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CLINICAL STUDY

# The prognostic role of D-dimer in hospitalized COVID-19 patients

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**ABSTRACT**

INTRODUCTION: In COVID-19 patients, the determination of the relationship between elevated D-dimer level and prognosis and the determination of thrombosis formation in the early stages of the disease are very important. The aim of this study was to investigate the prognostic role of D-dimer levels based on presentation in patients hospitalized with the diagnosis of COVID-19.

METHOD: The study was conducted on patients hospitalized with the diagnosis of laboratory-confirmed COVID-19 between March 11 and April 20, 2020. Patients with diseases that could have caused an increase in D-dimer were excluded from the study.

RESULTS: The evaluation was made across a total of 1,669 patients, comprising 782 (46.9 %) females and 887 (53.1 %) males. The effects of D-dimer, CRP, ferritin, and troponin on mortality were evaluated with Enter Logistic Regression Analysis, and the model was found to be significant, with an explanatory coefficient of the model at a very good level of 91.3 %. The D-dimer scores were determined to be higher in patients who did not survive. The risk of mortality was seen to be 7.325-fold higher in cases with D-dimer measurement ≥0.5.

CONCLUSION: The study results showed that the D-dimer test was an independent risk factor showing mortality in COVID-19 patients *(Tab. 6, Ref. 27)*. Text in PDF *www.elis.sk*

KEY WORDS: D-dimer, SARS-CoV-2, mortality.

## Introduction

Coronavirus disease 2019 (Covid-19) caused by the novel coronavirus, a severe acute respiratory syndrome virus (SARS-CoV-2), first emerged in Wuhan, China in December 2019, and in a short time affected the whole world. The disease was declared a pandemic and millions of people worldwide have become ill while the number of deaths has exceeded one million (1).

The disease is characterized by various pathophysiological disorders affecting systematic circulation, such as pulmonary inflammation and microthrombosis (2–4). Although the incidence of thrombosis has not yet been clearly determined in patients diagnosed with Covid-19, D-dimer, which is the most important biomarker of thrombosis, has been observed to be elevated in approximately 50 % of patients (5, 6). Plasma D-dimers are formed as a result of fibrin destruction of the endogenous fibrinolytic system. In contrast to fibrin degradation products derived from fibrinogen and fibrin, D-dimers are specific cross-linked fibrin derivatives and are laboratory markers showing coagulation activity (7). D-dimer levels increase in every situation where fibrin is formed and destroyed by plasmin. D-dimer levels are elevated in conditions such as pulmonary emboli, peripheral vascular diseases, deep vein thrombosis, acute stroke, pregnancy, haemolytic crises, malignancy, surgery, and chronic renal failure (8).

The determination of the relationship between elevated D-dimer and prognosis in Covid-19 patients and the determination of thrombosis formation with a biomarker in the early stages of the disease are very important. The aim of this study was to investigate the prognostic role of D-dimer levels on presentation in patients hospitalized with a diagnosis of Covid-19.

## Method

The study was conducted on patients hospitalized with a laboratory-confirmed diagnosis of Covid-19 in Bakirköy Dr Sadi Konuk Training and Research Hospital between March 11 and April 30, 2020. Patients with acute coronary disease, peripheral vascular disease, deep vein thrombosis, pulmonary emboli, acute stroke, pregnancy, sickle cell anaemia, haemolytic crises, malignancy, surgical interventions, or chronic renal failure were excluded from the study.

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**Tab. 1. Demographic data and disease characteristics of the patients.**

| | | n (%) |
|---|---|---|
| Age (years) | Min–Max (Median) | 16–96 (56) |
| | Mean ± SD | 55.82±16.74 |
| Gender | Female | 782 (46.9) |
| | Male | 887 (53.1) |
| Presence of chronic diseases | Diabetes | 317 (19.0) |
| | Hypertension | 335 (20.1) |
| | COPD | 66 (4.0) |
| | CAD | 172 (10.3) |
| WHO disease severity | Mild | 33 (2.0) |
| | Moderate | 1194 (71.5) |
| | Severe | 306 (18.3) |
| | Critical | 136 (8.1) |
| Pneumonia severity | None | 50 (3.0) |
| | Mild | 596 (35.7) |
| | Moderate | 690 (41.3) |
| | Severe | 234 (14.0) |
| | Atypical | 99 (5.9) |
| Length of stay in hospital (days) | Min–Max (Median) | 1–90 (8) |
| | Mean ± SD | 9.89±7.61 |
| Length of stay in intensive care unit | No | 1494 (89.5) |
| | Yes | 175 (10.5) |
| Mortality status | Survivor | 1526 (91.4) |
| | Non-survivor | 143 (8.6) |

