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RESEARCH ARTICLE

Is plasminogen activator inhibitor-1 level a prognostic marker in COVID-19?

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Abstract

Introduction: We aimed to investigate the relationship of plasminogen activator inhibitor-1 (PAI-1) level, which is the main inhibitor of the fibrinolytic system, with COVID – 19 severities.

Methods: A total of 88 cases diagnosed with COVID – 19, 42 with mild pneumonia and 46 with severe pneumonia, were prospectively included in the study. Serum PAI-1 level was studied by ELISA method. COVID – 19 diagnosis was made by reverse transcriptase-polymerase chain reaction test.

Results: PAI – 1 level was found to be higher in the group with severe pneumonia compared to the group with mild pneumonia (72.1 ng/mL vs 64.1 ng/mL, respectively; p=0.005). In the multivariate regression analysis high level of serum PAI – 1 was associated with severe pneumoniae (OR: 1.073; CI: 1.003 – 1.147; p=0.040). The cut off value of PAI – 1 for severe pneumoniae was determined as 65.8 ng/mL with 52.2% sensitivity, specificity of 78.6%, positive predictive value of 72.7% and negative predictive value of 60%. The patients whose PAI – 1 level were over 65.8 ng/mL were found to have 4.646 times increased risk of severe pneumoniae compared to the ones who had PAI – 1 lower than 65.8 ng/mL (OR: 4.646; CI: 1.186 – 18.202; p= 0.027).

Conclusion: In this study, we found out that the serum level of PAI – 1 was higher in patients with severe pneumoniae than the ones with mild pneumoniae. High level of serum PAI – 1 was associated with severe pneumoniae.

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Introduction

Coronavirus disease (COVID-19) prognosis can vary from asymptomatic infection to Acute Respiratory Distress Syndrome (ARDS), multiple organ failure and death.[1] In severe COVID – 19 cases, it is known that the coagulation system is active. In the pathogenesis of hypercoagulability in patients with COVID-19; there is direct invasion of endothelial cells by virus, cytokines causing systemic inflammatory response, especially Interleukin (IL) – 6, neutrophil extracellular traps and activated complement system.[2] The frequency of thromboembolic events has increased in patients with severe COVID-19. In a study evaluating the frequency of thromboembolic events in COVID – 19 patients receiving prophylactic doses of anticoagulants followed in the Intensive Care Unit (ICU) thromboembolic events were detected at a rate of 31% .[3] These findings show that the coagulation system is active in COVID – 19 and coagulation markers have prognostic significace in the disease.

Fibrinolysis is the breakdown of fibrin by plasmin.[4] In fibrinolysis, inactive plasminogen is converted into active plasmin with the effect of plasminogen activator. The main enzyme of the fibrinolytic system is plasmin. Plasmin is a serine protease responsible for the degradation of fibrin and extracellular matrix proteins. There are two types of plasminogen activators in humans: Tissue – type Plasminogen Activator (tPA) and Urokinase-type Plasminogen Activator (uPA). The main regulator of these plasminogen activators is the Plasminogen Activator Inhibitor – 1 (PAI-1) molecule. PAI – 1 is the principal inhibitor of the fibrinolytic cascade. There are many publications in the literature in which PAI – 1 is used as a prognostic marker in patients with sepsis and ARDS.[5-7] Studies have also evaluated the relationship between COVID – 19 and the fibrinolytic system. In the study of Wright et al. with 44 severe COVID – 19 patients, fibrinolytic activity was evaluated by thromboelastography and it was observed that fibrinolytic activity stopped in 57% of the patients participating in the study.[8] This condition was associated with an increased risk of thromboembolic events. In vitro studies have shown that IL – 6 induces PAI – 1 production and inhibition of IL – 6 mediated signaling with tocilizumab reduces PAI – 1 levels.[9] In another in vitro study, it was determined that the spike protein of SARS – COV – 2 stimulated PAI – 1 production in human pulmonary microvascular endothelial cells.[10]

Therefore, in this study, we aimed to investigate the effect of plasma PAI – 1 level on disease prognosis in patients diagnosed with COVID – 19.

Material and Methods

Study Population

This study was designed as a prospective cross-sectional study in Ankara Bilkent City Hospital Internal Medicine Clinic. Ethics committee approval was obtained from Ankara City Hospital Ethics Committee for the study (approval number: E2-20-117). Written and verbal informed consent was obtained from the patients included in the study.

