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A challenging issue in COVID-19 infection: The relationship between PA1-1 and TAFI levels in patients with coagulation disorder

A retrospective and observational study

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Abstract

COVID-19 disrupts the balance between coagulation and fibrinolysis. Especially in the clinical course of serious disease, plasminogen activator inhibitor-1 (PAI-1), thrombin activatable fibrinolysis inhibitor (TAFI), and tissue plasminogen activator levels increase in association with hypercoagulable state and hypofibrinolysis. This explains the increased incidence of thrombosis seen in COVID-19 infection. In this study, we aimed to examine the changes in PAI-1 and TAFI levels of COVID-19 patients. Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital—Ankara Turkey, between April 1 and May 7, 2021. Patients who were diagnosed with COVID-19 were included in this retrospective study. TAFI and PAI-1 levels were analyzed from the samples that had been stored at –80 °C formerly. One hundred thirty-five patients diagnosed with COVID-19 and followed up in the service or intensive care unit were included in the study. Thirty-four (25.2%) patients required follow-up in the intensive care unit. Mortality rate was 10.4%, the coagulation tests of these patients were also compared. PA1-1 levels were found to be statistically significantly higher in intensive care unit patients (median: 133 pg/mL vs 31 pg/mL; $P < .001$), and there was no significant difference in TAFI levels (median:7.31 ng/mL vs 9.80 ng/mL; $P = .171$) between the 2 groups. TAFI levels were found to be higher in patients who died. In COVID-19 infection, as the severity of the disease increases, the coagulation balance deteriorates and eventually a hypercoagulable state occurs with an increase in PAI-1 and TAFI levels. Markers such as PAI and TAFI can be illuminating in further studies in determining prognosis and mortality and developing new treatment options.

Abbreviations: CT = computed tomography, ICU = intensive care unit, PAI-1 = plasminogen activator inhibitor-1, PCR = polymerase chain reaction, TAFI = thrombin activatable fibrinolysis inhibitor, tPA = tissue plasminogen activator.

Keywords: COVID-19, hypofibrinolysis, PAI-1, TAFI

1. Introduction

Coronavirus disease-19 (COVID-19) was declared a pandemic in March 2020 and affected the whole world.[1] It has a wide clinical spectrum ranging from mild viral infection symptoms to acute respiratory distress syndrome.[2] In patients with comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease or cancer, the clinic progresses more aggressively and infection related death is more common.[3]

Severe illness develops, the patient needs to be followed up in intensive care units (ICU).[4] Mechanical ventilation is required in 50–70% of those patients. In the pre-vaccine period, the overall mortality rate for COVID-19 is determined as 1–5%;

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The authors have no conflicts of interest to disclose.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

This study was approved by the ethical review committee of the Health Sciences University Diskapi Training and Research Hospital (26.7.2021-116/11).

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whereas, if acute respiratory distress syndrome develops, mortality rate goes up to 64%.[5,6]

Coagulopathy which is one of the most important complications, especially in the course of serious disease, has been shown to be associated with poor prognosis.[7] In fact, abnormalities in platelet values and coagulation tests can be detected even in the initial and mild disease.[8,9] In a study, multiple site deep vein thrombosis was found to be 55% in COVID-19 patients and venous thrombosis rate in patients followed in ICU was reported to be 48%.[10] Spiezia et al determined COVID-19 related hypercoagulability by whole blood thromboelastometry and they observed a thromboembolism rate of 23% in the patients they included in the study.[11]

Under normal physiological conditions, the coagulation system is in state of equilibrium with thrombotic and fibrinolytic pathways, constantly working against each other.[12] When vascular injury occurs, the coagulation process is triggered, and thrombin is produced. Thrombin converts fibrinogen to insoluble fibrin clot. This coagulatory response is balanced by the fibrinolytic system. Plasmin, which is converted from plasminogen by the stimulus of plasminogen activators (tissue-type PA [tPA] and urokinase-type PA [uPA]), play a major role in the fibrinolysis pathway and degrades the fibrin clot into soluble fibrin degradation products. Plasminogen activator inhibitor-1 (PAI-1) inhibits tPA and uPA and regulates fibrinolytic system.[13] Another stabilizer of the fibrinolytic system is thrombin activatable fibrinolysis inhibitor (TAFI) which plays an important role in the persistence of the clot and prevents its lysis.[14]