•more than one disease present. COPD – chronic obstructive pulmonary disease, CAD – coronary artery disease

**Tab. 2. Distribution of laboratory findings.**

| | n | Min–Max (Median) | Mean±SD |
|---|---|---|---|
| AST | 1658 | 7–933 (30) | 39.47±45.44 |
| ALT | 1662 | 3–818 (22) | 31.39±38.23 |
| Troponin | 1638 | 0.1–898 (5) | 20.23±69.62 |
| Creatinine | 1668 | 0.2–13.7 (0.8) | 0.93±0.77 |
| D–dimer | 1669 | 0–9.8 (0.3) | 0.78±1.35 |
| Fibrinogen | 1541 | 43–968 (472) | 483.36±123.54 |
| Leukocytes | 1667 | 0.5–38.5 (6.1) | 7.26±4.16 |
| Hemoglobin | 1667 | 1.5–18 (12.5) | 12.44±1.87 |
| Lymphocytes | 1667 | 0.1–12.9 (1.3) | 1.49±0.86 |
| Thrombocytes | 1668 | 8–841 (204) | 220.53±89.83 |
| CRP | 1664 | 0–443.9 (33) | 63.35±72.60 |
| Ferritin | 1585 | 2–12264 (154.7) | 313.52±585.98 |

Approval for the study was granted by the Ethics Committee of Bakirköy Dr Sadi Konuk Training and Research Hospital (decision no 2020/10 dated 18.05.2020).

The demographic data of the patients, physical examination findings, and laboratory and radiological examination results were obtained retrospectively from the hospital records system. The patients were separated into 4 groups according to disease severity as defined by the World Health Organization (WHO) (9). According to these definitions, the diagnostic criteria are as follows: Mild cases: mild clinical symptoms and no radiological signs of pneumonia; Moderate cases: fever, cough, dyspnoea, rapid shallow breathing but no signs of severe pneumonia including $SpO_2 \geq 90$ % in room air or radiological signs of pneumonia; Severe cases: fever, cough, dyspnoea, rapid breathing plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or $SpO_2 < 90$ % in room air and radiological signs of pneumonia; Critical cases: respiratory failure, shock or multiorgan dysfunction.

Four typical categories of pneumonia were classified by means of thoracic tomography, namely mild, moderate, severe and atypical At the time of presentation, the D-dimer, full blood count, c-reactive protein (CRP), routine biochemical and microbiological test results of the patients were recorded.

*Biochemical analysis*

Internal quality control and external quality assurance were applied to monitor the accuracy and precision of tests. All venous blood samples were collected by venepuncture. All tests were performed within 2 hours of blood collection. D-Dimer levels were determined using Beckman Coulter AU5800 clinical chemistry analyser (Beckman Coulter, Brea, CA, USA). The D-dimer laboratory reference value was ≥ 0.5 mg/L.

*Statistical analysis*

Data obtained in the study were analysed statistically using NCSS software (Number Cruncher Statistical System, Kaysville, UT, USA). Descriptive statistical methods were used in the evaluations (mean ± standard deviation (SD), median, minimum and maximum values, numbers and percentage). The conformity of quantitative data to normal distribution was assessed with the Kolmogorov-Smirnov test, Shapiro-Wilk test and graphic methods. The Student's t-test was applied in the comparison of two groups of quantitative data showing normal distribution and the Mann-Whitney U-test was used for data not showing normal distribution. In the comparison of qualitative data, the Pearson Chi-square test was used. For the determination of cut-off values for parameters, diagnostic screening tests (sensitivity, specificity, PPV, NPV) and ROC curve analysis were used. Logistic regression analysis was applied in the multivariate analysis. A value of $p < 0.05$ was accepted as statistically significant.

## Results

Evaluation was made of a total of 1,669 patients, comprising 782 (46.9 %) females and 887 (53.1 %) males with mean age of 58.82 ± 16.74 years (range, 16–96 years). The demographic data, disease characteristics, and laboratory findings of the patients are shown in Tables 1 and 2.

Evaluations of the laboratory findings according to mortality are shown in Table 3. A statistically significant difference was determined between the cases in respect of D-dimer, AST, troponin, creatinine, leukocytes, CRP, and ferritin measurements according to mortality, while the measurements of the non-surviving cases were found to be higher ($p = 0.001$, $p < 0.001$). The haemoglobin and lymphocyte measurements of the non-surviving cases were determined to be statistically significantly lower than those of the surviving cases ($p = 0.001$, $p < 0.001$).

