an alternative route [22].

It is estimated that the lower incidence of venous thromboembolism in Asians is due to the lower prevalence of genetically induced anomalies that predispose to venous thromboembolism, such as Factor V Leiden [23]. Factor V Leiden is the most common genetic mutation that predisposes to venous thromboembolism [24, 25]. When thrombophilia screening was performed in Turks who had their first VTE attack, Factor V Leiden was detected in 15-20% of cases and the prothrombin gene mutation was detected in 5-7% of cases [26]. This frequency is reported to be 10% in the general Turkish population, which is higher than in the European population [27]. Differences in coagulation factors between Asians and Caucasians can be attributed to environmental factors, particularly diet and smoking, as well as genetic differences [25, 28]. Asians have been shown to have more effective inactivation of coagulation through activated protein C or greater fibrinolytic activity [23]. Most of the data on COVID-19 coagulopathy have been reported from China, where the incidence of venous thromboembolism is approximately 3 to 4 times lower in Chinese patients [29]. However, since the disease affects Caucasian individuals and Chinese individuals several times more than other ethnic groups, it is important to know the thrombogenic risk related to ethnic origin. Caucasians have a higher thrombotic risk than Chinese and other Asian populations, and the risk is even higher in African American and Hispanic patients in the United States [8, 30, 31]. In this case, the lower threshold value of D-dimer in Caucasians may increase mortality and require closer monitoring of these patients. Therefore, our study aims to determine whether the predictive value and cut-off point of D-dimer for mortality risk in the Turkish population are different from those in other races. In a study by Tang et al., examining laboratory parameters associated with poor prognosis, especially in patients with COVID-19 pneumonia who died in the late phase, it was found that fibrin-associated markers (D-dimer, fibrin degradation products) were moderately or significantly elevated [32]. This increase had significant effect on mortality, which is more than 2 times the normal value. The slightly higher predictive value we found may be related to the genetic, ethnic, and lifestyle differences between the Turkish and Asian populations.

Since, retrospective data were analyzed, other laboratory tests that could predict risk were not included in our study. The lack of effective antivirals and the lack of routine use of dexamethasone, which was known to reduce mortality at that time, may have contributed to poor clinical outcomes in some patients. The interpretation of our findings may be limited by the sample size. However, by including all adult patients identified for COVID-19, we believe our study population represents cases diagnosed and treated in the Turkish population.

The prognosis of COVID-19 is variable and poor in some patient groups. Unfortunately, an effective, globally accepted treatment algorithm for COVID-19 treatment has yet to be established. Additionally, the importance of anticoagulant therapy is increasing as thrombotic events play an important role in mortality. Our study shows that high D-dimer levels are strongly associated with disease severity and increased mortality. In the Turkish Caucasian ethnic group, D-dimer levels of 3.25 mg/L and above, strongly determine the risk of increased mortality. Future studies are needed to investigate whether anticoagulation treatment strategies reduce morbidity and mortality in COVID-19.

Compliance with Ethical Standards

Ethical Approval: The study was approved by the Marmara University, School of Medicine Clinical Research Ethics Committee (12.06.2020 approval number: 09.2020.697).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Authors' Contributions: ZM, SOY, DK, BB, BES, SK and EE: Medical practices, ZM, SK and EE: Concept, ZM and EE: Data collection or processing, ZM, CI, SK and EE: Analysis or interpretation, ZM and EE: Literature search and writing. All authors read and approved the final version of the manuscript.

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