The study included patients over the age of 18 who applied to our clinic with COVID-19 symptoms and were diagnosed with COVID – 19 through a reverse transcriptase-polymerase chain reaction (RT – PCR) test. The cases were divided into two groups: mild and severe pneumonia. Patients with diagnosis of pregnancy, chronic restrictive or obstructive pulmonary disease, chronic renal failure, malignancy, rheumatological disease, diabetes mellitus, obesity, coronary artery disease, cerebrovascular accident history, peripheral artery disease history, chronic liver disease, hematological disorder and anticoagulant and immunosuppressive therapy (Pulse steroid, anakinra, tocilizumab) were not included in the present study.

In line with the COVID-19 Diagnostic Guidelines of the Turkish Ministry of Health; patients were divided into two groups; i.e., mild and severe pneumonia according to their clinical condition at hospital admission. Mild pneumonia; was defined as patients having a respiratory rate <30/minute and a room air oxygen saturation (SpO2) level >90%. Severe pneumonia was defined as patients having respiratory rate ≥30/minute and/or SpO2 level ≤ 90% in room air (PaO2/FiO2<300 in the patient receiving oxygen).

Demographic, clinical characteristics and laboratory findings of the patients were recorded from the patient files. In addition to routine tests, blood samples were taken from the patients for the plasma PAI – 1 level.

Plasma Plasminogen Activator Inhibitor – 1 Level

Peripheral blood samples were taken from the patients during their hospitalization to measure plasma PAI-1 levels, and the samples were centrifuged for 5 minutes after collection. The obtained plasma samples were preserved until analysis at -80°C. PAI

– 1 level; Human PAI – 1 elisa kit (Elabscience Biotechnology Inc, Houston, Texas) (Catalogue Number: E-EL-H2104, LOT number: A4CCIFTMP6) and were measured with 96 test kit according to manufacturer's instructions. The lyophilized standard available in the kit was dissolved and diluted. Standards were obtained at different concentrations. Compliant with kit procedure of the samples, absorbances were measured at 450 nm. standard curve graph ng/mL, in which all absorbances corresponding with the formula obtained with the help of concentrations were calculated. The measurable range is 0.16-10 ng/mL and the sensitivity is 0.1 ng/ml.

COVID – 19 Reverse Transcriptase-Polymerase Chain Reaction Test

Samples were taken from the upper respiratory tract (nose and throat) by swab or sputum. In Ankara City Hospital Clinical Microbiology Laboratory; Severe Acute Respiratory-associated Coronavirus – 2 (SARS – CoV – 2) RNA detection is made with Bio Speedy Bioeksen COVID – 19 RT-qPCR diagnostic kit (Istanbul, Turkey).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Numerical variables showing normal distribution were expresssed with mean ± standard deviation, and numerical variables not showing normal distribution were expresed with median (min-max). Categorical variables were expressed with numbers and percentages. Student's T test or Mann-Whitney U test was used to compare numerical variables between the two groups. Chi-square test was used to compare categorical variables. The relationship between numerical variables was examined by Pearson and Spearman correlation analysis. Multivariate logistic regression analysis was used to identify risk factors affecting severe pneumonia. The ability of PAI – 1 level to distinguish severe pneumonia from mild pneumonia was evaluated with Receiver Operating Charecteristic (ROC) curve analysis, and the predictive values were determined according to the Youden index method. $P < 0.05$ (*) value was considered as significant in statistical analysis.

Results

The study population consisted of 88 patients, 42 with mild pneumonia and 46 with severe pneumonia. 68.2% of the patients was male (n:60) and their mean age was 55.5±16.2 years (range: 20-88 years). The median symptom duration of the patients was 12 days (range: 4-27). There was cough in 37.5% (n:33), headache in 10.2% (n:9), low back pain in 4.5% (n: 4), dyspnea in 46.6% (n:41), myalgia in 8% (n:7), anosmia in 1.1% (n:1), atralgia in 8% (n:7)) and 11.4% (n:10) had nausea symptoms. While 17% (n:15) of the patients received nasal oxygen, 21.5% (n:19) reservoir oxygen, 9.1% (n:8) high-flow oxygen support and 11.4% (n:10) were intubated, 41% (n:36) did not require oxygen. In the follow-up of the patients, the rate of need for ICU was found to be 33% (n:29). While no death was detected in mild pneumonia patients, the fatality rate was found to be 39.1% (n:18) in severe pneumonia patients (Table 1).

Table 1. Demographic and clinical characteristics of COVID-19 patients.