No statistically significant differences were determined in ALT, fibrinogen, and thrombocyte measurements of the cases according to mortality ($p > 0.05$).

**Tab. 3. Evaluation of the laboratory findings according to mortality.**

| | | Survivor (n=1526) | Non–survivor (n=143) | |
|---|---|---|---|---|
| AST | Min–Max (Median)<br>Mean ± SD | 8–629 (29)<br>37.26±36.30 | 7–933 (40)<br>63.44±97.96 | [c]**0.001**** |
| ALT | Min–Max (Median)<br>Mean ± SD | 3–819 (22)<br>31.00±37.14 | 5–439 (22)<br>35.60±48.40 | [c]**0.967** |
| Troponin | Min–Max (Median)<br>Mean ± SD | 0.1–866 (5)<br>14.81±49.05 | 2–898 (18)<br>77.86±165.23 | [c]**0.001**** |
| Creatinine | Min–Max (Median)<br>Mean ± SD | 0.2–13.7 (0.8)<br>0.88±0.64 | 0.2–11 (1)<br>1.51±1.48 | [c]**0.001**** |
| D-dimer | Min–Max (Median)<br>Mean ± SD | 0–8.6 (0.3)<br>0.66±1.16 | 0–9.8 (1.2)<br>2.12±2.26 | [a]**0.001**** |
| Fibrinogen | Min–Max (Median)<br>Mean ± SD | 43–946 (472)<br>481.12±119.09 | 43–968 (500)<br>507.62±162.93 | [c]**0.072** |
| Leukocytes | Min–Max (Median)<br>Mean ± SD | 2.1–33.7 (6)<br>6.95±3.75 | 0.5–38.5 (9)<br>10.55±6.43 | [c]**0.001**** |
| Hemoglobin | Min–Max (Median)<br>Mean ± SD | 1.5–18 (12.6)<br>12.52±1.81 | 4.9–17.4 (11.5)<br>11.52±2.23 | [a]**0.001**** |
| Lymphocytes | Min–Max (Median)<br>Mean ± SD | 0.2–12.9 (1.4)<br>1.52±0.84 | 0.1–6.5 (1.1)<br>1.26±0.98 | [c]**0.001**** |
| Thrombocytes | Min–Max (Median)<br>Mean ± SD | 8–841 (204)<br>220.34±86.36 | 30–664 (202)<br>222.50±121.19 | [a]**0.836** |
| CRP | Min–Max (Median)<br>Mean ± SD | 0–443.9 (30)<br>57.79±66.53 | 0.1–440 (107)<br>122.39±102.50 | [c]**0.001**** |
| Ferritin | Min–Max (Median)<br>Mean ± SD | 2–4503 (146.8)<br>267.76±379.35 | 8.2–12264 (404.5)<br>797.15±1486.66 | [c]**0.001**** |

[a]Student's t-test, [c]Mann Whitney U-test, ** p < 0.01

When the effects of D-dimer, CRP, ferritin, and troponin on mortality were evaluated with Enter Logistic Regression analysis (Tab. 4), the model was found to be significant, and the explanatory coefficient of the model at 91.3 % was seen to be at a very good level. The ODDS value of the effect of D-dimer at and above the laboratory reference value had a 4.332-fold effect on mortality (95% CI: 2.83–6.63), and the CRP value ≥ 62 had an ODDS ratio of 1.898-fold (95% CI: 1.258–2.865). An increase by one unit in troponin increased the effect on mortality with an ODDS ratio of 1.004–fold (95% CI: 1.00–1.01). An increase by one unit in ferritin increased the effect on mortality with an ODDS ratio of 1.001-fold (95% CI: 1.00–1.00).

**Tab. 4. The logistic regression analysis results of the factors with an effect on mortality.**

| | p | ODDS | 95% C.I. ODDS | |
|---|---|---|---|---|
| | | | Lower | Upper |
| D-dimer (≥ 0.5) | 0.0001** | 4.332 | 2.833 | 6.626 |
| CRP | 0.002** | 1.898 | 1.258 | 2.865 |
| Troponin | 0.0001** | 1.004 | 1.002 | 1.006 |
| Ferritin | 0.0001** | 1.001 | 1.001 | 1.001 |

*p<0.05 **p<0.01

*Determination of the cut-off value for D-dimer according to mortality*

In cases of patients who died, the D-dimer scores were determined to be higher. From this significance, the cut-off point for D-dimer was calculated. ROC analysis was used in the determination of the cut-off point according to mortality (Tab. 5).

