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# Mean serum D-dimer level to predict in-hospital mortality in COVID-19

Mert İlker Hayıroğlu[1], Vedat Çiçek[2], Şahhan Kılıç[2], Tufan Çınar[2]*

## SUMMARY

**OBJECTIVE:** The prognostic effect of the mean serum D-dimer levels, which was calculated from the first five days of hospitalization of the patients, has not been elucidated. This study aimed to evaluate the effect of mean D-dimer level about in-hospital mortality in patients hospitalized due to coronavirus disease-2019 (COVID-19) infection.

**METHODS:** In this observational retrospective study, we examined the in-hospital prognostic value of mean D-dimer [D-dimer$^{\text{first day}}$ +D-dimer$^{\text{third day}}$ +D-dimer$^{\text{fifth day}}$)/3 on 240 consecutive adult patients with COVID-19. Patients were stratified into tertiles according to their mean D-dimer starting from the lowest one. In-hospital mortality rates were compared between tertiles and the power of the mean D-dimer level was also presented by a receiver operating curve analysis.

**RESULTS:** After adjustment for confounding baseline variables, mean D-dimer in tertile 3 was associated with 4.2-fold hazard ratio of in-hospital mortality (odds ratio [OR] 4.2; 95% confidence interval [CI] 1.8–20.1, p<0.001). A receiver-operating curve analysis revealed that the optimal cutoff value of the mean D-dimer to predict in-hospital mortality was 779 µg/L with 77% sensitivity and 83% specificity (area under the curve [AUC] 0.87; 95%CI 0.81–0.94; p<0.001).

**CONCLUSION:** Patients with a higher mean D-dimer level should be followed-up more closely as they may be a candidate for a more aggressive treatment modality, such as biologic agents or convalescent plasma.

KEYWORDS: COVID-19. D-dimer. In-hospital mortality.

## INTRODUCTION

A newly defined 2019 coronavirus (SARS-CoV-2) has been declared as a pandemic by the World Health Organization (WHO) on March 2020[1]. Although there is no standard therapy worldwide in terms of anticoagulation following the diagnosis of SARS-CoV-2 infection, it has been already illustrated to activate procoagulation cascades especially in critically ill patients. As the pandemic becomes widespread over time, routinizing the treatment options and the prognostic factors to detect critically ill patients as early as possible becomes vital.

D-dimer has been presented as one of the most frequent and promptly elevated laboratory findings associated with coagulopathy in coronavirus disease 2019 (COVID-19) patients[2]. A strong synergy between SARS-CoV-2 infection and venous thromboembolism is a remarkable relation representative of the predictive value of D-dimer in these patients. The prevalence of venous thromboembolism has been reported to be 25% in patients with severe pneumonia due to SARS-CoV-2 infection[3]. On the contrary, high serum levels of D-dimer are not disease specific and are usually related to several medical circumstances such as infection, inflammation, and pregnancy[4].

[1]Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey
[2]Department of Cardiology, Haydarpasa Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey
*Corresponding author: drtufancinar@gmail.com
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Despite the high level of D-dimer which appears as a nonspecific marker, more than half of the patients who have serum D-dimer levels >3.0 μg/mL have a thrombotic complication necessitating imaging modalities for the etiologic investigation[5]. In COVID-19 era, D-dimer >0.5 μg/mL has been first reported as a prognostic indicator in a retrospective analysis with a large cohort from China[6]. Moreover, D-dimer levels were compared between the intensive care unit (ICU) and non-ICU patients showing a remarkable highness in the ICU patients[1,2]. However, there is very little evidence about the prognostic effect of D-dimer level follow-up during the index hospitalization period in COVID-19 patients.

Therefore, we hypothesized a new score calculated from the first-, third-, and fifth-day level of D-dimer to predict in-hospital prognosis. The purpose of this study was both to test the in-hospital mortality predictive value of mean D-dimer level and to draw the attention toward the anticoagulation treatment strategies in COVID-19 patients.

