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ASSOCIATION BETWEEN D-DIMER AND MORTALITY IN COVID-19 PATIENTS: A SINGLE CENTER STUDY FROM A TURKISH HOSPITAL

Mazlum Kilic[1], Ummahan Dalkilinc Hokenek[2]

[1]Fatih Sultan Mehmet Education and Research Hospital, Department of Emergency Medicine, Istanbul, Turkey
[2]Clinic of Anesthesiology and Reanimation, University of Health Sciences, Kartal Dr. Lutfi Kırdar City Hospital, Istanbul, Turkey

ABSTRACT

INTRODUCTION: Early and effective laboratory parameters are required to determine the prognosis of COVID-19. In this study, our aim was to investigate the relationship between the D-dimer levels of patients with COVID-19 and their in-hospital mortality status.

MATERIAL AND METHODS: This retrospective observational study was conducted with patients diagnosed with COVID-19 in the emergency department of a tertiary hospital between January 1, 2022, and June 1, 2022. Patients with a negative reverse transcription-polymerase chain reaction test result and those with unavailable D-dimer records were not included in the study.

RESULTS: The population of this study consisted of 517 patients, 241 women and 276 men. The mean age of the patients was 72.4 years. The patients were divided into two groups as survivors and non-survivors. There were 320 patients in the survivor group and 197 in the non-survivor group. As a result of the statistical analysis, D-dimer was found to be statistically significant in predicting in-hospital mortality in patients with COVID-19 ($p < 0.001$).

CONCLUSIONS: In this study, it was concluded that COVID-19 cases with high D-dimer levels had a higher in-hospital mortality rate. In addition, it was observed that patients admitted to the intensive care unit had higher D-dimer levels than those that did not require intensive care.

KEY WORDS: D-dimer; COVID-19; mortality

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection caused by a novel coronavirus first detected in Wuhan, China in December 2019 was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). The disease is highly contagious and its main clinical symptoms are fever, dry cough, myalgia, fatigue, and shortness of breath. Since the first reported case of COVID-19 in Wuhan at the end of 2019, the disease has spread rapidly across China and then to all countries of the world [1–3].

In the literature, there are many research articles and case reports examining the relationship between COVID-19-related abnormal coagulation and laboratory parameters and prognosis [4–7]. According to

ADDRESS FOR CORRESPONDENCE:
Mazlum Kilic, Department of Emergency Medicine, Fatih Sultan Mehmet Education and Research Hospital;
Hastane Sokak no:1/8 Icerenkoy — Atasehir 34752 Istanbul, Turkey
e-mail: drmazlumkilic@gmail.com
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one study, key features of the first 99 hospitalized patients in Wuhan included increased activated partial thromboplastin time (aPTT) in 6% of patients, increased prothrombin (PT) in 5%, elevated D-dimer and biomarkers of increased inflammation in 36%, and thrombocytopenia in 12% [1]. In particular, it was observed that the D-dimer levels of intensive care patients were significantly higher than those that did not require intensive care [8]. Prothrombin time and D-dimer levels present as markers related to the severity of the disease. In addition, coagulation tests are important in the diagnosis and evaluation of disseminated intravascular coagulation, which is an important complication in patients with COVID-19. In another study, the D-dimer value measured at admission being higher than 2.0 μg/mL was reported to effectively predict in-hospital mortality in patients with COVID-19, suggesting that this parameter could be an early and useful sign to improve the management of this patient population [9].

In this study, our aim was to examine the relationship between D-dimer levels and in-hospital mortality in patients with COVID-19.

MATERIAL AND METHODS

This retrospective observational study was carried out in the emergency department of a tertiary hospital between January 1, 2022, and June 1, 2022. The institutional review board approved the analysis and issued a waiver of consent (ethics committee ruling number: 2022/514/228/25, date: 30.06.2022). All the patients with COVID-19 aged over 18 years, who presented to the emergency department between January 1, 2022, and June 1, 2022 were included in this study. The diagnosis of COVID-19 was determined based on the WHO guidelines. The digital records of the Hospital Information Management System were used to collect data. For the patients who were included in this study, age, gender, vital signs, chronic diseases, and laboratory test results, including D-dimer values, were recorded in a format at the time of presentation to the emergency department. Patients with a negative reverse transcription-polymerase chain reaction test result, those with unknown mortality status, those that had been referred from another hospital, and those with unavailable D-dimer values were not included in the study.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 for Windows and MedCalc. Descriptive criteria were presented as mean and standard deviation, median and minimum-maximum values, and percentage distribution. The conformity of the data to the normal distribution was checked with the Kolmogorov-Smirnov test. The receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values of risk scores in determining the need for intensive care. The ROC curves of the risk scores were compared. Using the DeLong method, the optimal cut-off value with Youden's index, 95% confidence interval (CI), area under the curve (AUC), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were calculated. The significance level was taken as $p < 0.05$.

