ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

D-Dimer/Fibrinogen Ratio as a Prominent Predictor of Mortality in COVID-19 Patients Admitted To the Intensive Care Unit

Yoğun Bakım Ünitesinde Yatan COVID-19 Hastalarında Mortalitenin Belirgin Bir Belirleyicisi Olarak D-Dimer/Fibrinojen Oranı

Avşar ZERMAN[1] Cihan AYDIN[2] Nermin ZERMAN[1]

ÖZ

Amaç: Bu retrospektif kohort çalışmada komorbidite varlığı üzerinden herhangi bir kısıtlama olmaksızın D-dimer/fibrinojen oranının COVID-19'da bir belirleyici olarak değerlendirilmesi amaçlandı.
Araçlar ve Yöntem: Yoğun bakım ünitesine kabul edilen hastalarla retrospektif kohort çalışması yapıldı. Demografik veriler (cinsiyet, yaş, vücut kitle indeksi, komorbiditeler), prognostik klinik skorlar, sıralı organ yetmezliği değerlendirme (SOFA) skoru ve Glasgow Koma Skalası (GKS) skorları, Yoğun bakımda yatan hastaların laboratuvar sonuçları ve invazif mekanik ventilasyon (İMV) ihtiyacı ve süresi kaydedildi.
Bulgular: Kronik böbrek hastalıkları, akut böbrek yetmezliği, kalp hastalıkları ve şiddetli sepsis, çıkış grubunda anlamlı olarak daha yüksekti. Daha düşük lenfosit seviyelerinin artan ölüm oranıyla ilişkili olduğu bulunmuştur. Ayrıca nötrofil/lenfosit oranı (NLR) ve nötrofiller artan mortaliteyle ilişkiliydi. Daha yüksek D-dimer/fibrinojen oranı (DDFR) mortalite için bir risk faktörüydü, ancak yoğun bakım ünitesinde yatış süresi için bir risk faktörü değildi.
Sonuç: DDFR'nin, COVID-19'da hastane içi mortaliteyi öngörmede potansiyel bir etkisi vardır.

Anahtar Kelimeler: COVID-19; doğuştan gelen inflamatuar yanıt; kan pıhtılaşması; ölüm oranı

ABSTRACT

Purpose: In this retrospective cohort study, evaluating the role of the D-dimer/fibrinogen ratio in predicting the in-hospital mortality rate of COVID-19 regardless of the presence of comorbidities was aimed.
Materials and Methods: This retrospective cohort study included patients admitted to the intensive care unit. The demographic data of the patients (sex, age, body mass index, comorbidities), their prognostic clinical scores, laboratory results, and need for and duration of invasive mechanical ventilation (IMV) were recorded.
Results: The rates of chronic renal diseases, acute renal failure, cardiac diseases, and severe sepsis were significantly higher in the exitus group. It was found that lower levels of lymphocytes were associated with increased mortality. Furthermore, neutrophil counts and the neutrophil to lymphocyte ratio (NLR) were associated with increased mortality. A higher D-dimer/fibrinogen ratio (DDFR) was a predictor of mortality but not a predictor of the duration of hospitalization in the ICU.
Conclusion: DDFR has a potential impact in anticipating mortality rates in COVID-19 patients.

Keywords: COVID-19; blood coagulation; innate inflammatory response; mortality rate

Received: 30.08.2023; Accepted: 07.10.2024

[1]Department of Internal Medicine, Kırşehir Ahi Evran University, Kırşehir, Turkey.
[2]Department of Chest Diseases, Department of Internal Medicine, Yozgat Bozok University, Yozgat, Turkey.
[3]Kırşehir Ahi Evran University Training and Research Hospital, Kırşehir, Turkey.

