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Evaluation of the relationship between TAFI level and prognosis in COVID-19 patients

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Abstract. – OBJECTIVE: Serum thrombin-activated fibrinolysis inhibitor (TAFI) levels were measured in coronavirus disease 2019 (COVID-19) patients requiring intensive care, clinical hospitalization, and outpatient follow-up. The relationships between serum TAFI levels and prognosis were determined.

PATIENTS AND METHODS: Ninety patients who had positive COVID-19 PCR test results were randomly selected and included in the study. Subgroups were formed according to the clinical characteristics of the patients as follows: mild, moderate, and severe. Venous blood samples were taken from all patients, and serum C-reactive protein (CRP), lactate dehydrogenase (LDH), fibrinogen, D-dimer, ferritin, and TAFI levels were measured. The results were evaluated by comparing each group.

RESULTS: The one-way ANOVA test to determine differences between subgroups resulted in p-values lower than 0.05 for all biochemical analytes (CRP, LDH, fibrinogen, D-dimer, ferritin, and TAFI). Regarding serum TAFI levels, there were significant differences in the severe group (853.04 ± 338.58 ng/mL) compared to the mild group (548.33 ± 264.17 ng/mL). ROC curve analysis to predict mortality revealed that TAFI levels were able to detect 85% of deaths. In addition, ROC analysis revealed that serum TAFI levels could detect 86% of intubated cases.

CONCLUSIONS: The disease progression is more severe in patients with high TAFI levels, and high TAFI levels are associated with mortality and intubation rates. Further studies are needed to determine serum TAFI levels as a biomarker of prognosis in COVID-19 patients.

Key Words:
COVID-19, Health, Pulmonary thromboembolism, TAFI, Mortality, Intubation.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first seen in China in December 2019 and reached the size of a pandemic. It has been named COVID-19. Although it is generally considered a mild respiratory infection, it can cause dysfunctions in many vital organs, especially in the lungs[1]. Acute respiratory distress syndrome (ARDS) is the main cause of mortality in COVID-19[2].

COVID-19 has many clinical, pathological, and radiological features in common with Middle East respiratory syndrome (MERS) caused by SARS and MERS-CoV virus[3-6]. These viruses enter host cells by attaching a protein on their envelope to angiotensin-converting enzyme 2 (ACE2) expressed on cell surfaces. The main target is type 2 alveolar cells found in the lungs. This may result in severe pneumonia[6-8]. Alveolar edema occurs secondary to macrophage infiltration and intra-alveolar fibrin deposition due to inflammation in the lungs. The result is ARDS and acute respiratory failure. Diffuse alveolar damage, microthrombus in perialveolar vessels, and intra-alveolar hemorrhage were observed in autopsy samples[9-12]. The main reason for this situation is the deterioration of the fibrinolytic system balance due to acute tissue damage and inflammation.

Deterioration of the fibrinolytic system balance causes hypercoagulability. The fibrinolytic system is regulated by serine protease inhibitors at various activation sites to maintain physiological balance. Factors inhibiting the conversion of plasminogen to plasmin are plasminogen activator inhibitor 1 (PAI-1), plasminogen activator inhibitor 2 (PAI-

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2), activated protein C inhibitor (APC), plasminogen activator inhibitor (PAI-3), protease nexin 1 and defensin. Factors that inhibit plasmin are several serine proteases, including α2-antiplasmin, α2-macroglobulin, antithrombin, α2-antitrypsin, and the protease nexin 1. Under physiological conditions, activators and inhibitors are in balance and regulate hemostasis[13,14]. This balance has been disrupted by COVID-19. In addition to the mentioned factors, thrombin-activated fibrinolysis inhibitor (TAFI) is one of the main components of the coagulation system and prevents plasminogen binding and plasmin formation. TAFI is a member of the metallocarboxypeptidase family, which is a zinc-dependent exopeptidase that cleaves carboxy-terminal peptide bonds[15]. TAFI is activated by thrombin and weakens the fibrinolytic response, creating an important molecular link between coagulation and fibrinolysis[16,17].

