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D-dimer levels and lymphocyte counts as prognostic and predictive factors in patients with COVID-19

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ABSTRACT

Objective: Coronavirus Disease 2019 (COVID-19) is characterized by high fever, sudden developing respiratory distress, and radiological findings failing to respond to conventional treatments. The purpose of this study is to identify the association of D-dimer levels and lymphocyte counts with poor prognosis and to predict the clinical course in patients with COVID-19.

Methods: A total of 118 hospitalized adult patients diagnosed with COVID-19 were included in the study. According to the National Institutes of Health (NIH) COVID-19 treatment guidelines, patients were divided into two groups with severe disease (n= 26) and non-severe (n= 92) disease. Detected at the time of diagnosis, D-dimer levels and lymphocyte counts were compared between severe and non-severe COVID-19 patient groups. Distinctive performance analysis of these values was performed, and cut-off values were determined.

Results: The mean age of patients was 63±7 years (range 42-80 years), and 63 (53.4 %) were female. The lymphocyte count was lower ($p < 0.001$), and D-dimer was higher in patients with severe COVID-19 compared to non-severe patients ($p < 0.001$). D-dimer's cut-off point when the sum of specificity and sensitivity is maximized was 2 mg/L (sensitivity, 0.731; specificity, 0.913), and 1500/mm3 was for lymphocyte count (sensitivity, 0.692; specificity, 0.609). Lymphocyte count and D-dimer had a significant discrimination power (AUC: 0.745 [95 CI: 0.644 - 0.846], AUC: 0.928 [95% CI: 0.879 - 0.978] respectively, $p < 0.0001$).

Conclusion: The lymphocyte value of $\leqslant$ 1500/mm3 and D-dimer value of $\geqslant$ 2 mg/L can be used in the early determination of patients with poor prognosis in COVID-19. Using these cut-off values for D-dimer and lymphocyte count will help predict prognosis and make rapid treatment decisions in patients with COVID-19.

Keywords: COVID-19, prognosis, D-dimer, lymphocyte

Research Article

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INTRODUCTION

In December 2019, it was revealed that a novel coronavirus-related pneumonia cases were observed in Wuhan, China. It resulted in an epidemic spreading all over China, followed by an increasing number of cases in other countries (1). The International Virus Taxonomy Committee Coronavirus Working Group suggested name this virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). On January 30, 2020, the World Health Organization (WHO) declared the epidemic as a global emergency (3). In February 2020, the WHO designated the disease as COVID-19, which refers to Coronavirus Disease 2019 (4). The disease is characterized by high fever, normal or decreased white blood cells, lymphopenia, sudden developing respiratory distress, and radiological findings (1). In the early stages of the disease, severe symptoms of acute respiratory failure occur. Some patients develop acute respiratory distress syndrome (ARDS) and other serious complications, followed by multiple organ failure (5).

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Severe COVID-19 is often complicated by coagulopathy, and disseminated intravascular coagulation (DIC) is detected in most deaths (**6**). The SARS-CoV-2 has not been shown to have specific procoagulant effects. However, it is considered that coagulation test abnormalities in patients infected with SARS-CoV-2 are likely to develop as a result of the severe inflammatory response (**7**). COVID-19 has been reported to be associated with hemostatic abnormalities and significantly higher D-dimer levels in patients (**8**). Excessive inflammatory response, increased proinflammatory cytokines and acute-phase responses cause a life-threatening condition called cytokine storm characterized by persistent fever. Abnormalities in some laboratory values (such as lymphocyte count) are associated with this profile (**9**). In this study, the association between D-dimer and lymphocyte count of patients with COVID-19 and poor prognosis has been investigated.

MATERIAL AND METHODS

The objective of this study is to identify factors related to thromboembolism and poor prognosis in patients with COVID-19, predict the clinical course and develop treatment strategies to prevent poor prognosis.

Study design: A total of 118 hospitalized adult patients (63 female, 55 male) diagnosed with COVID-19 were included in the study (laboratory-confirmed cases, SARS-CoV-2 RNA detected by molecular method). Patients under 18 years of age, patients with comorbid diseases (including those with autoimmune and hematological diseases), those who are pregnant, a history of thromboembolic events, those using anticoagulant and/or antiaggregant treatment for any reason, and those receiving corticosteroid treatment were excluded from the study **(Figure1)**. According to the National Institutes of Health (NIH) COVID-19 Treatment Guidelines, patients with COVID-19 were divided into two groups as patients with severe disease (1- Hypoxia presence: Oxygen saturation $\leqslant$ 93% on room air or PaO_2 / FiO_2 <300. 2- Tachypnea (respiratory rate> 30 breaths per minute) or respiratory distress. 3- lung infiltrates> 50% on chest imaging) and with non-severe disease (mild or moderate) (10). In consideration of this classification, 26 patients were included in the severe COVID-19 group, while 92 were included in the non-severe group. D-dimer level and lymphocyte count values were compared between severe and non-severe COVID-19 patient groups. Distinctive performance analysis of the values that were significantly different between the groups was performed, and cut-off values were determined.