COVID-19 disrupts the balance between coagulation and fibrinolysis. The process begins with pathological activation of the endothelial cell by the virus.[8] Especially in the clinical course of serious disease, PAI-1, TAFI, and tPA levels increase in association with hypercoagulable state and hypofibrinolysis.[15] In the pathophysiology of coagulopathy and thrombosis in COVID-19 patients, high amount of inflammatory mediator release, platelet activation and endothelial cell dysfunction play major roles. Disruption of the fibrinolytic system also makes an important contribution.[16] In autopsy studies in COVID-19 patients, diffuse vascular thrombosis has been demonstrated accompanied by severe endothelial damage, increased angiogenesis, microangiopathy, and alveolar capillary occlusions.[17,18]

2. Objectives

In this study, we aimed to examine the changes in PAI-1 and TAFI levels that may indicate hypofibrinolytic status, and to examine the thrombin production and fibrinolysis profiles of COVID-19 patients.

3. Materials and methods

3.1. Study design and setting

Patients who were diagnosed with COVID-19 in our clinic between April 1 and May 7, 2021 and were followed up in our hospital (ICU Department of Infectious diseases) were included in this retrospective study. Patients younger than 18 years old, and those with known bleeding disorders were excluded. A total of 135 patients diagnosed with COVID-19 were included.

The diagnosis of COVID-19 was based on positivity in the polymerase chain reaction (PCR)-based test or typical findings on thorax computed tomography (CT). PCR samples from patients were submitted to the National Virology Reference Laboratory of the Public Health Institution of Turkey. The COVID-19 Reporting, and Data System (CO-RADS) was used to determine CT findings showing pulmonary involvement. CT findings were classified as no (CORADS-1), mild (CO-RADS 2-3), moderate (CO-RADS-4) and severe (CO-RADS 5). Patients who were at least 14 days postvaccination were considered vaccinated against COVID-19.

The patients were divided into 2 subgroups as those followed in the inpatient clinics and those followed in the ICUs. These groups were compared with each other in terms of demographic and laboratory findings and PAI-1, TAFI levels. In addition, the patients followed in the intensive care unit were divided into 2 groups as survivor and non-survivor and analyzed.

3.2. Data sources and measurement

The clinical and laboratory data of the patients were obtained from the electronic hospital records. Demographic information and laboratory findings (hemogram, biochemistry, and hemostasis tests at the time of diagnosis) of all patients included in the study were recorded. Age and gender data were collected as demographic characteristics. Neutrophils, lymphocytes, platelet, creatinine, ferritin, fibrinogen, C-reactive protein, procalcitonin, activated partial thromboplastin time, prothrombin time, D-dimer, were collected as laboratory data and evaluated by including the neutrophil to lymphocyte ratio, plasminogen activator inhibitor-1 levels, thrombin activatable fibrinolysis inhibitor levels.

TAFI and PAI-1 levels were analyzed from the samples that had been stored at –80 °C formerly. That blood samples had been obtained from the patients with vein puncture method on the first day of their hospitalization in the infectious disease inpatient clinic or intensive care unit for analysis of PAI-1 and TAFI levels. First, blood samples were centrifuged at 1500 g for 10 minutes then plasma samples were placed in capped eppendorf tubes and stored at –80 °C. On the day of evaluation of the plasma samples, frozen samples were kept at room temperature firstly and then analyzed using commercially produced ELISA kits and according to the procedure given by the manufacturer. (TAFI: USCN ELISA Kit (China, 2022) Lot: L220310449; PAI-1: ELK Biotechnology ELISA Kit (CHİNA,2022) Lot: L201125694).

As recommended by our national guideline at that time, all hospitalized patients were given thrombosis prophylaxis with low molecular weight heparin (enoxaparin 40 mg once daily if 50–100 kg and 40 mg twice daily, if > 100 kg or fibrinogen > 8 g/L or D-dimer > 3000 ng/mL). The patient's TAFI and PAI tests were examined before anticoagulation. Dexamethasone (6 mg/day) was administered for 7 days to all patients who had lung involvement. All other supportive treatments and antibiotics were given as needed.

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3.2.1. Statistical analysis. Data were summarized as the mean ± standard deviation and median (minimum-maximum) for continuous variables and frequencies (percentiles) for the categorical variables. The Student *t* test or Mann–Whitney U-test was used for 2 group comparisons, depending on the distributional properties of the data. Correlations were assessed using Spearman correlation coefficient along with related *P*-values. Statistical significance was set at a value of $P < .05$. The data was analyzed using the SPSS 11.5 for Windows (SPSS Inc., Chicago, IL).