## METHODS

The consecutive 240 patients, who were either diagnosed with COVID-19 in our emergency department or referred to our hospital with the COVID-19 diagnosis, were included in our study retrospectively following their index hospitalization period. All of the patients enrolled in this study were hospitalized in the Sultan Abdulhamid Han Training and Research Hospital between March 2019 and May 2019. Patients were involved in the study if their D-dimer serum levels of first, third, and fifth days were obtained from the hospital database. If one of the D-dimer levels was missing among the first, third, or fifth day in their hospitalization period, the patients were excluded. The patients were also excluded if they were under anticoagulation treatment. The baseline characteristics, presenting symptoms, laboratory and computed tomography findings were attained from the hospital database. The treatment approach of the patients was determined according to the consensus between the attending physicians and the specialist of infectious and clinical microbiology in compliance with national ministry of health COVID-19 guidelines. The diagnosis of COVID-19 had two steps: (1) specific signs and symptoms or imaging findings in computed tomography consistent with COVID-19 and (2) the confirmation of active COVID-19 infection was provided with the real-time polymerase chain reaction (RT-PCR) test. The investigators first obtained approval of the study from the Turkish Ministry of Health Scientific Research Committee. The investigation was later approved by the Local Ethics Committee (approval number 2020/KK/132). Our study was conducted in compliance with the "Good Clinical Practice" guidelines of the Declaration of Helsinki as revised in 2008. There was no need for an informed consent as the study had an observational and retrospective design. Blood samples were gathered from the patients within 24 h of their admission to the hospital. The Sysmex XN 9000 hematology analyzers (Sysmex Corporation, Kobe, Japan) were used to analyze the complete blood count parameters. Beckman Coulter, Inc. kits and calibrators were used to perform biochemical measurements. Serum D-dimer levels were calculated via particle-enhanced immunoturbidimetric methods by using Roche Cobas 6000 c501 analyzer (Roche Diagnostics International AG, Rotkreuz, Switzerland). The reference range of D-dimer in our hospital is 0–500 μg/L. The mean serum D-dimer levels were calculated as follows: $(\text{D-dimer}^{\text{first day}} + \text{D-dimer}^{\text{third day}} + \text{D-dimer}^{\text{fifth day}})/3$. According to our hospital's approach to patients with COVID-19, patients with D-dimer levels >1000 μg/L were administered enoxaparin at anticoagulation doses. A single value >1000 μg/L was defined as the level for the start of anticoagulation.

In our study, in-hospital mortality was defined as the primary outcome. A trained physician evaluated the medical data of the patients and notified the patients with in-hospital mortality.

### Statistical analysis

In a first step, our study group was divided into tertiles according to their mean serum D-dimer levels calculated according to the definition in the method section. All of the tertiles included 80 patients. In a second step, baseline characteristics, admission symptoms, laboratory parameters, and pneumonia regions in the lungs were compared between these tertiles. Quantitative variables were presented as mean value ± standard deviation. Kolmogorov–Smirnov test was used for evaluation of normality. All continuous variables showed skewed distributions and these are compared using Kruskal–Wallis test. Categorical variables were presented as numbers and percentages. Analyses of categorical variables were performed by Pearson's chi-square test. Univariable and multivariable logistic regression analyses were performed to determine the independent predictors of in-hospital mortality other than serum D-dimer levels. Variables that could be a predictor of in-hospital mortality and with a significant *p*-value in Table 1 were entered into univariable analysis. Variables with a $p<0.05$ in univariable regression were included into binary logistic regression analysis. The results of regression analysis were presented as odds ratio (OR) with 95% confidence interval (CI). Two multivariable models were used: model I (unadjusted) and model II (adjusted). The variables covaried in model II were age, white blood cells, lactate dehydrogenase and lymphocytes,

Table 1. Baseline clinical characteristics, laboratory parameters, and pneumonia regions in the lungs of all patients.