Laboratory Analysis: Hemogram parameters and D-dimer levels were reviewed during the hospitalization process. Hemogram analysis was performed with Sysmex XN-1000 (Sysmex, Kobe, Japan). Reference range for lymphocyte count was 1260-3350 cell/mm3. D-dimer analyzes were performed with Siemens BCS XP (Siemens, Marburg, Germany). The reference range for D-dimer was 0-2 mg/L.

Settings: The study was conducted in patients with COVID-19 hospitalized in the University of Health Sciences, Konya Training and Research Hospital, Infectious Diseases and Clinical Microbiology Service and General Intensive Care Unit, located in an area with a high prevalence of COVID-19, is accepted as a reference center for COVID-19 care.

Ethical Approval: The study was approved by the Local Ethics Committee of University of Health Sciences, Konya Training and Research Hospital (decision no: 08.05.2020/38-09) and the study was conducted according to the Declaration of Helsinki 1975.

Statistical Analysis

SPSS version 22.0 statistical package software (IBM Corp., Armonk, NY, United States) was used for statistical analyses. Continuous variables are demonstrated as mean±standard deviation, median (min-max), and categorical variables as numbers and percentages. Kolmogorov–Smirnov test was used for evaluating the normality of distribution. When parametric test assumptions are provided, Independent-Samples T-Test and when parametric test assumptions are not provided, Mann-Whitney U test were used to compare independent group differences. The chi-square test was performed to compare the study groups in terms of categorical variables. ROC analysis method was used for diagnostic performance analysis of variables. The threshold for significance was defined at $p < 0.05$.

RESULTS

A total of 118 hospitalized patients with COVID-19 were included in the final analysis. The mean age was 63±7 years and 63 (53.4 %) were female. There was no statistically significant difference between severe COVID-19 patient group (n= 26, 22.1 %) and non-severe COVID-19 patient group (n=92, 77.9 %) in terms of age (p= 0.862) (**Table 1**).

Lymphocyte count was found as statistically significantly low (p <0.001) in the severe COVID-19 group while D-dimer level was statistically significantly higher in the group with severe disease (p <0.001) (**Table2**). As for the effectiveness of lymphocyte count in distinguishing severe and non-severe patients with COVID-19 when cut-off score 1500/mm3 was taken, sensitivity was 69.2% and specificity was 60.2%. Lymphocyte count was found to have a significant discrimination power (AUC = 0.745, p <0.0001, 95% CI (lower bound – upper bound) = 0.644 - 0.846) (**Table3**)(**Figure2**).

As for the effectiveness of D-dimer level in distinguishing severe and non-severe patients with COVID-19 when cut-off score 2 mg/L was taken, sensitivity was 73.1% and specificity was 91.3%. D-dimer level was found to have a significant discrimination power (AUC = 0.928, p <0.0001, 95% CI (lower bound – upper bound) = 0.879 - 0.978) (**Table 3**) (**Figure3**).

Table 1. Distribution of the numbers and mean ages of the severe and non-severe COVID-19 patients between genders

	Mild	Severe	p
Female : n (%)	50 (% 54.3)	13 (% 50)	0.728 *
Age (year)	61 ± 7	62 ± 8.5	
Male: n (%)	42 (%45.7)	13 (% 50)	0.240 *
Age (year)	66 ± 7	63 ± 5	
Total: n (%)	92 (%100)	26 (%100)	0.862 *
Age (year)	63 ± 7	63 ± 6	

*Independent-Samples T-Test (data were shown as mean ± standard deviation)

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Table 2. Comparison of severe and non-severe COVID-19 patients' findings

	(n=92)	Severe (n=26)	p
Lymphocyte count(cell/mm3)	1729 ± 698	1129 ± 540	**< 0.001** *
D -Dimer (mg/L)	0.6 (0.2 – 21.3)	10 (0.7 – 35)	**< 0.001**†

*Independent-Samples T-Test (data were shown as mean ± standard deviation), †Mann-Whitney U test (data were shown as median (min-max))

Table 3. Determination of the ability of lymphocyte count and D-dimer level to predict severe and non-severe COVID-19 patients through ROC curve