4. Results

4.1. Descriptive data

One hundred thirty-five patients diagnosed with COVID-19 and followed up in the service or intensive care unit were included in the study. The patients comprised 75 (44.4%) males and 60 (55.6%) females with a median age of 56 years (range, 24–88 years). Covid PCR positivity was detected in 124 patients. The rate of patient with serious finding on torax computerized tomography was 17%. Thirty-four (25.2%) patients required ICU follow-up. Invasive mechanical ventilation was required in 8% of patients.

4.2. Outcome data

The comparison of laboratory tests is given in Table 1. While no statistically significant difference was found between the ferritin, fibrinogen and creatinine values of these patients, a statistically significant difference was found between C-reactive protein, procalcitonin, neutrophil (N), lymphocyte (L), and platelet values. aPTT, PT and D-dimer levels were found to be statistically significantly higher in ICU patients compared to non-ICU patients. PA1-1 levels were higher in ICU patients (median: 133 pg/mL vs 31 pg/mL; $P < .001$), and there was no significant difference in TAFI levels (median:7.31 ng/mL vs 9.80 ng/mL; $P = .171$) between the 2 groups.

When relations of TAFI and PAI-1 levels with blood parameters; PAI-1 levels had a positive correlation with prothrombin time (PT) in non-ICU patients. In the ICU patients, PAI-1 levels were negatively correlated with PT, ferritin levels and N/L ratio (Table 2).

Mortality rate was 10.4%, almost all related to ICU patients. Of the 34 patients followed in the ICU, 13 died (38.2%). Comparison of laboratory parameters of survivor and nonsurvivor patients is shown in Table 3. Among those, only TAFI levels had a statistically significant difference, being higher in nonsurvivors ($P = .032$).

5. Discussion

In the 3rd year of being declared a pandemic and affecting the whole world, the pathophysiology and immunology of COVID-19 infection is better understood. The relationship between severe clinical course with coagulopathy and hypercoagulable state was demonstrated in studies.[19]

Many mechanisms may be responsible for coagulopathy due to COVID-19 disease. Virus-induced endothelial activation, mediators released from the endothelium, mediators released from the endothelium may be related to microthrombi seen during or after the course of the disease.[8]

The more severe the COVID, the more the coagulation balance deteriorates. Critically ill COVID-19 patients have significant hypercoagulability and have higher D-dimer prothrombotic burden caused by prolonged inflammation levels related with poor outcome.[20] D-dimer are known as major fibrin degradation product (FDP) and have been used as a biomarker of trombosis. Interestingly, D-dimer elevation was shown even when no thrombosis was detected in studies.[21] This may be due to fibrinolytic activity leading to fibrin destruction, as triggered by increased coagulation activity before the development of hypofibrinolysis with insufficient fibrinolysis. In other words, while the D-dimer levels initially increase with activated coagulation and fibrinolysis, it may cause confusion in demonstrating hypercoagulability as

Table 1

Laboratory parameters of ICU and non-ICU patients.

	ICU patients n:34	Non-ICU patients n:101	P*
Neutrophils (N) ($\times 10^9$/L) median (range)	7.3 (4.1–19.0)	4 (4.1–16.0)	**<.001**
Lymphocytes (L) ($\times 10^9$/L) median (range)	0.5 (0.2–1.9)	1 (0.2–3.1)	**<.001**
N/ L ratio mean (±SD)	13.09 ± 6.87	5.02 ± 3.78	**<.001**
Plt ($\times 10^9$/L) median (range)	239 (75–560)	203 (37–557)	**<.001**
Creatinine mg/dL mean (±SD)	1.03 ± 0.66	1.23 ± 1.52	.174
Ferritin mg/dL median (range)	694 (52–3935)	453 (26–2620)	.130
CRP median (range)	107 (14–343)	68 (3–309)	**.004**
Procalcitonin, µg/L mean (±SD)	0.71 ± 1.26	0.36 ± 1.08	**<.001**
aPTT, s median (range)	35.65 (20.90–62.80)	32.60 (19.00–51.90)	**.009**
PT, s median (range)	9.61 (7.54–42.40)	9.12 (7.47–23.80)	**.002**
Fibrinogen, gr/L median (range)	556.50 (380.00–814.00)	527.50 (59.00–1417.00)	.429
D-dimer, µg/mL median (range)	0.85 (0.20–47.80)	0.45 (0.20–8.75)	**<.001**
PAI-1, pg/mL, median (range)	133 (19–2041)	31 (1–1631)	**<.001**
TAFI, ng/mL, median (range)	7.31 (2.41–36.79)	9.80 (1.45–38.61)	.171

aPTT = activated partial thromboplastin time, CRP = C-reactive protein, CU = intensive care unit, PAI-1 = plasminogen activator inhibitor-1; Plt = platelet, PT = prothrombin time, TAFI = thrombin activatable fibrinolysis inhibitor.