Corresponding Author: Cihan Aydın, Department of Chest Diseases, Department of Internal Medicine, Yozgat Bozok University, Yozgat, Turkey.
e-mail: dr.cihanaydin@hotmail.com

How to cite: Zerman A, Aydın C, Zerman N. D-Dimer/fibrinogen ratio as a prominent predictor of mortality in COVID-19 patients admitted to the intensive care unit. Ahi Evran Med J. 2025;9(1):17-23. DOI: 10.46332/aemj.1352549

INTRODUCTION

COVID-19 has spread all over the world since December 2019. COVID-19 infection has been shown to have a considerable potential for high mortality and morbidity.[1]

In the early phase of the COVID-19 pandemic, several studies were conducted to determine risk factors for poor prognosis.[2,3] These studies found comorbidities such as diabetes mellitus (DM), ischemic heart diseases, and heart failure which include the pathological inflammation and coagulation processes in the cellular background as risk factors.[4,5] COVID-19 infection may cause a fatal course via the dysregulation of coagulation and inflammation responses.[1,3-5]

The interrelations between coagulation and inflammation in COVID-19 infections led researchers and clinicians to evaluate COVID-19 as a thrombo-inflammatory syndrome.[6,7] Widespread endothelial dysfunction, severe coagulopathy, and thromboembolism occur in severe COVID-19 infection cases.[8] Anticoagulants and proteases activated in the coagulation process regulate inflammation through specific cell receptors, whereas proinflammatory cytokines and chemokines affect procoagulant and anticoagulant processes.

D-dimer forms after fibrin decomposition during fibrinolysis.[9] D-dimer and fibrinogen are both products in the coagulation cascade, and their high levels have been found as predictors of poor outcomes in COVID-19 cases.[1,3,10-12]

In previous studies, the D-dimer/fibrinogen ratio (DDFR) was shown to be a predictor of poor outcomes of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and heart failure.[9,13]

Elevated DDFR was found to have a worsening impact on outcomes of COVID-19 with concomitant heart failure.[14]

In this retrospective cohort study, we aimed to research the predictive role of DDFR in COVID-19 without regard to the presence of comorbidities and to contribute to the current literature considering the limited number of studies investigating this parameter in this context.

MATERIALS and METHODS

Patients

This study was approved by the Clinical Research Ethics Committee of Kırşehir Ahi Evran University (dated 09.08.2022 and numbered 2022-15/137). Patients hospitalized with COVID-19 infection in the intensive care unit (ICU) between April 2020 and September 2022 were included. Patients with pregnancy and life-threatening conditions such as severe heart failure, renal failure, malignancy, and acute coronary syndrome were not included in the sample.

Methods

The demographic data of the patients (sex, age, body mass index, comorbidities), their prognostic clinical scores, their laboratory results, and their need for and duration of inva-sive mechanical ventilation (IMV) were recorded.

APACHE II

APACHE II is a clinical parameter used to predict the chances of mortality in patients hospitalized in the ICU.[15] Age, body temperature, mean arterial pressure, arterial blood gas pH results, heart rate, respiratory rate, laboratory test results (sodium, potassium, creatinine, acute renal failure, white blood cell count, and hematocrit), Glasgow Coma Scale (GCS) scores, and the fraction of inspired oxygen (FiO_2) are all included in the clinical score. The concentration of oxygen in room air is approximately 21%. The APACHE II score represents the probability of mortality as a percentage (%).

SOFA

SOFA is a sepsis-related organ failure assessment score that includes the partial pressure of oxygen, FiO_2, need for mechanical ventilation, platelets, bilirubin, creatinine, GCS, and mean arterial pressure or need for vasopressor medication. The SOFA score refers to the probability of mortality as a percentage.[16,17]

Glasgow Coma Scale

The GCS is used to systematically assess the degree of compromised consciousness and includes three aspects of responsiveness: eye-opening, motor responses, and verbal responses. GCS scores vary in the range of 3-15.[18]

Statistical Analysis

The rate of in-hospital mortality was the primary outcome measure, while the length of hospital stay in the ICU and the requirement of invasive mechanical ventilation were the secondary outcome measures. The Statistical Package for the Social Sciences version 28.0 software for Windows (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp., USA) was used to conduct the statistical analyses. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality assumptions of the quantitative variables. Depending on the type of variable and the normality of distributions, the Chi-Squared test, Fisher-Freeman-Halton test, and the Mann Whitney-U test were employed for the univariate analysis of the variables. The relationship between ICU hospitalization duration and DDFR was analyzed using Spearman correlation test. The descriptive statistics of the variables are presented as mean±standard deviation, frequencies (n), and percentages (%). Bivariate logistic regression analysis was performed to determine the effective risk factors in determining the mortality rates of the patients. Forward: The conditional logistic regression analysis method was used to determine the most accurate logistic model.