RESULTS

The population of this study consisted of 517 patients, 241 women, and 276 men. The mean age of the patients included in the study was 72.4 years. The patients were divided into two groups as survivors and non-survivors. There were 320 patients in the survivor group and 197 in the non-survivor group (Tab. 1). Table 1 summarizes the vital signs, laboratory parameters, chronic diseases, and hospitalization status of the patients included in the study. It was observed that the patients in the non-survivor group had higher D-dimer, creatinine, white blood cell count, and age values compared to the survivor group ($p < 0.001$).

As a result of the statistical analysis, D-dimer was found to be statistically significant in predicting in-hospital mortality in patients with COVID-19 ($p < 0.001$). The ROC analysis was performed to evaluate the power of D-dimer to predict in-hospital mortality (Fig. 1). The AUC value of D-dimer was determined as 0.698 (95% CI: 0.655–0.738). According to the results of the ROC analysis, the optimum cut-off value of D-dimer was determined using Youden's index. The cut-off value of D-dimer for this outcome was calculated as 1,020 ng/mL, at which it had 81.3% sensitivity, 47.9% specificity, 46.4% PPV, and 82.4% NPV (Tab. 2).

Table 1. Baseline characteristics of the study population

Variables	Survivors		Non-survivors		Total		
	Mean number	SD prcentage	Mean number	SD percentage	Mean number	SD percentage	p-value
Gender							
Female	160	50	81	41.1	241	46.6	**0.049**
Male	160	50	116	58.9	276	53.4	
Age	69.9	14.6	76.6	9.8	72.4	13.4	**0.001**
Systolic blood pressure (mmHg)	125.6	17.9	126.9	26.1	126.1	21.4	0.492
Diastolic blood pressure (mmHg)	71.5	10.9	71.1	15.1	71.4	12.6	0.677
Pulse (beats/min)	84.9	14.9	95.3	20.4	88.8	17.9	**0.001**
Respiratory rate	22.8	5.9	27.7	8.2	24.5	7.2	**0.001**
Body temperature (°C)	36.8	0.7	36.8	0.8	36.8	0.8	0.180
Chronic obstructive pulmonary disease	24	15.6	23	19.0	47	17.1	0.454
Diabetes mellitus	91	51.4	47	37.9	138	45.8	**0.021**
Hypertension	116	63.0	68	51.9	184	58.4	**0.038**
Congestive heart failure	19	12.5	26	22.2	45	16.7	**0.034**
Atrial fibrillation	6	4.1	4	3.6	10	3.9	0.816
Chronic renal Failure	12	8.0	22	19.1	34	12.8	**0.007**
White blood cell (10^9/L)	7.8	4.2	10.3	5.7	8.8	5.0	**0.001**
Neutrophil (10^3/uL)	6.3	5.8	8.7	5.5	7.2	5.8	**0.001**
Lymphocyte (10^3/mm^3)	1.3	2.3	1.2	2.2	1.3	2.2	0.653
Hemoglobin (g/dL)	12.5	1.9	12.0	2.3	12.3	2.1	**0.012**
Platelet (109/L)	220.7	96.7	232.9	103.3	225.4	99.3	0.173
Blood urea nitrogen (mg/dL)	47.7	31.9	81.7	58.9	60.5	46.9	**0.001**
Albumin (g/dL)	34.4	5.4	31.6	6.4	33.3	5.9	**0.001**
D-dimer (ng/mL)	1581.0	1673.9	2849.5	3821.4	2033.8	2713.7	**0.001**
Aspartate aminotransferase (IU/L)	41.2	29.8	74.9	311.1	53.9	193.2	0.053
Alanine aminotransferase (IU/L)	30.3	23.1	45.5	164.5	36.1	102.9	0.102
Creatinine (mg/dL)	1.2	2.5	1.7	1.7	1.4	2.2	**0.007**
Admission status							
Inpatient unit	301	92.9	79	40.1	380	72.9	**0.001**
Intensive care unit	23	7.1	118	59.9	141	27.1	

SD — standard deviation

DISCUSSION

In this study, the relationship between the D-dimer level and the in-hospital mortality status of patients with COVID-19 was examined, and it was concluded that the patients with high D-dimer levels had a higher mortality rate.

As the number of individuals infected with SARS-CoV-2 continues to increase globally and the effects of the disease on health systems are observed, it is clear that clinical laboratory tests will play an increasingly important role, contributing to patient screening, diagnosis, follow-up, and treatment. The definition of laboratory tests that contribute to the diagnosis and follow-up of COVID-19 is very important in order to distinguish between severe and non-severe cases, and identify those with low or high mortality risk, in addition to assisting in diagnosis.