A substantial increase in thrombotic complications has been observed[18] due to hypercoagulability in the course of COVID-19. Thrombosis was observed in both superficial and deep veins and arteries in studies[18,19] also showing that the use of low molecular weight heparin in the early period reduces the mortality rate. Fibrin deposits occur in the pulmonary microcirculation secondary to acute lung injury in COVID-19 patients. Microthrombi occur as a result of this and endothelial damage, which is thought to be secondary to the virus. The incidence of pulmonary thromboembolism (PTE) has increased significantly in COVID-19, and it is more common in severe patients hospitalized in intensive care units[20-22].

Coagulation disorders are frequently seen[23] in COVID-19, especially in severe patients requiring intensive care. High levels of fibrinogen and D-dimer can also be seen[23,24] in COVID-19. The acute inflammatory response secondary to infection is responsible for a part of the increase in fibrinogen levels. In response to acute inflammation, hepatic synthesis of fibrinogen has been shown[25] to increase two- to tenfold as an acute phase reactant. Studies[26] have found that the increase in fibrinogen is concordant with the severity of the disease. A D-dimer increase is also observed[26] in the majority of patients, but it is associated not only with the severity of the infection but also with thrombotic events. Based on observations in acute lung injury and ARDS in SARS-CoV-2, it is generally believed[27,28] that the majority of circulating D-dimer originates from pulmonary lesions. The breakdown of fibrin by plasmin leads to the production of D-dimer as a result of the continuous accumulation of fibrin degradation products in the alveoli. D-dimer formation increases despite the antifibrinolytic effects of TAFI, protein C inhibitor, and PAI-1[29].

This study examined the serum TAFI levels in patients requiring intensive care, clinical hospitalization, and outpatient follow-up in COVID-19. We aimed to compare the level of TAFI and determine its relationship with clinical course and mortality. In addition, we tried to determine the relationship between the increase in acute phase reactants and the level of TAFI in these patient groups. Thus, we tried to determine the relationship between the TAFI level and mortality and the need for intubation.

Patients and Methods

This study was conducted with COVID-19-positive patients who were admitted to the COVID-19 Clinics of Erzurum City Hospital. Ninety patients who met the inclusion criteria were included in the study at the time of hospital admission. Patients who had at least one positive COVID-19 real-time PCR result within 7 days were included. All of the patients included in the study had COVID-19 delta variant. The patient population consisted of both males and females between 18-90 years of age. Patients with known systemic diseases, pregnant patients, and lactating patients were not included in the study. The study was conducted following the Declaration of Helsinki. Patients or their legal representatives were informed written and verbally about the study. The Local Clinical Research Ethics Committee of Erzurum City Hospital (Ministry of Health) approved the study.

Subgroups were formed according to the clinical characteristics of the patients at hospital admission. The "mild" group consisted of patients who had normal chest X-ray graphs and were not hospitalized or treated in outpatient clinics. The "moderate" group consisted of patients hospitalized in the clinic without needing intensive care. The "severe" group consisted of patients hospitalized in the intensive care clinic.

COVID-19 treatment protocols for the patients included in our study were determined according to clinical severity as specified in the Turkish Ministry of Health COVID-19 adult diagnosis and treatment guidelines[30]. Mild patients were given favipiravir antiviral therapy at a loading dose of 2 x 1,600 mg and a maintenance dose of 2 x 600 mg for 5 days. Patients hospitalized with moderate COVID-19 were treated with dexamethasone

6 mg/day and nasal oxygen 2-4 l/min for 7 days in addition to favipiravir treatment. Hospitalized patients with severe COVID-19 pneumonia were given favipiravir treatment in accordance with national guidelines[30], oxygen treatment with a high-flow nasal cannula with SpO_2 > 92%, and methylprednisolone treatment for 3 days at a dose of 250 mg/day. Patients with elevated CRP, ferritin, LDH and increased oxygen demand after 72 hours of systemic steroid treatment were evaluated for macrophage activation syndrome and tocilizumab 400 mg/day was added to their treatment. Twenty-four hours later, the same dose (maximum 800 mg) was repeated in patients with no response. Patients who did not respond to oxygen therapy with high-flow nasal cannula were followed-up with noninvasive or invasive mechanical ventilation according to treatment response and compliance. According to the culture results obtained during the follow-up of the patients, antibiotherapies were organized for the co-infections that developed.