Variables	AUC (% 95 CI)	Cut-off	p	Sensitivity (%)	Specifity (%)
Lymphocyte count	0.745 (0.644 – 0.846)	1500	< 0.001*	69.2	60.9
D-dimer level	0.928 (0.879 – 0.978)	2	< 0.001*	73.1	91.3

* ROC analysis of lymphocyte and D-dimer baseline values; AUC: Area under the curve; CI: Confidence interval; COVID-19: Coronavirus disease 2019; ROC: Receiver operating characteristic

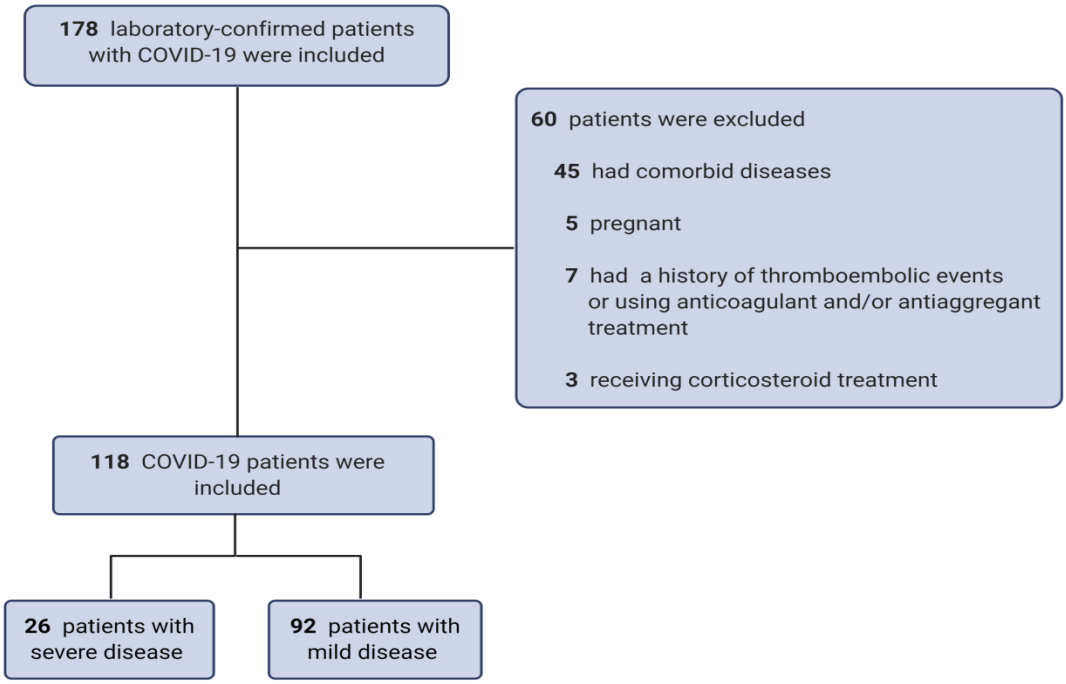

Figure 1. Flow chart of patients screening. Inclusion criteria and exclusion criteria were strictly applied throughout the screening process.

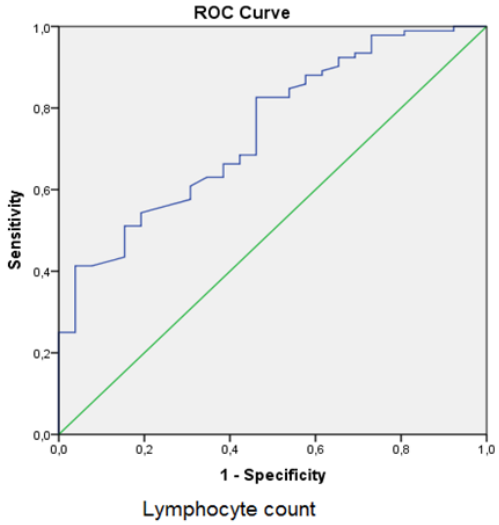

Figure 2. ROC analysis of lymphocyte baseline values. Notes: Lymphocyte count was set to a positive influence, and specificity and sensitivity of lymphocyte baseline values were plotted. Thecut-off point of lymphocyte count when the sum of specificity and sensitivity is maximized was 1500 cell/mm3 (sensitivity, 0.692; specificity, 0.609). Areaunderthecurve: 0.745 and 95% CI: 0.644-0.846. Abbreviations: CI, confidence interval; ROC, receiver operating characteristic.