| | Mean D-dimer level through index hospitalization period | | | |
|---|---|---|---|---|
| | T1, n=80 | T2, n=80 | T3, n=80 | p-value |
| Baseline characteristics | | | | |
| Age, years | 50.1±14.8 | 53.8±14.6 | 59.6±15.1 | 0.001 |
| Male gender, n (%) | 42 (52.5) | 43 (53.8) | 43 (53.8) | 0.983 |
| Hypertension, n (%) | 25 (31.3) | 30 (37.5) | 39 (48.8) | 0.071 |
| Diabetes mellitus, n (%) | 20 (25.0) | 15 (18.8) | 26 (32.5) | 0.135 |
| Insulin dependency, n (%) | 3 (3.8) | 2 (2.5) | 7 (8.8) | 0.158 |
| Hyperlipidemia, n (%) | 1 (1.3) | 3 (3.8) | 8 (10.0) | 0.033 |
| COPD, n (%) | 5 (6.3) | 8 (10.0) | 13 (16.3) | 0.121 |
| Coronary artery disease, n (%) | 3 (3.8) | 5 (6.3) | 14 (17.5) | 0.007 |
| Chronic renal failure, n (%) | 2 (2.5) | 3 (3.8) | 7 (8.8) | 0.158 |
| Atrial fibrillation, n (%) | 1 (1.3) | 1 (1.3) | 1 (1.3) | 1.000 |
| Cerebrovascular disease, n (%) | 0 (0.0) | 2 (2.5) | 2 (2.5) | 0.362 |
| Dementia, n (%) | 1 (1.3) | 1 (1.3) | 1 (1.3) | 1.000 |
| Cancer, n (%) | 0 (0.0) | 2 (2.5) | 5 (6.3) | 0.061 |
| Congestive heart failure, n (%) | 0 (0.0) | 2 (2.6) | 6 (7.5) | 0.028 |
| Smoking, n (%) | 10 (12.8) | 11 (13.8) | 6 (7.5) | 0.406 |
| Alcohol, n (%) | 12 (15.0) | 16 (20.0) | 13 (16.3) | 0.682 |
| Admission symptoms n (%) | | | | |
| Fever | 27 (33.8) | 45 (56.3) | 47 (58.8) | 0.002 |
| Cough | 46 (57.5) | 45 (56.3) | 44 (55.7) | 0.973 |
| Dyspnea | 10 (12.5) | 18 (22.5) | 22 (27.5) | 0.059 |
| Diarrhea | 3 (3.8) | 3 (3.8) | 6 (7.5) | 0.454 |
| Myalgia | 25 (31.6) | 27 (33.8) | 26 (32.5) | 0.960 |
| Weakness | 28 (35.0) | 25 (31.3) | 21 (26.3) | 0.485 |
| Asymptomatic | 13 (16.3) | 5 (6.3) | 3 (3.8) | 0.012 |
| Laboratory parameters | | | | |
| White blood cells, cells/μL | 6.0±2.4 | 5.8±2.7 | 7.4±4.3 | 0.070 |
| Lymphocytes | 1.5±0.7 | 1.5±0.7 | 1.1±0.7 | <0.001 |
| Platelets, cells/μL | 204.6±62.1 | 190.8±54.9 | 207.2±73.8 | 0.408 |
| Hemoglobin, g/dL | 13.4±1.7 | 13.2±1.8 | 13.0±1.6 | 0.192 |
| Glucose, mg/dL | 106.6±28.2 | 117.3±41.9 | 126.2±62.9 | 0.169 |
| Lactate dehydrogenase, U/L | 449.8±261.0 | 452.1±137.3 | 634.3±594.7 | <0.001 |
| Alanine aminotransferase, U/L | 36.3±27.0 | 35.7±27.2 | 39.1±45.0 | 0.298 |
| Aspartate aminotransferase, U/L | 28.4±15.8 | 26.6±13.5 | 32.0±30.7 | 0.729 |
| Creatinine, mg/dL | 0.9±0.2 | 0.9±0.2 | 1.0±0.4 | 0.074 |
| Potassium, mEq/L | 4.2±0.3 | 4.1±0.3 | 4.2±0.5 | 0.264 |
| Sodium, mEq/L | 137.1±3.8 | 136.8±3.7 | 136.3±3.9 | 0.317 |
| D-dimer, μg/L$^{\text{first day}}$ | 213.0±72.3 | 372.9±184.3 | 1630.1±1682.0 | <0.001 |
| D-dimer, μg/L$^{\text{third day}}$ | 213.0±71.5 | 383.8±114.5 | 1127.7±963.0 | <0.001 |
| D-dimer, μg/L$^{\text{fifth day}}$ | 279.9±61.3 | 390.5±137.9 | 1405.2±1020.3 | <0.001 |
| Mean D-dimer, μg/mL | 247.4±28.3 | 382.4±86.4 | 1387.6±957.1 | <0.001 |
| C-reactive protein, mg/dL | 35.3±46.5 | 50.0±68.5 | 75.8±74.8 | <0.001 |
| Albumin, g/L | 42.2±6.0 | 40.3±5.5 | 37.0±6.3 | <0.001 |
| Troponin, ng/L | 10.9±15.4 | 11.3±17.8 | 93.7±535.4 | <0.001 |
| Pneumonia region in the lungs | | | | |
| Bilateral | 57 (71.3) | 64 (80.0) | 60 (75.0) | 0.435 |
| Left | 16 (20.0) | 12 (15.0) | 9 (11.3) | 0.307 |
| Right | 7 (8.8) | 4 (5.0) | 11 (13.8) | 0.157 |