Variables	Patients n (%)
Age, years	55.5±16.2
Male, n (%)	60 (68.2)
Symptoms, n (%)	
Fever	33 (37.5)
Cough	33 (37.5)
Headache	9 (10.2)
Backache	4 (4.5)
Dyspnea	41 (46.6)
Myalgia	7 (8.0)
Anosmia	1 (1.1)
Arthralgia	7 (8.0)
Nausea- diarrhea	10 (11.4)
Symptom duration, day	12 (4-27)
10 and below	34 (38.6)
>10	54 (61.4)
Severe pneumonia, n (%)	46(52.3)
Respiratory status, n (%)	
Room air	36(41.0)
Nasal Cannula	15(17.0)
Reservoir oxygen	19(21.5)
High flow oxygen	8(9.1)
Mechanical ventilation	10(11.4)
Hospitalization duration, day	12(1-58)
ICU need, n (%)	29(33.0)
Exitus, n (%)	
Mild pneumonia	0(0)
Severe pneumonia	18(39.1)

Numerical variables were shown as mean±standard deviation or median (min-max) according to their normal distribution. Categorical variables were shown as numbers (%).
Abbreviations: ICU: Intensive Care Unit

Laboratory findings according to pneumonia severity are shown in Table 2 in detail. The mean PAI-1 level (72.1±15.8 ng/mL vs 64.1±9.5 29, respectively; p=0.005) was found to be higher in severe pneumonia cases compared to mild pneumonia cases.

Table 2. Distribution of laboratory findings according to pneumonia severity

Variables	Pneumonia		p
	Severe n=46	Mild n=42	
AST (U/L)	44.5(11-125)	36.5(17-211)	0.345
ALT (U/L)	48(8-291)	41.5(18-454)	0.917
Troponin (ng/L)	4.5(1-5037)	1(1-37.8)	0.001*
CK (U/L)	70(12-873)	59.5(12-614)	0.547
ALP (U/L)	91.5(30-210)	62(30-144)	<0.001*
GGT (U/L)	46(10-827)	28.5(8-194)	0.002*
Total bilirubin (mg/dL)	0.5(0.2-3.1)	0.4(0.2-0.9)	0.003*
Albumin (g/L)	32.8±6	39.7±4.2	<0.001*
Urea (mg/dL)	47(21-173)	32.5(17-71)	<0.001*
LDH (U/L)	442(209-873)	261(153-670)	<0.001*
Creatinine (mg/dL)	0.7(0.4-2.9)	0.8(0.5-1.6)	0.025*
WBC (x109/L)	10(4.8-22.4)	6.3(1.7-29.4)	<0.001*
Neutrophil (x109/L)	8.7(4-20.7)	4.3(1.3-26.5)	<0.001*
Eosinophil (x109/L)	0.04(0-0.43)	0.05(0-0.39)	0.563
Lymphocyte (x109/L)	0.6(0.1-3.2)	1.4(0.3-2.9)	<0.001*
Hemoglobin (g/dL)	12.5±2.1	13.9±1.6	0.001*
Thrombocyte (x109/L)	302(31-681)	236(105-599)	0.232
CRP (g/L)	0.05(0-0.2)	0.01(0-0.17)	<0.001*
Procalcitonin (µg/L)	0.07(0.02-20.65)	0.02(0.02-1.62)	<0.001*
Ferritin (µg/L)	654(20-3369)	243.5(19-1711)	<0.001*
Fibrinogen (g/L)	4.8±1.5	4.1±1.4	0.022*
aPTT (second)	22.5(18-127)	23.7(19.5-29.6)	0.204
D-Dimer (mg/L)	1(0.2-16.9)	0.4(0.2-6)	<0.001*
INR	1.1±0.3	1.0±0.1	0.025*
PAI-1 (ng/mL)	72.1±15.8	64.1±9.5	0.005*

Numerical variables were shown as mean±standard deviation or median (min-max) according to their normal distribution. Categorical variables were shown as numbers (%). *p<0.05 indicates statistical significance.

Abbreviations: AST: Aspartate aminotransferase, ALT: Alanine aminotranferase, CK: Creatinine kinase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, LDH: Lactate dehydrogenase, WBC: White blood cell, CRP: C – reactive protein, aPTT: Active partial thromboplastin time, INR: International normalized ratio, PAI – 1: Plasminogen activator inhibitor-1

Factors predicting severe pneumonia in patients were analyzed by univariate and multivariate logistic regression. Accordingly, low albumin (OR:0.843; p=0.045), high lactate dehydrohenase (LDH) (OR:1.010; p=0.002), low hemoglobin (OR:0.666; p=0.044), and high PAI – 1 (OR:1.073; p=0.040) were factors associated with severe pneumonia in the multivariate analysis. Univariate and multivariate regression analyzes for factors predicting severe pneumonia are shown in Table 3.