*$P < .05$ indicates statistical significance.

Table 2

The relations of TAFI and PAI-1 levels with blood parameters of the patients in the inpatient service and ICU.

	Inpatient service				ICU			
	TAFI		PAI-1		TAFI		PAI-1	
	r	*P**	r	*P**	r	*P**	r	*P**
D-dimer	–0.081	.422	0.090	.370	0.240	.172	0.011	.953
aPTT	0.001	.991	–0.051	.618	–0.201	.326	–0.316	.116
PT	–0.079	.438	0.213	**.034**	0.104	.560	–0.377	**.028**
CRP	0.143	.163	0.095	.360	0.213	.227	–0.175	.323
Neutrophil (N)	0.023	.822	0.032	.750	–0.165	.352	–0.265	.130
Lymphocyte (L)	–0.120	.232	0.172	.085	–0.153	.389	–0.022	.904
N/L ratio	0.119	.237	–0.119	.237	0.054	.760	–0.383	**.025**
Platelets	–0.002	.981	0.000	.998	–0.065	.713	–0.144	.415
Creatinine	–0.097	.333	–0.010	.920	–0.059	.740	0.168	.342
Fibrinogen	0.010	.925	–0.036	.726	0.316	.069	–0.077	.663
Ferritin	0.068	.532	–0.062	.573	0.058	.743	–0.356	**.039**
Procalcitonin	–0.039	.698	–0.003	.976	0.117	.510	–0.205	.245

aPTT = activated partial thromboplastin time, CRP = C-reactive protein, ICU = intensive care unit, PAI-1 = plasminogen activator inhibitor-1, Plt = platelet, PT = prothrombin time, TAFI = thrombin activatable fibrinolysis inhibitor.

*$P < .05$ indicates statistical significance.

the disease progresses with insufficient fibrinolysis and the development of hypofibrinolysis. In addition, it has been demonstrated that elevated D-dimer levels is associated with increased mortality.[22] In our study, D-dimer was found to be higher in ICU patients. However, although D-dimer was numerically higher in patients who died, no statistically significant difference was found between survivors and non-survivors. This may be due to more predominant hypofibrinolytic process in non-survivor patients and accordingly there may be a decrease in D-dimer formation, which better indicates hyperfibrinolysis.

It is expected that TAFI and PAI-1 levels will increase in severe COVID-19 patients. These markers can be used as potential indicators of hypofibrinolysis and possible thrombotic complications. In the study of Oran et al, it has been shown that; PAI-1 and TAFI a/i plasma levels are higher in patients diagnosed with COVID-19 compare with control group.[23]

Nauger et al showed high levels of TAFI a/i and PAI-1 in patients with severe COVID-19 (patients in need of ICU support than in those who did not), and emphasized that the elevation of these markers reflect impaired pro-anticoagulant balance and their increases indicate hypofibrinolysis related hypercoagulability.[15] In this study, PAI-1 was detected to be statistically higher in ICU patients compared to non-ICU patients. According to this result, it can be inferred that as the severity of the disease increases, PAI-1 level increases in relation to the hypofibrinolytic state, depending on the pathophysiological mechanisms we discussed earlier.

In the current study, TAFI level was determined to be similar in ICU patients and non-ICU patients. However, we found that the TAFI level was increased in ICU patients who died, compared to the patients who survived. Similar to our results, another study found a correlation between TAFI level and mortality, unlike PAI-1.[23] The fact that PAI-1 level is higher in ICU patients than in non-ICU patients, but there is no significant difference in non-survivor patients compared to survivors, on the contrary, the fact that TAFI level is significantly higher in non-survivor patients can be discussed as following: In the early period when the infection became serious, the level of PAI increased more significantly. As the infection progresses, the fibrinolytic step of the coagulation cascade becomes insufficient due to coagulopathy, a hypofibrinolytic state develops and there is a progressive increase in thrombin production. All these can lead to an increase in TAFI level and an increase in thrombotic complications and eventually mortality. TAFI level may be more significant than PAI-1 as a marker associated with mortality.[24]

One of the paradoxes in COVID-19 coagulopathy is that despite routine thromboprophylaxis in high-risk patients, hypercoagulability may persist and cause mortality. Despite antithrombosis prophylaxis, serious thromboembolism has been reported in patients followed up in intensive care units.[22] In these patients, in addition to COVID-related coagulopathy immobility, obesity, hypoxia and inflammation also contribute to the thrombosis.[15] Prophylactic heparin treatment was started in our patients during their intensive care follow-up and no proven thromboembolism developed in any of our patients.