D-dimer is a soluble fibrin degradation product resulting from the regular breakdown of thrombus by the fibrinolytic system. It is generated following cross-linking of two D-fragments of fibrin protein

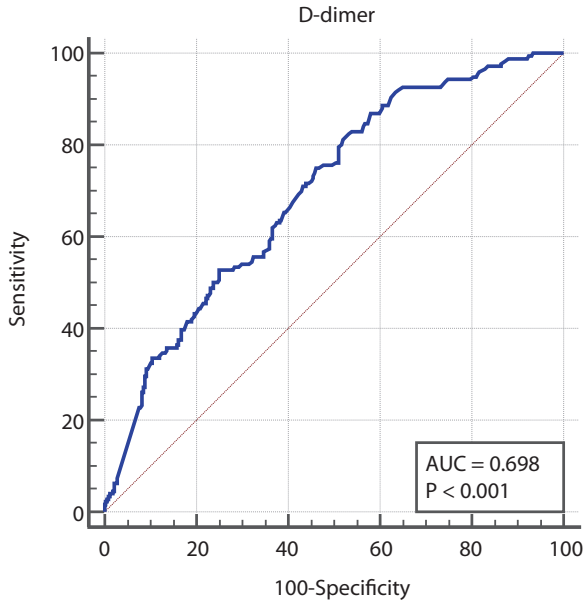

FIGURE 1. Receiver operating characteristic curve of D-dimer in predicting in-hospital mortality in patients with COVID-19; AUC — area under the curve

after lysis by thrombin, plasmin, and factor XIIIa enzymes [10]. Many studies have shown that D-dimer serves as a valuable marker of coagulation and fibrinolysis activation [11, 12]. It has been reported that a high D-dimer level can be used as a prognostic factor in the early period in severe COVID-19 cases [13].

In our study, it was determined that the patients admitted to the intensive care unit had higher D-dimer levels. We also concluded that a D-dimer level above 1020 ng/mL predicted in-hospital mortality with an AUC value of 0.698. In the literature, there are studies reporting thrombotic complications related to COVID-19 and suggesting that the D-dimer level can be used as a prognostic tool [14, 15]. Zhang et al. [9], evaluating the relationship between the D-dimer level and mortality in 343 patients with COVID-19, found the optimum cut-off value of this parameter in predicting mortality as 2.0 μg/mL, sensitivity as 92.3%, specificity as 83.3%, and determined that the relationship between D-dimer level and mortality was statistically significant. In a meta-analysis of 13 studies including a total of 3027 patients, Zheng et al. [16] compared a critically ill group and a non-critical group and reported a statistically significant correlation between the D-dimer level and the prognosis of the disease ($p < 0.00001$), noting that a D-dimer value of > 0.5 mg/L was associated with clinical worsening in patients with COVID-19. In a multicenter study, Zhou et al. [17] showed that a D-dimer level greater than 1 μg/mL at admission was a potential risk factor, and it had a statistically significant relationship with mortality. In another meta-analysis including 5350 patients, Huang et al. [18] reported a significant relationship between the D-dimer level and mortality, with the sensitivity being reported as 58% and specificity as 69% for a cut-off value of > 0.5 mg/L. Yao et al. [19], evaluating 248 COVID-19 cases, determined the optimum cut-off value of D-dimer as > 2.14 mg/L, sensitivity as 88.2%, and specificity as 71.3% in predicting mortality.

A meta-analysis of 100 studies found a strong association between D-dimer and COVID-19 progression, and researchers suggested that D-dimer should be evaluated early in predicting adverse outcomes in COVID-19 patients [20]. In another meta-analysis involving 14,862 COVID-19 patients, it was emphasized that increased D-dimer levels were associated with both mortality and complications [21]. In our study, we obtained findings consistent with the data reported by previous studies.

Having a retrospective design, our study has some limitations. In this single-center study, the patients' D-dimer levels were obtained by screening the hospital's electronic database, and those with unavailable D-dimer results were not included in the study, limiting the sample size.

CONCLUSIONS

In this study, it was concluded that patients with high D-dimer levels had a higher in-hospital mortality rate. In addition, it was observed that the patients admitted to the intensive care unit had higher D-dimer levels than those that did not require intensive care. Further studies with a larger sample size are needed to confirm the findings of our study.

Table 2. Predictive performance of D-Dimer in terms of mortality in patients with COVID-19

	AUC	Cut-off	Sensitivity	Specificity	LR+	LR-	PPV	NPV	Youden index
D-dimer	0.698 (0.655–0.738)	> 1.020	81.3	47.9	1.6	0.4	46.4	82.4	0.29

AUC — area under the curve; LR — likelihood ratio; PPV — positive predictive value; NPV — negative predictive value

Author contributions

Concept, design, supervision, materials, data: UDH; Analysis, literature search, writing, critical revision: UDH, MK.

Availability of data and materials

The authors agree to the conditions of the publication including the availability of data and materials in our manuscript.

Human rights

The principles outlined in the Declaration of Helsinki have been followed.

Informed consent

Written informed consent was not necessary because no patient data have been included in the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

Ethical approval

The study was approved by the ethical review board. (Kartal Dr. Lütfi Kırdar City Hospital- non-interventional clinical trials ethics committee, number: 2022/514/228/25 and date: 30/06/2022).

Written or verbal informed consent was not obtained from the patients because it was a retrospective study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

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