Table 3. Parameters predicting severe pneumonia in univariate and multivariate regression

Variables	Univariate analysis			Multivariate analysis		
	OR	%95 confidence interval	p	OR	%95 confidence interval	p
Age	1.052	1.020-1.085	0.001			
LDH	1.013	1.007-1.018	<0.001	1.010	1.004-1.016	0.002
Albumin	0.761	0.673-0.862	<0.001	0.843	0.714-0.996	0.045
ALP	1.029	1.013-1.045	<0.001			
Neutrophil	1.266	1.112-1.442	<0.001			
WBC	1.215	1.081-1.366	0.001			
Ferritin	1.002	1.001-1.003	0.001			
Hemoglobin	0.649	0.499-0.844	0.001	0.666	0.449-0.989	0.044
Urea	1.057	1.023-1.093	0.001			
PAI-1	1.059	1.014-1.106	0.009	1.073	1.003-1.147	0.040

Only parameters that were significant (p<0.05) in the univariate regression model were included.

Abbreaviations: LDH: Lactate dehyrogenase, ALP: Alkaline phosphatase, WBC: White blood cell, PAI – 1: Plasminogen activator inhibitor – 1

The ability of PAI – 1 level to distinguish severe pneumonia from mild pneumonia was evaluated by ROC Curve analysis. In multivariate analysis, the ability of factors associated with severe pneumonia to distinguish severe pneumonia from mild pneumonia was evaluated by ROC Curve analysis and the area under the curve (AUC) was calculated (Figure 1). Accordingly, AUC values for LDH, albumin, hemoglobin, and PAI – 1, respectively, were 0.855 (95% CI: 0.774-0.936), 0.821 (95% CI: 0.735-0.908), 0.686 (95% CI: 0.575- 0.797) and 0.688 (95% CI: 0.576-0.799).

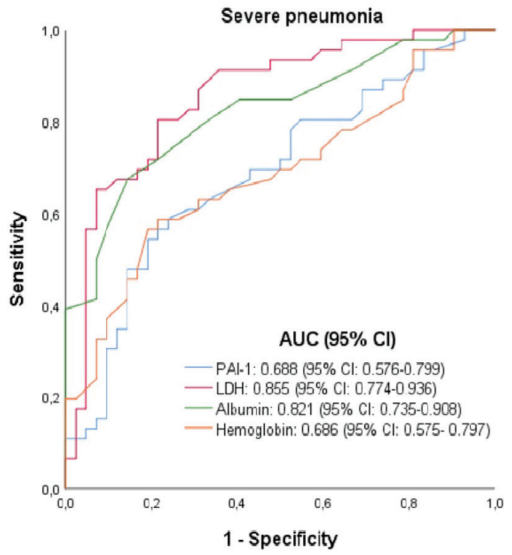

Figure 1. ROC curve evaluating the ability to distinguish factors associated with severe pneumonia from mild pneumonia in multivariate analysis

Appropriate cut-off values were calculated for these four parameters using the Youden index with ROC curve analysis. Accordingly, the appropriate cut-off values for LDH, albumin, hemoglobin, and PAI-1 were determined as> 401.5 U/L, <35.5 g/L, <12.9 g/dL, and >65.8 ng/mL, respectively. Multivariate logistic regression analysis was performed again with the cut-off values of these predictors. Accordingly, those with LDH>401.5 U/L had 21,643 times higher risk of severe pneumonia than those with LDH<401.5 U/L, those with albumin <35.5 g/L had 5.721 times higher risk than those with albumin> 35.5 g/L, those with hemoglobin <12, 9 g/dL had 5.328-fold increased risk of severe pneumonia compared to those with hemoglobin>12.9 g/dL, and those with PAI – 1>65.8 ng/mL had a 4.646 – fold increased risk compared to those with PAI – 1<65.8 ng/mL. Multivariate regression analysis with predictors' cut-off values is shown in Table 4.