RESULTS

We included 267 patients in this study. Among these patients, 55.8% (n:149) died due to COVID-19 infection. The results of the group of patients who died from COVID-19 were compared with those of the group who survived (Supplement Table 1). The differences between the sex (p=0.937) and BMI (p=0.254) distributions of the two groups were not statistically significant. A significant mortality risk factor was older age (p=0.000). A 1-unit increase in age corresponded to a 0.077-unit increase in the probability of mortality (OR: 1.077, 95% CI: 1.046-1.109, p=0.000). A 1-unit increase in ferritin levels was found to increase the probability of mortality by 0.001 units (OR: 1.001, 95% CI: 1.000-1.002, p=0.022) (Table 1).

Following the univariate analysis conducted to evaluate the differences in mortality status among patients based on the included parameters, bivariate logistic regression analysis was performed to determine whether these parameters were significant risk factors for mortality. The forward conditional logistic regression analysis method was used to determine the most accurate logistic model, and the percentage correct value was 85.7%. The model's correct estimation value was also appropriate according to the Hosmer-Lemeshow test score (χ^2=5.857, P=0.663). The coefficients found as a result of the bivariate logistic regression analysis are shown in Table 1.

Table 1. Bivariate logistic regression analysis results.

Variables	B	S.E.	Sig.	OR	95% CI for Exp(B) Lower-Upper
Age	0.074	0.015	0.000	1.077	1.046-1.109
Serum albumin	1.392	0.447	0.002	4.022	1.674-9.663
Ferritin	0.001	0.002	0.022	1.001	1.000-1.002
LDH	0.002	0.001	0.007	1.002	1.001-1.004
IMV	3.827	0.573	0.000	45.903	14.928-141.150
Hospitalization duration	0.085	0.024	0.000	1.089	1.039-1.142

LDH: Lactate dehydrogenase, IMV: invasive mechanical ventilation

Clinical Scores

The clinical scores of the exitus group, including their APACHE-II (p=0.000), SOFA (p=0.000), and GCS (p=0.000) scores, were significantly higher than those of the non-exitus group.

Comorbidities

Chronic renal diseases (p=0.028), acute renal failure (p=0.014), cardiac diseases (p=0.014), and severe sepsis (p=0.000) were associated with mortality.

Hemogram Parameters

Lower lymphocyte counts (p=0.006), higher neutrophil to lymphocyte ratios (NLR) (p=0.000), and higher neutrophil counts (p=0.044) were risk factors for an increased risk of mortality.

Biochemical Parameters

Lower plasma serum albumin levels (p=0.000) were a predictor of increased mortality. Furthermore, higher levels of procalcitonin, C-reactive protein (CRP) (p=0.034), neutrophils (p=0.044), ferritin (p=0.002), lactate dehydrogenase (LDH) (p=0.003), uric acid (p=0.001), troponin (p=0.000), CK-MB (p=0.005), lactate (p=0.013), and aspartate aminotransferase (AST) (p=0.005) were related to increased mortality rates.

A 1-unit decrease in serum albumin values corresponded to a 3.022-unit increase in mortality rates (OR: 4.022, 95% CI: 1.674-9.663, p=0.002). A 1-unit increase in ferritin values corresponded to a 0.001-unit increase in mortality rates (OR: 1.001, 95% CI: 1.000-1.002, p=0.022). A 1-unit increase in LDH 1 values corresponded to a 0.002-unit increase in mortality rates (OR: 1.002, 95% CI: 1.001-1.004, p=0.007).

Other Clinical Parameters

The requirement of invasive mechanical ventilation was related to mortality (55.7% vs 6.0%, p-value: 0.000). A 1-unit increase in the requirement of invasive mechanical ventilation corresponded to a 44.903-unit increase in mortality rates (OR: 1.089, 95% CI: 14.928-141.150, p=0.000).