*Determination of the cut-off value for D-dimer measurements according to mortality*

The cut-off point for the measurement of D-dimer according to mortality was determined to be ≥ 0.5, with sensitivity of 72.73 %, specificity of 73.3147 %, positive predictive value (PPV) of 20.35 %, negative predictive value (NPV) of 96.63 %, and accuracy of 73.26 %. The area under the curve (AUC) in the ROC curve was determined to be 77.0 % at 2.3 % standard error (Tab. 5).

A statistically significant correlation was determined between the 0.5 cut-off value for D-dimer and mortality (p = 0.001, p < 0.001) (Tab. 6). In cases with D-dimer ≥ 0.5, the risk of death was 7.325-fold higher. The ODDS ratio for the D-dimer measurement was 7.325 (95% CI: 4.984–10.766) (Tab. 5).

## Discussion

The prognostic value of D-dimer is important in infections. Higher mortality rates have been shown in patients with sepsis with high D-dimer levels on presentation (10). Similarly, it has been reported that high D-dimer levels may be helpful in the prediction of the severity of community-acquired pneumonia (11).

The results of this study showed that the D-dimer level was an independent risk factor for Covid-19 mortality, and in cases with D-dimer measured at ≥ 0.5 mg/L, the risk of mortality was 7.325-fold greater. In other mortality studies, the cut-off value has been found to be ≥ 0.5mg/L (12–14), 1 mg/L, and 2 mg/L (15, 16).

**Tab. 5. Diagnostic screening tests and ROC curve results for D-dimer measurements according to mortality.**

| | Diagnostic Scan | | | | | ROC Curve | | p |
|---|---|---|---|---|---|---|---|---|
| | Cut-off value | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Area | 95% confidence interval | |
| D-dimer | ≥0.5 | 72.73 | 73.31 | 20.35 | 96.63 | **0.770** | 0.726-0.814 | **0.001**** |

**p<0.01

**Tab. 6. The relationships between the cut-off value of D-dimer measurement and mortality.**

| | | Mortality (-) | | Mortality (+) | | [b]p |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| D-dimer | **<0.5** | 1118 | 73.3 | 39 | 27.3 | **0.001**** |
| | **≥0.5** | 407 | 26.7 | 104 | 72.7 | |

[b]Pearson Chi-square Test, **p<0.01

Unlike in previous studies, patients were excluded from the current study if they had any other disease which could have caused an elevation in D-dimer.

In a meta-analysis that evaluated the prognostic role of D-dimer in patients infected with Covid-19, the analysis results showed that D-dimer levels in patients with severe Covid-19 infection and in those who died were higher than in non-severe cases and survivors. It was determined that patients with high D-dimer levels were at greater risk of developing severe Covid-19 infection than those with normal D-dimer levels and were at greater risk of all-cause mortality (17).

A high D-dimer level is one of the abnormal laboratory parameters found in patients with Covid-19 infection. Information about relatively widespread clotting disorders in Covid-19 patients increases especially in severe cases. SARS-CoV-2 infection seems to cause hypercoagulation in the blood, because most patients have been reported to have a high D-dimer level and this shows a gradual increase associated with progression of the disease (18, 19). This can be explained by excessive activation of thrombocytes and clotting cascade and then by the accumulation of intra-alveolar fibrin. Therefore, there is a prothrombotic response that attempts to prevent widespread alveolar damage and leakage of the infectious agent into the blood circulation, but this effect may cause pulmonary endothelial damage and formation of pulmonary microthrombi which have harmful effects (20).

Consistent with previous studies, the results of the current study showed that CRP, troponin and ferritin tests were independent risk factor markers for mortality in Covid-19 (21–26).

In conclusion, the results of this study showed that the D-dimer test was an independent risk factor showing mortality in Covid-19 patients, while the risk of mortality was 7.325-fold higher in cases when its value was ≥ 0.5 mg/L. As the cut-off value for poor prognostic measurement of D-dimer is 1mg/L in the blood tests in line with the hospitalization criteria in Turkey (27), whereas the determination of an increase in mortality that is > 7-fold at > 0.5mg/L as is the case in this study suggests that the D-dimer cut-off value should be revised in the hospitalization criteria in Turkey.

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