A blood sample was taken from all patients included in the study once at the time of admission to the hospital. Sera were obtained and kept at -20°C until analysis. Serum CRP, LDH, fibrinogen, D-dimer, ferritin, and TAFI levels were determined in each sample. Serum CRP, LDH, and ferritin levels were measured in a Beckman Coulter AU5800 autoanalyzer (Brea, CA, USA). Serum fibrinogen levels were measured with an STA R Max 3 (Stago, Asnières-sur-Seine, France) hemostasis and coagulation analyzer. Serum TAFI levels were measured by ELISA using a commercial ELISA kit (BT Lab, Catalog No.: E1134Hu, Lot No: 202111018, Shanghai, China).

Statistical Analysis

Statistical analysis was performed using SPSS (version 25.0, IBM Corp., Armonk, NY, USA) package program. The Kolmogorov-Smirnov test was used to evaluate the normality of the data. The results are shown as the mean ± standard deviation. Comparisons of results obtained from mild, moderate, and severe groups were performed by using one-way ANOVA. A post hoc Tukey test was used to determine the differences between subgroups. Statistical significance was set at $p < 0.05$. Receiver operating characteristic (ROC) analysis was performed to define serum TAFI cutoff values determining mortality, intubation status, and noninvasive mechanical ventilation need.

Results

The demographic characteristics (age, gender) and clinical characteristics (death ratio, intubation ratio, and noninvasive mechanical ventilation need ratio) of the patients are shown in Table I. The mean age of all COVID-19 patients (n = 90) was 56.8 ± 14.1 years. There was no significant difference between the ages of the patients in the mild, moderate and severe groups. All positive cases of death, intubation, and noninvasive mechanical ventilation needed to be included in the severe group.

One-way ANOVA performed to define the differences between subgroups resulted in *p*-values lower than 0.05 for all biochemical analytes (CRP, LDH, fibrinogen, D-dimer, ferritin, and TAFI) (Table II). The mean serum TAFI level of all patients was 695.46 ± 324.42 ng/mL. There were significant differences in terms of serum TAFI levels between the mild and severe groups, with the highest in the severe group (853.04 ± 338.58 ng/mL) compared to the mild group (548.33 ± 264.17 ng/mL) (Figure 1). Serum TAFI levels were not significantly different between mild and moderate patients or moderate and severe patients ($p > 0.05$ for both comparisons).

Table I. Demographic and clinical characteristics of the patients.

	All (n = 90)	Mild (n = 27)	Moderate (n = 29)	Severe (n = 34)
Age (years)	56.8 ± 14.1	46.2 ± 9.3	58.7 ± 12.6	63.7 ± 18.4
Gender, M/F (%)	55/45	52/48	55/45	58/42
Death, n (%)	9 (10%)	0 (0%)	2 (6.9%)	7 (20.6%)
Intubation, n (%)	15 (16.6%)	0 (0%)	4 (13.7%)	11 (32.3%)
Non. Mech. Vent. n (%)	26 (28.8%)	0 (0%)	7 (24.1%)	19 (55.9%)

Age is presented as the mean ± standard deviation, M/F: male/female, Non. Mech. Vent.: Noninvasive Mechanical Ventilation Need.

Table II. Biochemical values of patients and comparisons between groups.

Groups	All (n = 90)	Mild (n = 27)	Moderate (n = 29)	Severe (n = 34)
CRP (mg/L)	61.7 ± 45.8*	19.8 ± 11.2[a]	75.4 ± 49.3	82.7 ± 79.2[b]
LDH (U/L)	431.1 ± 176.5*	235.1 ± 54.5[a]	402.6 ± 188.4[c]	611.2 ± 264.4[b]
Fibrinogen (mg/dL)	389.1 ± 159.6*	342.6 ± 110.42[a]	481.3 ± 162.7[c]	349.9 ± 196.2
D-Dimer (ng/mL)	1,983.3 ± 1,232.9*	298.1 ± 220.4	1,982.7 ± 1,498.1	3,321.76 ± 1,811.7[b]
Ferritin (ng/ml)	718.6 ± 537.2*	171.2 ± 190.8[a]	821.7 ± 765.2	1,065.5 ± 618.3[b]
TAFI (ng/mL)	695.46 ± 324.42*	548.33 ± 234.17	685.01 ± 300.66	853.04 ± 338.58 [b]

The results are expressed as the mean ± standard deviation; *: $p<0.05$ for one-way ANOVA test; [a,b,c]show one-way ANOVA Tukey post hoc test p-values ([a]Significant difference between mild and moderate patients; [b]Significant difference between mild and severe patients; [c]Significant difference between moderate and severe patients).