Tablo 4. Predictors of severe pneumonia according to appropriate cut-off values in multivariate regression

Variables	OR	%95 confidence interval	p
LDH (>401.5 U/L)	21.643	4.312-108.620	<0.001
Albumin (<35.5 g/L)	5.721	1.520-21.530	0.010
Hemoglobin (<12.9 g/dL)	5.328	1.378-20.599	0.015
PAI-1 (>65.8 ng/mL)	4.646	1.186-18.202	0.027

Abbreaviations: LDH: Lactate dehyrogenase, PAI – 1: Plasminogen activator inhibitor – 1

In patients with severe pneumoniae it was also found that the PAI – 1 level was positively correlated with the levels of alkaline phosphatase (ALP) (r= 0.290; p=0.050), urea (r=0.410; p=0.005), neutrophil (r=0.310; p=0.036), and D – Dimer (r=0.321; p=0.030) (Table 5).

Table 5. Relation of parameters with PAI-1 Level in Severe Pneumonia Patients

Variables	PAI	
	r	p
Age	0.102	0.498
Symptom duration	0.274	0.065
Hospitalization duration	-0191	0.204
AST	0.268	0.072
ALT	0.142	0.347
Troponin	0.256	0.086
CK	0.169	0.261
ALP	0.290	0.050*
GGT	0.183	0.223
T. bilirubin	0180	0.231
Albumin	-0.275	0.064
Urea	0.410	0.005*
LDH	0.251	0.092
Creatinine	0.102	0.499
WBC	0.281	0.058
Neutrophil	0.310	0.036*
Eosinophil	0.082	0.588
Lymphocyte	-0.075	0.620
Hemoglobin	-0.171	0.257
Thrombocyte	-0.040	0.791
CRP	-0.106	0.481
Procalcitonin	0.128	0.397
Ferritin	0.064	0.670
Fibrinogen	-0.094	0.536
aPTT	0.145	0.336
D-Dimer	0.321	0.030*
INR	0.164	0.275

Abbreviations: AST: Aspartate aminotransferase, ALT: Alanine aminotranferase, CK: Creatinine kinase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, LDH: Lactate dehydrogenase, WBC: White blood cell, CRP: C – reactive protein, aPTT: Active partial thromboplastin time, INR: International normalized ratio, PAI – 1: Plasminogen activator inhibitor-1

Discussion

In this study, we examined whether PAI - 1 is associated with the prognosis of COVID - 19 infection. In our study, PAI - 1 levels were found to be higher in COVID - 19 cases with severe pneumonia compared to cases with mild pneumonia. We found that PAI - 1 levels are associated with severe pneumonia due to COVID - 19.

Hypofibrinolytic state associated with elevated PAI-1 levels has been observed in SARS-COV coagulopathy.[11,12] Studies perfromed previously supports impaired fibrinolysis in COVID-19 disease. [8] In in vitro studies, the spike protein of SARS-COV-2 has been shown to stimulate PAI-1 production in human pulmonary microvascular endothelial cells.[10] However, in COVID-19 infection; Angiotensin converting enzyme-2 (ACE-2) expression, which is the receptor of the virus, decreases and the amount of angiotensin-2 increases. There are also studies reporting that increased angiotensin-2 promotes hypercoagulant state by increasing PAI-1 level.[13]

In the present study, according to the multivariate regression, high PAI-1 and LDH and low hemoglobin and albumin levels are factors associated with severe pneumonia in COVID-19. There are few studies in the literature examining the relationship between PAI-1 level and pneumonia severity in patients diagnosed with COVID-19. Zuo et al evaluated this relationship in patients with COVID-19.[14] In their study examining plasma PAI-1 level in 118 COVID 19 patients, it was determined that the patients in need of oxygen had a higher plasma PAI-1 level compared to the patients followed up with room air. Results of the same study showed a negative correlation between plasma PAI-1 level and arterial oxygen saturation/percentage of oxygen in inspired air. In the present study, high PAI-1 level was found to be a predictor for severe pneumonia, and those with PAI-1>65.8 ng/ml were associated with a 4.646-fold increased risk of severe pneumonia compared to those with PAI-1 level of <65.8 ng/ml. In the study by Masi et al., the mean PAI-1 value was found to be 95.2 ng/mL in COVID-19 patients with severe pneumonia.[15] In our study, mean PAI-1 level was found to be 72.1 ng/mL in severe pneumonia patients. The reason for the higher level of PAI-1 in their study may be related to the inclusion of patients with comorbidity in the study. Because previous studies in the literature have shown that diabetes mellitus, atherosclerotic disease, stroke, cardiovascular disease, malignancy and obesity are associated with high PAI-1 levels.[4,16] In the study of Umemura et al., in which serum PAI-1 levels were examined in 24 patients with ARDS caused by COVID-19 and in patients with ARDS caused by non-COVID-19 diseases, PAI-1 levels (median: 28 ng/ml) were found in the normal range in patients with a diagnosis of COVID-19.[17] According to the results of the study, it was argued that there is no suppression of systemic fibrinolysis in COVID-19, where coagulopathy of COVID-19 and sepsis are different from each other. However, low number of patients with a diagnosis of COVID-19 participating in the study may be the reason why the PAI-1 value was found within the normal range.