Continuous variables were presented as mean ± Standard Deviation; COPD: chronic obstructive pulmonary disease.

and troponin. The cutoff values of mean serum D-dimer levels and in-hospital mortality with the highest sensitivity and specificity were calculated by nonparametric receiver-operating characteristics (ROC) curve analysis. Data were analyzed by using the Statistical Package for Social Sciences (SPSS) software program, version 24.0 (IBM, Armonk, New York).

## RESULTS

Table 1 presents the baseline features, laboratory parameters, and pneumonia region in the lungs stratified by tertiles. This retrospective study included 240 patients (mean age 54.5±15.3; 53.3% male). The patients in tertile 1 had a mean D-dimer level 181–284 µg/L, tertile 2 286–559 µg/L, and tertile 3 570–4380 µg/L through their index hospitalization period. Tertile 3 had notably older, and had a higher frequency of hyperlipidemia, coronary artery disease, and congestive heart failure compared to other tertiles. According to their admission symptoms, patients stratified in tertile 1 had a higher frequency of fever and were more frequently hospitalized in an asymptomatic manner compared to other tertiles. Total lymphocyte count and the serum level of albumin on admission were remarkably lower in tertile 3. The levels of lactate dehydrogenase, D-dimer$^{\text{first day}}$, D-dimer$^{\text{third day}}$, D-dimer$^{\text{fifth day}}$, mean D-dimer, C-reactive protein, and troponin were statistically higher in tertile 3. The prevalence of pneumonia region in the lungs did not differ between the tertiles. Univariable analysis excepting D-dimer levels was implemented and revealed that hypertension, coronary artery disease, age, diabetes mellitus, chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, white blood cells, lymphocytes, lactate dehydrogenase, troponin, albumin, and C-reactive protein as predictors of in-hospital mortality. In the multivariable analysis, white blood cells (OR 1.605; 95%CI 1.287–2.001), age (OR 1.091; 95%CI 1.010–1.179), lymphocytes (OR 0.437; 95%CI 0.195–0.978), lactate dehydrogenase (OR 1.003; 95%CI 1.001–1.006), and troponin (OR 1.045; 95%CI 1.002–1.093) were appeared as the independent indicators to have an effect on in-hospital mortality (Table 2). The logistic regression models for in-hospital mortality by mean D-dimer level through index hospitalization period tertile are presented in Table 3. In-hospital mortality has the higher rates at tertile 3 and that had 6.9 times higher than tertile 1, which was determined as the reference group. The relevancy slightly decreased after the adjustment for the confounders revealed to predict in-hospital mortality; tertile 3 had 4.2 times higher rates of in-hospital mortality compared to tertile 1. There were no major bleeding complications among our study population during hospitalization period.