ROC curve analysis for predicting mortality revealed that TAFI levels could detect 85% of deaths. The results of ROC curve analysis for predicting mortality were as follows: area under ROC curve (AUC): 0.85 [95% confidence interval (CI) 0.70-0.95] ($p = 0.04$), cut off TAFI value to predict intubation status with high sensitivity 818.05 ng/mL (83.3% sensitivity and 71.4% specificity), likelihood ratio (LR): 2.91. LR is small and cannot be used as a strong cutoff value. Nevertheless, ROC analysis revealed that serum TAFI levels could detect 85% of deaths (Figure 2).

The results of ROC curve analysis for predicting intubation status were as follows: AUC: 0.86 (95% CI 0.78-0.94) ($p < 0.01$), cut off TAFI value to predict intubation status with high sensitivity 818.05 ng/mL (100% sensitivity and 74.1% specificity), LR: 3.85. LR is small and cannot be used as a strong cut-off value. Nevertheless, ROC analysis revealed that serum TAFI levels could detect 86% of intubated cases (Figure 3).

The results of ROC curve analysis for predicting noninvasive mechanical ventilation needs (invasive and noninvasive) were as follows: AUC: 0.66 (95% CI 0.51-0.81) ($p = 0.043$), cut-off TAFI value to predict intubation status: 705.05 ng/mL (70.6% sensitivity and 63.8% specificity), LR: 1.94. LR is small and cannot be used as a strong cutoff value. ROC analysis revealed that serum TAFI levels could detect only 66% of cases that needed noninvasive mechanical ventilation (Figure 4).

Discussion

In our study, we observed that TAFI levels were higher in the severe group than in the mild group. In addition, we found statistically that the TAFI level is an important guide in predicting intubation and mortality.

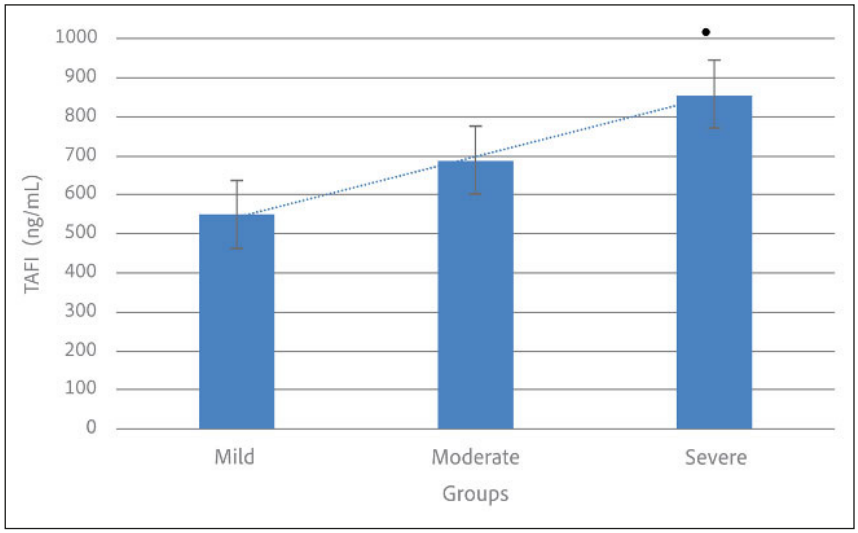

Figure 1. TAFI values of mild, moderate and severe groups.

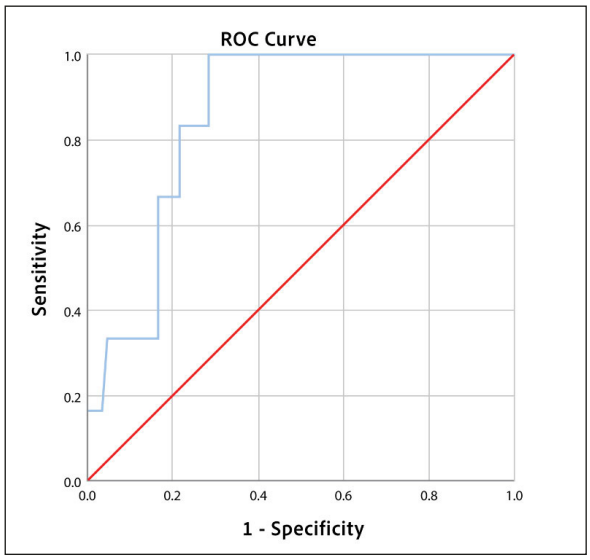

Figure 2. ROC curve for prediction of mortality with TAFI values.