5.1. Limitations of the study

There are some limitations of this study. Firstly, the study has a retrospective design. We found different results from some other studies, which we cannot explain. If the study had been designed prospectively, more parameters could have been analyzed together to evaluate coagulation disorders and it would have been easier to solve this complex system. PAI-1 and TAFI levels could not be compared with the healthy control group. If it could be compared with the healthy control group, deviations in TAFI and PAI-1 values could be indicated. Further studies involving more patients are needed.

6. Conclusion

In summary, in the clinical course of COVID-19, as the inflammation increases, the balance of hemostasis is disturbed. As a result, after excessive thrombin production and fibrinolysis, hypofibrinolysis and hypercoagulable state dominate the clinical picture with an increase in PAI-1 and TAFI. Nevertheless, it confuses the minds with the unique complexity and perfection of the coagulation system. But still, markers such as PAI and TAFI can be illuminating in further studies in determining prognosis and mortality and developing new treatment options.

Table 3

Comparisons of blood parameters between the patients who survived and lost in ICU patients.

	Survived patients			Dead patients			*P** value
	N	Mean ± SD	Median (Min-Max)	N	Mean ± SD	Median (Min-Max)	
TAFI, ng/mL median (range)	21	7.24 ± 3.01	6.70 (3.60–14.41)	13	14.41 ± 10.83	10.76 (2.41–36.79)	.032
PAI-1, pg/mL median (range)	21	420.78 ± 618.58	132.00 (19.40–2040.90)	13	240.50 ± 355.33	134.60 (18.90–1262.50)	.675
D-dimer, µg/mL median (range)	21	4.37 ± 10.80	0.81 (0.20–47.80)	13	6.01 ± 6.98	4.65 (0.43–21.00)	.181
aPTT, s median (range)	14	40.02 ± 9.41	38.90 (27.40–62.80)	12	35.91 ± 10.96	34.75 (20.90–62.30)	.313
PT, s median (range)	21	10.51 ± 2.64	9.60 (8.10–19.30)	13	12.29 ± 9.14	9.62 (7.54–42.40)	1.000
CRP median (range)	21	97.86 ± 61.43	87.00 (14.00–246.00)	13	149.54 ± 98.08	117.00 (16.00–343.00)	.067
Neutrophil ($\times 10^9$/L) median (range)	21	7737.14 ± 2614.19	8400.00 (2500.00–14,500.00)	13	6746.92 ± 4388.67	6100.00 (410.00–19,000.00)	.082
Lymphocyte ($\times 10^9$/L) median (range)	21	648.10 ± 362.47	580.00 (260.00–1930.00)	13	643.85 ± 348.22	540.00 (240.00–1620.00)	.972
N/L ratio mean (±SD)	21	13.89 ± 6.83	12.59 (4.40–33.85)	13	11.78 ± 7.00	13.38 (1.08–23.33)	.552
Platelet ($\times 10^9$/L) median (range)	21	255.14 ± 88.90	242.00 (143.00–560.00)	13	220.62 ± 92.11	236.00 (75.00–382.00)	.362
Creatinine mg/dL mean (±SD)	21	1.09 ± 0.79	0.83 (0.55–3.71)	13	0.93 ± 0.36	0.84 (0.61–1.92)	.834
Ferritin mg/dL median (range)	21	769.05 ± 629.53	586.00 (52.00–2820.00)	13	1000.31 ± 1000.38	869.00 (134.00–3935.00)	.552
Fibrinogen, gr/L median (range)	21	579.76 ± 128.71	567.00 (382.00–814.00)	13	544.15 ± 107.93	550.00 (380.00–758.00)	.412
Procalcitonin, µg/L mean (±SD)	21	0.78 ± 1.56	0.15 (0.07–6.97)	13	0.59 ± 0.53	0.60 (0.08–2.11)	.138

aPTT = activated partial thromboplastin time, CRP = C-reactive protein, ICU = intensive care unit, PAI-1 = plasminogen activator inhibitor-1, Plt = platelet, PT = prothrombin time, SD = standard deviation, TAFI = thrombin activatable fibrinolysis inhibitor.

* $P < .05$ indicates statistical significance.

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