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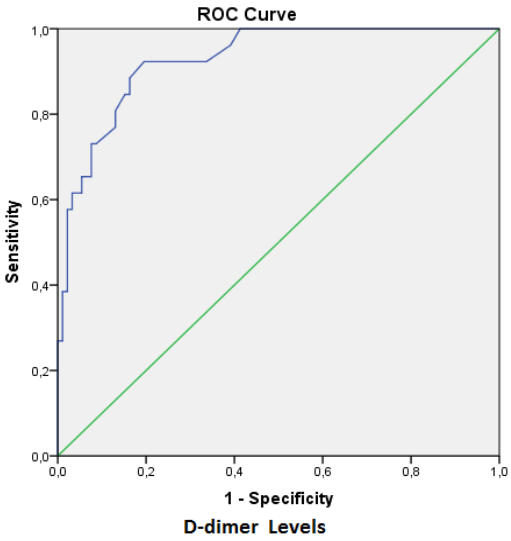

Figure 3. ROC analysis of D-dimer baseline values. Notes: D-dimer was set to a negative influence, and specificity and sensitivity of D-dimer baseline values were plotted. The cut-off point of D-dimer when the sum of specificity and sensitivity is maximized was 2 mg/L (sensitivity, 0.731; specificity, 0.913). Area under the curve: 0.928 and 95% CI: 0.879-0.978. Abbreviations: CI, confidence interval; ROC, receiver operating characteristic.

DISCUSSION

In the current study, our results indicate that lymphocyte count was lower and the D-dimer level was higher in patients with severe COVID-19 than non-severe COVID-19 patients. It was concluded that serum D-dimer levels and lymphocyte count had a significant discrimination power in predicting the prognosis of COVID-19 patients.

D-dimer is a product of the enzymatic breakdown of cross-linked fibrin by plasmin. However, high D-dimer levels are common in patients with a range of acute infectious and inflammatory diseases (**11**). In patients with COVID-19, the predominant coagulation abnormalities progress with clinical conditions that progress with hypercoagulation, and the risk of venous thromboembolism increases uncontrollably. This condition has been called by some experts as thrombo-inflammation or COVID-19-associated coagulopathy (CAC). Disseminated intravascular coagulation (DIC) has been reported in severely affected patients (**12**). Recent studies have shown that high D-dimer levels correlate with the severity of COVID-19 (**13**).

In severe COVID-19 patients, proinflammatory cytokines (IL-1, IL-6, and TNF-α) and chemokines (IL-8) were higher than those in non-severe cases. Although there is no direct evidence that cytokines and chemokines are responsible for lung pathology due to COVID-19, hyperinflammatory responses are considered to play a role in laboratory parameters (elevated serum chemokine and cytokine levels, increased neutrophil counts) in those with severe disease (**14**). In COVID-19, lymphopenia have been shown to be a severe disease predictor (**15**).

The study conducted by Wang et al. in 339 patients with COVID-19 was divided into four groups as mild, moderate, severe, and critical. Lymphopenia was detected in approximately 60% of all patients and 81.5% in patients who deceased.

It was concluded that the degree of lymphopenia might indicate the severity of the SARS-CoV-2 invasion or the state of antiviral immunity, thereby predicting the prognosis (**16**). In another study in this regard, it has been demonstrated that the lymphocyte count was found to be significantly lower in COVID-19 patients who were followed up in the intensive care unit compared to those followed in other clinical services (**17**). Our study shows that the lymphocyte level is significantly lower in the severe disease group than the non-severe group. Lymphocyte count 1500/mm3 and below were found to be reliable in predicting poor prognosis in COVID-19 patients. In COVID-19 patients, a decrease in CD4 and CD8 T cell numbers has been found, and this is considered to contribute to the progression of the disease with impaired immunity (**18**). The mechanism of reduced lymphocyte count in severe disease remains uncertain. The explanation of this mechanism shall serve as a guide for the treatment of severe patients. Apoptosis of lymphocytes is regulated by pro and anti-apoptotic mechanisms through endogenous and exogenous factors (**19**).

In SARS-CoV and MERS-CoV infections, T lymphocytes apoptosis induced lymphopenia has been reported (**15**). Patients with SARS have been found to have higher plasma Fas-ligand levels associated with higher intracellular cleavage caspase-3 positive CD4 and CD8 lymphocytes in the acute phase of the disease (**20**). In SARS-CoV-2 infection, the cytopathic effect caused by direct infection of T cells is emphasized. Other predicted lymphopenia mechanisms are sequestration in the lungs during extensive bilateral pneumonia and bone marrow suppression during cytokine storm (**21**). Flow cytometric analyzes have shown that the percentage of CD4+ T cells (CD3+ CD4+ CD45RA+) in peripheral blood increase and memory helper T cells (CD3+ CD4+ CD45RO+) decrease (**14**).