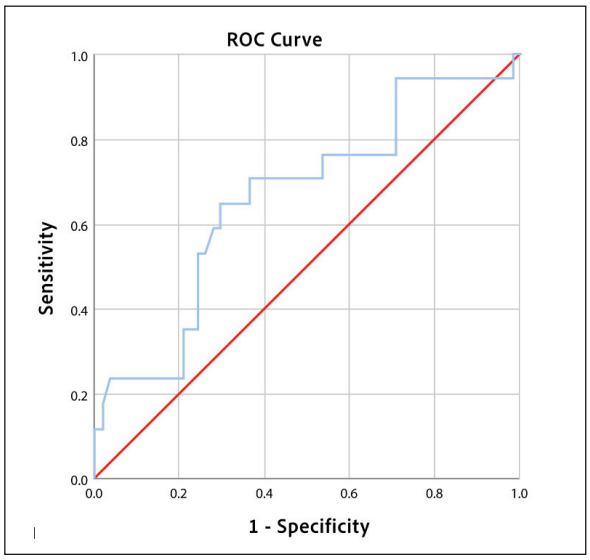

Figure 4. ROC curve for prediction of noninvasive mechanical ventilation need with TAFI values.

In COVID-19, the course of the disease varies. The disease can be asymptomatic or cause severe pneumonia, ARDS, multiple organ failure and death[31]. Due to this variable clinic in COVID-19 patients, markers that will be useful in predicting the course of the disease and early diagnosis are needed. Studies[32] have shown that lung tomography may play a role in the early diagnosis of RT-PCR-negative patients. In addition, CRP, D-dimer, ferritin, LDH, neutrophil/lymphocyte ratio, chest radiograph score and many other markers have been used[33-36] to determine the level of severity and predict mortality in COVID-19 patients.

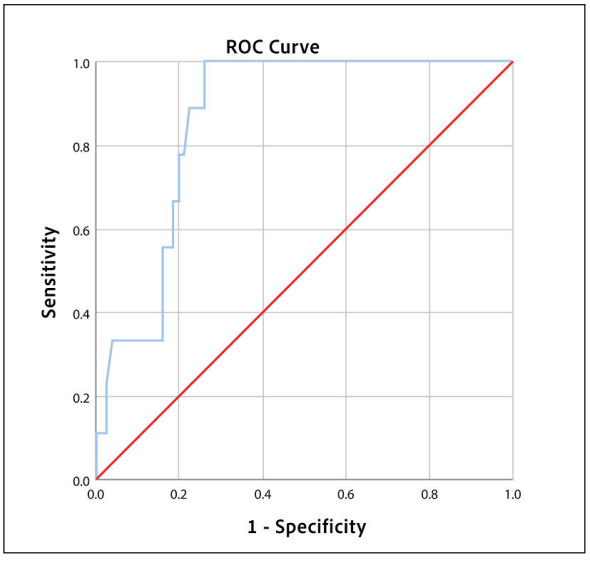

Figure 3. ROC curve for prediction of intubation status with TAFI values.

Although respiratory failure is the main cause of mortality, thromboembolic complications are frequently observed[37,38] in COVID-19. The main reason for this situation is the deterioration of the hemostatic balance in favor of the hypercoagulable and hypofibrinolytic state. When the coagulation parameters are considered, in general, prolonged prothrombin time, low antithrombin concentrations and high fibrinogen levels stand out[24,39]. In addition, increased plasma D-dimer concentrations in COVID-19 are an important indicator for plasmin-mediated fibrinolysis due to activation of the coagulation cascade[40].

In a study[41], the levels of carboxypeptidase U (CPU, TAFIa, CPB2) were examined in COVID-19 patients. In accordance with our study, a progressive increase in carboxypeptidase U concentrations was observed[41] in patients who required hospitalization. These changes contribute to the reduction of fibrinolysis in patients with COVID-19, thereby increasing the risk of thrombosis. In addition, it was also shown in the same study[41] that carboxypeptidase U concentration levels at admission were associated with disease severity and duration of hospitalization.