A ROC analysis revealed that the optimal cutoff value of the mean D-dimer to predict in-hospital mortality was 779 µg/L with 77% sensitivity and 83% specificity (AUC 0.87; 95%CI 0.81–0.94; p<0.001) (Figure 1).

Table 2. Univariable predictors and multivariable model for in-hospital mortality.

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | p-value | OR | 95%CI | p-value | OR | 95%CI |
| Age | <0.001 | 1.098 | 1.055–1.142 | 0.027 | 1.091 | 1.010–1.179 |
| Hypertension | 0.017 | 3.019 | 1.214–7.509 | – | – | – |
| Diabetes mellitus | 0.028 | 2.729 | 1.114–6.684 | – | – | – |
| COPD | <0.001 | 6.349 | 2.351–17.148 | – | – | – |
| Coronary artery disease | <0.001 | 8.327 | 2.992–23.175 | – | – | – |
| Chronic renal failure | 0.001 | 8.866 | 2.541–30.928 | – | – | – |
| Congestive heart failure | 0.014 | 6.663 | 1.477–30.053 | – | – | – |
| White blood cells | <0.001 | 1.475 | 1.296–1.679 | <0.001 | 1.605 | 1.287–2.001 |
| Lymphocytes | 0.009 | 0.282 | 0.110–0.725 | 0.044 | 0.437 | 0.195–0.978 |
| Lactate dehydrogenase | 0.002 | 1.002 | 1.001–1.004 | 0.012 | 1.003 | 1.001–1.006 |
| Troponin | <0.001 | 1.052 | 1.029–1.076 | 0.048 | 1.045 | 1.002–1.093 |
| Albumin | <0.001 | 0.844 | 0.780–0.913 | – | – | – |
| C-reactive protein | <0.001 | 1.011 | 1.006–1.016 | – | – | – |

CI: confidence interval; OR: odds ratio, COPD: chronic obstructive pulmonary disease. All clinical relevant parameters were included in the model. Only parameters that reached statistical significance at univariable analysis were given in the leftmost column.

Table 3 Logistic regression models for in-hospital mortality by mean D-dimer level through index hospitalization period tertile.

| | Mean D-dimer level through index hospitalization period | | |
|---|---|---|---|
| | T1, n=80 | T2, n=80 | T3, n=80 |
| In-hospital mortality | | | |
| Number of patients | 0 | 3 | 19 |
| Case rate, % | 0.0 | 3.8 | 23.8 |
| In-hospital mortality, OR (95% CI) | | | |
| Model 1: unadjusted | 1[Reference] | 4.7 (1.5–8.1) | 7.9 (2.2–28.2) |
| Model 2: adjusted for all covariates[a] | 1[Reference] | 2.8 (1.2–6.9) | 5.2 (1.8–20.1) |

CI: confidence interval; OR: odds ratio. [a]Only parameters that reached statistical significance at multivariable analysis were age, white blood cells, lactate dehydrogenase and lymphocytes and troponin.

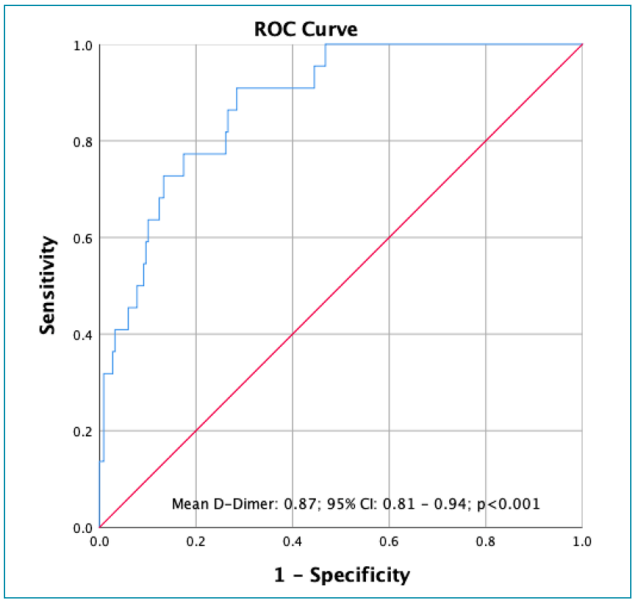


Figure 1. Receiver-operating characteristic curve analysis of mean D-dimer levels for in-hospital mortality.