D-Dimer/Fibrinogen Ratio

A higher DDFR was a predictor of mortality (p=0.000), but it was not a predictor of the duration of hospitalization in the ICU (p=0.313). Spearman's Rho coefficients showing the relationship between ICU hospitalization durations and DDFR values are shown in Table 3. There was no statistically significant relationship between DDFR values and ICU hospitalization durations (ρ=-0.062, p=0.313) (Table 2).

Table 2. The relationship between the D-dimer/Fibrinogen ratio and ICU hospitalization durations.

Spearman's rho	ICU hospitalization duration	DDFR
ICU hospitalization duration	Rho	-0.062
	1.000	
	p	0.313
DDFR	Rho	
	p	1000

ICU: Intensive care unit, DDFR: D-dimer/Fibrinogen ratio.

DISCUSSION

We found that the D-dimer/Fibrinogen ratio (DDFR) was a potential predictor of the mortality of COVID-19 in the ICU. The exitus group had significantly higher DDFR values than the non-exitus group (p<0.005). The elevation of this biomarker is caused by the dysregulation of inflammation and thrombosis. The comparison of the laboratory results of the two groups also supported this implication. Lower plasma serum albumin and higher values of procalcitonin, CRP, neutrophils, ferritin, and LDH were associated with increased mortality. The results of this study were consistent with the current literature. Previously, older age, chronic renal diseases, acute renal failure, cardiac diseases, and severe sepsis have been identified as predictors of poor prognosis.[19-22] Considering our laboratory results and those reported in previous studies, it can be concluded that higher levels of troponin, NLR, LDH, AST, CRP, procalcitonin, and ferritin, in addition to lower levels of serum albumin and lymphocytes, are predictors of mortality in COVID-19 cases.[21-25]

An important aspect to emphasize is the limited number of studies that have evaluated the worsening impact of higher DDFR values in COVID-19 cases. Most previous studies have revealed that D-dimer and fibrinogen are independent predictors of poor outcomes.[26-29]

In the review article by Bivona et al., the potential of laboratory parameters to affect COVID-19 severity was analyzed comprehensively.[30] An evaluation was carried out separately for each laboratory parameter with qualified

studies. Similar to our results, higher levels of troponin, NLR, LDH, AST, CRP, procalcitonin, and ferritin, in addition to lower levels of serum albumin and lymphocytes, were identified as predictors of severe infection. These results considered along with our results demonstrate the need for more research about new biomarkers in this context.

In the meta-analysis study conducted by Zhan et al., 33 studies were included. Elevated D-dimer values were found as a risk factor for thromboembolism, infection severity, and mortality in COVID-19 cases.[26] These findings were also strongly linked to the underlying mechanism of death. The interaction between inflammation and coagulation, as well as dysregulated inflammation, lead to severe COVID-19 infection. Thrombotic processes can also cause fatal outcomes via thromboembolism.[26]

Fibrinogen was also found to be an important product in the coagulation cascade and identified as a critical laboratory parameter in the study conducted by D'Ardes et al.[28] The underlying mechanism of the prognostic role of fibrinogen was explained by altered polymerization kinetics, partly accounted for by an increase in sialic acid on the cellular level.[29] These findings also indicated the crucial role of coagulation, inflammation, and endothelial damage in these processes. Anticoagulants and proteases activated during coagulation regulate inflammation through specific cell receptors, whereas proinflammatory cytokines and chemokines affect procoagulant and anticoagulant processes.

The expression of tissue factor in endothelial surfaces is increased by IL-6, TNF-, IL-1, and CRP, and the presentation of tissue factor is the first step in the coagulation cascade.[31]

Aydin et al. found that DDFR was a predictor in AECOPD, which is characterized also by respiratory failure similar to the case in patients with COVID-19 infection.[9]

Murat et al. conducted a retrospectively designed two-center study with 232 COVID-19 patients with concomitant heart failure (HF) hospitalized in the ICU.[14] The tertiles 1-3 of patients with HF and COVID-19 were categorized. DDFR values below 0.37, between 0.38 and 1.13, and above 1.13 were included in the first tertile, second tertile, and third tertile, respectively. The optimal cutoff value of serum DDFR was calculated to be 0.61. DDFR was related to in-hospital mortality. Our findings were consistent with these results, and we analyzed this marker in a sample formed without a restriction based on the presence of comorbidities. Patients with severe heart failure were probably included in their study, as far as understood from the inclusion and exclusion criteria. Besides, to make clear conclusions, we excluded patients with life-threatening conditions such as severe heart failure, renal failure, malignancy, and acute coronary syndrome.