When we look at the literature, studies have shown[42] that serum TAFI levels are high in patients diagnosed with PTE, regardless of the anticoagulant use. One of the important causes of mortality in COVID-19 is PTE, which develops secondary to the deterioration of the coagulation

cascade. Although the causes of death of the patients were not recorded in our study, when the laboratory parameters of the patients who died were examined, it was noted that D-dimer levels, one of the indirect indicators of PTE, increased statistically significantly with the severity of the disease. Considering all these data, it can be concluded that TAFI plays a role in the etiology of PTE development in COVID-19.

Since the beginning of the pandemic, significant efforts have been made to understand COVID-19, and significant progress has been made in discovering its pathogenesis, epidemiology and clinical features. The results obtained from clinical and autopsy studies show that direct viral damage, infiltration of organs by immune cells, and excessive cytokine production are responsible for the pathology in severe COVID-19. This situation is similar to sepsis syndromes caused by other pathogens[43]. In one study[44], plasma TAFI levels were examined in patients with sepsis and in the control group. The plasma TAFI levels of patients with sepsis were found to be statistically significantly higher. Considering that sepsis and septic shock are the most important causes of mortality in COVID-19, especially in intensive care hospitalizations, TAFI levels were thought to be an important biomarker in the prediction of COVID-19 mortality and sepsis.

As the TAFI level increases, it causes a decrease in fibrinolysis and increases the risk of thrombosis. This situation increases the risk of thromboembolic events and, in some cases, is mortal. In previous studies[44], the role of TAFI in the pathophysiology of sepsis, PTE, and various infectious diseases was examined, and in our study, we examined the level of TAFI in COVID-19. There was no significant difference between the ages and sexes of the patients included in our study, and our patients were grouped by the severity of the disease. LDH, CRP, D-dimer, and ferritin levels, which were also stated in previous studies[45] to have prognostic importance for COVID-19, were significantly higher in the severely ill group. We observed that the TAFI level was statistically significantly higher in severe patients than in mild and moderate patients. We also found that the TAFI level had a high sensitivity in indicating that patients were intubated and died. However, the TAFI level could not detect the rate of noninvasive mechanical ventilation with high sensitivity.

In our study, patients who were followed-up as outpatients or hospitalized with a diagnosis of COVID-19 were included and only serum material was taken at the time of diagnosis for the measurement of serum TAFI levels. The most important limitation of our study was that TAFI level could not be measured during follow-up. However, serum samples could not be taken during the follow-up of the patients because it was thought that the revised treatment for comorbidities that developed in addition to the treatment recommended by our national guideline for COVID-19 might have an effect on the serum TAFI level. In addition, only patients diagnosed with COVID-19 were evaluated in our study and TAFI level can be examined in other viral infections and can be used as a biomarker in predicting the severity of the disease and mortality. More comprehensive studies can be conducted by increasing the number of patients and the follow-up period after hospitalization.

Conclusions

COVID-19 disease progresses more severely in patients with high TAFI levels and that high TAFI levels are associated with mortality and intubation rates. We can speculate that, the use of those agents preventing the increase in TAFI may prevent thromboembolic complications by increasing fibrinolysis capacity in the future. Our study reveals that TAFI may be used as a promising biomarker showing mortality and prognosis in COVID-19, which is still a global epidemic and has difficulties in treatment.

Conflict of Interest

None to declare.

Authors' Contributions

Alperen Aksakal: Conceptualization, Methodology, Data curation, Investigation, Resources, Writing- Original draft preparation. Adil Furkan Kiliç: Methodology, Data curation, Investigation, Resources. Dursun Erol Afşin: Data curation, Investigation. Nurcan Kiliç Baygutalp: Data curation, Writing- Reviewing and Editing. Buğra Kerget: Methodology, Data curation, Investigation, Resources.

Informed Consent

Patients or their legal representatives provided written and verbal consent about the study.

Ethics Approval

The Institutional Review Board at Health Science University Faculty of Medicine approved this study (BEAH KAEK 2022/04-10), which was conducted in compliance with the 2013 version of the 1975 Helsinki Declaration.

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