## DISCUSSION

This investigation is the pilot study representing the mean serum D-dimer level to estimate in-hospital mortality in hospitalized patients with COVID-19 infection. Mean serum D-dimer level, which is easily attainable from the first five days data of hospitalization due to COVID-19, was proved to have both high sensitivity and specificity to predict in-hospital mortality remarking the high procoagulant nature of SARS-CoV-2 infection.

D-dimer is identified as the soluble plasmin-mediated breakdown product of fibrin which is triggered following the initiation of coagulation and fibrinolysis cascade[1]. D-dimer has been already appeared as one of the criteria of disseminated intravascular coagulation in addition to its use for excluding thrombotic events[2]. Before the pandemic of COVID-19, D-dimer within the normal range has been already shown to have a higher sensitivity but remarkably lower specificity to predict thromboembolic circumstances. However, clinicians are accustomed to experience higher levels of serum D-dimer in hospitalized patients in the COVID-19 era, thereby bringing into prominence the follow-up serum D-dimer levels. Admission serum D-dimer level has been demonstrated to be notably higher in non-survivors compared to survivors in several investigations with different cohorts with COVID-19[1,7-11]. Moreover, D-dimer has been associated with COVID-19 disease severity as higher levels of serum D-dimer have been defined as an indicator of acute respiratory distress syndrome[9]. As long as COVID-19 has been strongly associated with procoagulation cascades which have been repeatedly confirmed, the follow-up serum D-dimer levels gain serious importance regarding in-hospital outcomes[12]. Therefore, it is extremely reasonable that higher mean serum D-dimer level has been linked to an increase in in-hospital mortality in hospitalized patients due to COVID-19.

Anticoagulation medical preferences and doses are still the question of debate in the COVID-19 era. Heparin treatment has been found to be related to lower mortality in severe SARS-CoV-2 infection[13]. Even though heparin treatment also has an additional anti-inflammatory effect, the main benefit in the aforementioned investigation is considered to be secondary to the anti-coagulation properties of the heparin. The main worth of notice is the beneficiary effects of heparin occurs if the serum D-dimer levels exceed sixfold of the upper limit of normal[13]. High levels of serum D-dimer and fibrinogen have been indicated as signs of the initiation of the procoagulation cascade; the disease severity may be manifested by the increase

in serum D-dimer level as clearly presented in our study. In the pandemics such as COVID-19, it is invaluable to determine prognostic factors in order to specify the disease severity before the occurrence of complications. The beginning treatment strategies such as biologic agents, anticoagulation, or convalescent plasma may dependently change to a patient-based approach, which may have a role to minimize disease-associated vital complications. As a result, the mean D-dimer level appears to have a substantial role to predict in-hospital mortality in hospitalized patients with COVID-19.

## STUDY LIMITATIONS

This study has several limitations. The investigation was a single-center, retrospective, and observational study; therefore, our study has a slight limitation for generalizability. There may be a possible presence of unmentioned residual confounding factors, which may have an effect on the outcomes of the investigation.

## CONCLUSION

The present investigation showed that mean D-dimer level obtained during the first five days of hospitalization was an independent predictor of in-hospital mortality in COVID-19 patients.

## AUTHORS' CONTRIBUTION

**MİH**: Conception, Formal Analysis, Writing – Review & Editing. **TÇ**: Supervision, Writing – Review & Editing. **VÇ**: Data Curation Funding Acquisition, Resources. **ŞK**: Data Curation, Funding Acquisition, Resources.

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