A fatal course via the dysregulation of the thrombotic and inflammatory processes occurs at on cellular level.[1] The interrelations between thrombosis and inflammation led researchers and clinicians to evaluate COVID-19 as a thrombo-inflammatory syndrome.[6,7]

D-dimer forms after fibrin decomposition during fibrinolysis.[9] Both D-dimer and fibrinogen have functions in the coagulation cascade and have been reported to be markers of poor prognosis in COVID-19 cases.[1,3,10-12]

It was determined that elevated levels of D-dimer and fibrinogen were brought on by pulmonary inflammation led by COVID-19, along with localized platelet activation, blood coagulation, and relative hypofibrinolysis.[7] Hyperinflammation is triggered by COVID-19 through the impairment of innate and adaptive antiviral defense mechanisms. The renin-angiotensin-aldosterone system (RAAS) activates pathological hypercoagulability and immunothrombosis. At this point, it should also be emphasized that the COVID-19 infection process in the human body is facilitated through the ACE-2 receptors on the cell surface.

This study, with an optimal design, has the potential to contribute to the current literature considering the low number of previous studies on the topic in this context and the suboptimal designs in these studies. DDFR has a potential role in the anticipation of mortality in COVID-19. Besides, physicians can contribute to the current literature by researching new biomarkers.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

This study was approved by the Clinical Research Ethics Committee of Kırşehir Ahi Evran University (dated 09.08.2022 and numbered 2022-15/137).

Authors' Contributions

Concept/Design: AZ, CA. Data Collection and/or Processing: AZ, NZ. Data analysis and interpretation: AZ, CA. Literature Search: NZ, CA. Drafting manuscript: CA, NZ. Critical revision of manuscript: AZ.