In the present study, low albumin level was found to be a factor associated with severe pneumonia, and those with albumin level of <35.5 g/L were associated with a 5.721-fold increased risk of severe pneumonia compared to those with albumin >35.5 g/L. When previous studies were examined, it was determined that low albumin level was associated with mortality and disease severity in severe inflammation conditions such as sepsis and ARDS.[18,19] In this context, low albumin level was found to be associated with disease severity in many studies conducted in COVID-19 patients with severe systemic inflammation.[20] Our results are in agreement with the available literature data.

In the present study, low hemoglobin level was found to be associated with severe pneumonia. Those with hemoglobin level of <12.9 g/dL had a 5.328-fold increased risk of severe pneumonia compared to those with hemoglobin>12.9 g/dL. Anemia is commonly encountered in patients followed up for pneumonia. In the study of Bellmann-Weiler et al., the frequency of anemia in COVID-19 was found to be 24.7%.[21] In the presence of anemia, the oxygen carrying capacity decreases, thus increasing the severity of respiratory diseases. In the study of Wang et al. in COVID-19 patients, low hemoglobin level was found to be an independent predictor for severe disease.[22]

In the present study, high LDH level was established to be a factor associated with severe pneumonia. The LDH cut-off value for severe pneumonia was determined to be>401.5 U/L. Those with LDH>401.5 U/L had a 21,643-fold increased risk of severe pneumonia compared to those with LDH<401.5 U/L. In

the study of Li et al. in COVID-19 patients, high LDH level at the time of admission to the hospital was found to be an independent risk factor for severe illness and death.[23] The high LDH level in patients with severe pneumonia can be explained by the fact that plasma LDH level reflects lung injury and tissue damage.

It was found that plasma PAI-1 level was positively correlated with neutrophil, urea, ALP and D-Dimer levels in severe pneumonia patients. Neutrophils are an important factor in the occurrence of organ damage in COVID-19.[17] One of the hallmarks of COVID-19-induced ARDS is the sequestration of neutrophils in lung microvascularity.[24] This local proinflammatory environment is further enhanced by the formation of neutrophil extracellular traps (NETs), resulting in the release of proinflammatory cytokines. These cytokines probably promote the release of PAI-1 by endothelial cell activation. Zuo et al.'s study in COVID-19 patients found a positive correlation between PAI-1 and absolute neutrophil count.[14] In our study, as mentioned above, a positive correlation was found between PAI level and neutrophils in severe pneumonia patients.

Organ damage in COVID-19 patients with severe pneumonia is not limited to the lung. Severe COVID-19 affects many organs and systems with its severe inflammation, cytokine storm and coagulopathy.[25] Liver and kidney dysfunction is a common condition associated with poor prognosis in critically ill COVID-19 patients.[18,19] Indeed, in our study, a positive correlation was found between plasma PAI-1 level, which is an indicator of severe pneumonia in COVID-19, and ALP and urea levels, which are liver-kidney function tests.

D-dimer is a fibrin degradation product produced during fibrinolysis. In a study conducted by Oualim et al in COVID-19 patients, it was revealed that high D-Dimer levels are associated with poor prognosis.[26] In the current study, the D-dimer level was found to be higher in patients with severe pneumonia compared to those with mild pneumonia, and a positive correlation was shown between PAI-1 level and D-dimer level in patients with severe pneumonia. This can be explained by the fact that both molecules are predictors of the prothrombotic state. In a study conducted in patients with breast cancer, a positive correlation was found between PAI-1 and D-Dimer levels.[27]

The small number of patients and the fact that the PAI-1 level was not determined in the clinical follow-up of the patients are the limitations of our study. In addition, another limitation is that anticoagulant drugs and low-dose steroid treatments administed in the treatment of the disease can affect PAI-1 level, which may change plasma PAI-1 levels.

Conclusions

In Conclusion, in our study, plasma PAI-1 level was found to be associated with disease prognosis. If this result is supported by larger-scale studies, early identification of patients who are thought to have a poor prognosis may make it possible for these patients to be treated earlier and more aggressively.

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