In a study conducted with 60 patients with COVID-19, total lymphocyte, CD4+ and CD8+ T cells, B cells and natural killer (NK) cells numbers were decreased. The authors emphasized the independent predictive value of the decrease in CD8+ T cells for COVID-19 severity and treatment efficacy (22).

The authors have conducted that D-dimer levels were higher in deceased patients due to COVID-19 than survivors (23). In a study investigating the relationship between D-dimer levels and mortality in patients with COVID-19, it was concluded that D-dimer levels higher than 2.0 µg/mL were independent predictors of mortality at the initial admission (24). According to our data, D-dimer levels at the time of admission were significantly higher in severe COVID-19 patients than non-severe group (p <0.001). Levels of 2 mg/L and above for D-dimer have been shown to be a reliable indicator that can be used to identify patients with poor prognosis. It is considered that this elevation of D-dimer in patients with COVID-19 may be due to increased systemic pro-inflammatory activation triggering the prothrombotic process. In autopsy findings of deceased patients with COVID-19, microvascular thrombosis has been observed in the lungs. The mechanism of thrombosis remains uncertain. It is considered that hypercoagulability may be directly related to endothelial injury, complement activation, or other procedures (12, 25).

SARS-CoV2 penetrates human cells by binding to angiotensin-converting enzyme 2 (ACE-2), which is highly expressed primarily in alveolar lung cells, cardiac myocytes, and vascular endothelial cells. Renin-angiotensin-aldosterone system (RAAS) pathway is activated by binding of the virus to ACE-2 and decreasing enzyme expression. Theoretically, RAAS activation leads to platelet adhesion and aggregation, thus carrying a risk of pulmonary embolism, pulmonary hypertension, and fibrosis (26).

Moreover, the dysfunction of endothelial cells induced by infection results in excessive thrombin production and inhibition of fibrinolysis, indicating the condition of hypercoagulability in patients with COVID-19 (10, 11). However, hypoxia observed in patients with severe COVID-19 increases blood viscosity and stimulates thrombosis through a signal pathway linked to hypoxia-induced transcription factors (HIF) (27). Viral infections cause a systemic inflammatory response and disrupt the balance between procoagulant-anticoagulant homeostatic mechanisms (28). Endothelial dysfunction, increased von Willebrand factor, tissue factor pathway and Toll-like receptor activation are considered to play a role in pathogenesis.Activation and interactions of monocytes, macrophages, platelets, lymphocytes, and endothelial cells play an important role in the formation of thromboembolic events observed in viral infections (29). Thromboembolic events have been reported in patients with influenza virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), herpes simplex virus (HSV), and other viral infections (30).

SARS-CoV and MERS-CoV infections are also associated with thrombotic events, similar to SARS-CoV-2 infection (31, 32). The prothrombotic effect of SARS-CoV remains mainly on the pulmonary vessels (33). Mononuclear cells infected with SARS-CoV have been revealed to express the procoagulant gene panel, characterized by an increase in factor II-II-X, fibrinogen, and SERPINs (D1 and A3). The Toll-like receptor 9 (TLR9) and thromboxane synthase (TBXAS) gene have been reported to be the target of SARS-CoV. Increased thromboxane production results in endothelial dysfunction, vasoconstriction, and platelet aggregation. TLR9 receptor is expressed from platelets and provides platelet activation, aggregation, and degranulation (34). DIC is one of the major complications reported in fatal MERS-CoV infections. It has been further reported that the effect of MERS-CoV on the coagulation cascade is associated with human dipeptidyl peptidase 4 (hDPP4) (35).

This study has a few limitations. The first one is that only the values of the laboratory parameters examined during the application have been taken into consideration and the changes in the following days have not been not followed. The second one is that patients with high D-dimer had not been further investigated for pulmonary embolism.

CONCLUSION

The values of ⩽ 1500/mm3 lymphocyte and ⩾2 mg/L D-dimer are can be used in the early determination of patients with good and poor prognosis in COVID-19. Thanks to the precautions to be taken as a result of determining patients with poor prognosis in the early stages and rapid treatment decisions, the morbidity, and mortality of these patients will be reduced.We think that targeted therapies will replace standard treatment regimens in viral infections. The relationship between viral infections and thromboembolic complications will be clearly enlightened and prevention and treatment strategies will be developed for this. Immune-modulator treatment options will come to the fore in viral infections.

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