REFERENCES

1. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol. 2020;13(11):1265-1275.
2. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalizations: systematic review and meta-analysis. BMJ Evid Based Med. 2021;26(3):107-108.
3. Qeadan F, Tingey B, Gu LY, Packard AH, Erdei E, Saeed AI. Prognostic Values of Serum Ferritin and D-Dimer Trajectory in Patients with COVID-19. Viruses. 2021;13(3):419.
4. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res. 2020;69(12):1181-1189.
5. Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. Int J Hematol. 2021;113(1):45-57.
6. Ciceri F, Beretta L, Scandroglio AM et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit. Care Resus. 2020;22(2):95-97.
7. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin. Chim. Acta 2020;507:167-173.
8. Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2021;17(1):46-64.
9. Aydin C, Yıldız BP, Hattatoğlu DG. D-dimer/Fibrinogen ratio and recurrent exacerbations might have a potential impact to predict 90-day mortality in patients with COPD exacerbation. Malawi Med J. 2021;33(4): 276-280.
10. Du WN, Zhang Y, Yu Y, et al. D-dimer levels is associated with severe COVID-19 infections: A meta-analysis. Int J Clin Pract. 2021;75(8):e14031.
11. Miltiades A, Houck PJ, Monteleone M, et al. Insights into Fibrinogen-Mediated COVID-19 Hypercoagubility in Critically Ill Patients. J Neurosurg Anesthesiol. 2022;34(1):136-140.
12. Sui J, Noubouossie DF, Gandotra S, Cao L. Elevated Plasma Fibrinogen Is Associated With Excessive Inflammation and Disease Severity in COVID-19 Patients. Front Cell Infect Microbiol. 2021;11:734005.
13. Zhao TJ, Yang QK, Tan CY, Bi LD, Li J, Miao ZL. Prognostic value of D-dimer/fibrinogen ratio in the adverse outcomes of patients hospitalized for heart failure. Biomark Med. 2020;14(18):1733-1745.
14. Murat S, Murat B, Dural M, Mert GO, Cavusoglu Y. Prognostic value of D-dimer/fibrinogen ratio on in-hospital outcomes of patients with heart failure and COVID-19. BiomarkMed. 2021;15(16):1519-1528.
15. Sungono V, Hariyanto H, Soesilo TEB, et al. Cohort study of the APACHE II score and mortality for different types of intensive care unit patients. Postgrad Med J. 2022;98(1166):914-918.
16. Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Crit Care Med. 2009;37(5):1649-1654.
17. Fleiss N, Polin RA. Sequential organ failure assessment scores to predict outcomes: from adults to neonates. Curr Opin Pediatr. 2023;35(2):218-222.
18. Jain S, Iverson LM. Glasgow Coma Scale. In: StatPearls. Treasure Island: America.. https://www.ncbi.nlm.nih.gov/books/NBK 513298/ Accessed date 07 December, 2024.
19. Eryilmaz-Eren E, Ture Z, Kilinç-Toker A, Korkmaz S, Çelik İ. The course of COVID-19 in patients with hematological malignancies and risk factors affecting mortality: A cross-sectional study. Hematol Transfus Cell Ther. 2024;46(1):3-7.
20. Vardavas CI, Mathioudakis AG, Nikitara K, et al. Prognostic factors for mortality, intensive care unit and hospital admission due to SARS-CoV-2: a systematic review and meta-analysis of European cohort studies. Eur Respir Rev. 2022;31(166):220098.
21. Menditto A, Protic O, Di Rosa M, Bonfigli AR, Lattanzio F, Antonicelli R. Admission high-sensitivity cardiac troponin levels as a prognostic indicator for in-hospital mortality rates in the elderly and very elderly COVID-19 patients. Arch Gerontol Geriatr. 2023;104:104822.
22. Finfer S, Venkatesh B, Hotchkiss RS, Sasson SC. Lymphopenia in sepsis-an acquired immunodeficiency? Immunol Cell Biol. 2023;101(6):535-544.
23. Geraili Z, Hajian-Tilaki K, Bayani M, et al. Evaluation of Time-Varying Biomarkers in Mortality Outcome in COVID-19: an Application of Extended Cox Regression Model. Acta Inform Med. 2022;30(4): 295-301.
24. Ergenc Z, Ergenc H, Araç S, et al. Predictors of disease severity, clinical course, and therapeutic outcome in COVID-19 patients: our experience with 1,700 patients. Eur Rev Med Pharmacol Sci. 2022;26(21): 8180-8187.
25. Elouadani M, Konzi C, Addi Y, et al. C-Reactive Protein, Ferritin, and Procalcitonin in 300 Moroccan Patients with COVID-19. Clin Lab. 2022;68(10).
26. Zhan H, Chen H, Liu C, et al. Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression. Clin Appl Thromb Hemost. 2021;27:1-10.
27. Qeadan F, Tingey B, Gu LY, Packard AH, Erdei E, Saeed AI. Prognostic Values of Serum Ferritin and D-Dimer Trajectory in Patients with COVID-19. Viruses. 2021;13(3):419.
28. D'Ardes D, Boccatonda A, Cocco G, et al. Impaired coagulation, liver dysfunction, and COVID-19: Discovering an intriguing relationship. World J Gastroenterol. 2022;28(11):1102-1112.
29. Moiseiwitsch N, Zwennes N, Szlam F, Sniecinski R, Brown A. COVID-19 patient fibrinogen produces dense clots with altered polymerization kinetics, partially explained by increased sialic acid. J Thromb Haemost. 2022;20(12):2909-2920.

30. Bivona G, Agnello L, Ciaccio M. Biomarkers for Prognosis and Treatment Response in COVID-19 Patients. Ann Lab Med. 2021;41(6):540-548.

31. Bester J, Matshailwe C, Pretorius E. Simultaneous presence of hypercoagulation and increased clot lysis time due to IL-1β, IL-6 and IL-8. Cytokine. 2018;110:237-242.