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Fibrinogen-to-albumin ratio predicts mortality in COVID-19 patients admitted to the intensive care unit

Abstract

Introduction: Coronavirus disease 2019 (COVID-19) is an inflammatory disease, and serum albumin and fibrinogen are two important factors in systemic inflammation. We aimed to investigate the relationship between the fibrinogen-to-albumin ratio (FAR) and in-hospital mortality in COVID-19 patients admitted to the intensive care unit (ICU).

Material and methods: Patients diagnosed with COVID-19 admitted to the Adiyaman Training and Research Hospital from August to November 2020 were enrolled in this retrospective cohort study. They were divided into 2 groups based on in-hospital mortality: a survivor group (n = 188) and a non-survivor group (n = 198). FAR was calculated by dividing the fibrinogen value by the albumin value. Mortality outcomes were followed up until December 15, 2020.

Results: The average age of the patients was 71.2 ± 12.9 years, and 54% were male. On multivariate logistic analysis, diabetes mellitus (OR: 1.806; 95% CI: 1.142–2.856; p = 0.011), troponin I levels (OR: 1.776; 95% CI: 1.031–3.061; p = 0.038), and FAR (OR: 1.004; 95% CI: 1.004–1.007; p = 0.010) at ICU admission were independent predictors of in-hospital mortality in patients with COVID-19.

Conclusions: The FAR at admission was associated with mortality in patients infected with SARS-CoV-2 in the ICU.

Key words: coronavirus disease 2019, intensive care unit, fibrinogen-to-albumin ratio, mortality

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Introduction

Severe respiratory distress syndrome caused by coronavirus-2 (SARS-CoV-2) has affected the whole world in terms of health, social, educational, and economic aspects. The main cause of morbidity and mortality in patients with COVID-19 is viral pneumonia leading to acute respiratory distress syndrome [1]. In COVID-19 patients, D-dimer, troponin, procalcitonin, ferritin, and fibrinogen levels progressively increase in parallel with disease severity, while lymphocyte counts and albumin levels gradually decrease. A thromboembolic state, thrombo-inflammation, and coagulopathy have been suggested to play pivotal roles in the severity of clinical deterioriation in COVID-19 patients [2].

Fibrinogen is a positive acute phase reactant secreted from the liver, and it plays an active role in both the coagulation cascade and inflammation. Its synthesis increases in both acute and chronic inflammation as well as cardiovascular diseases and malignancy. Fibrinogen stimulates the production of proinflammatory cytokines such as interleukins-1β, IL-6 and tumor necrosis factor alpha [3]. In clot formation, fibrinogen is converted to fibrin by the enzyme thrombin; it also increases blood viscosity and stimulates thrombocyte aggregation.

Albumin, a major plasma protein, is a negative acute phase reactant, and its plasma level decreases in inflammatory diseases. Low albumin levels in hospitalized patients at the time of admission are associated with increased short- and

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long-term mortality rates [4]. Previous studies have shown significant associations of hypoalbuminemia with increased cardiovascular morbidity and mortality [5, 6].

Recent studies have also shown that the fibrinogen-to-albumin ratio (FAR) is associated with poor clinical outcomes in patients with cardiovascular diseases characterized by inflammation and thrombosis, and in those with malignancies [7, 8]. In addition, the FAR is an independent risk factor predicting disease severity in COVID-19 [9]. A meta-analysis investigating the mortality of patients with COVID-19 admitted to the intensive care unit (ICU) has been published. It included 52 studies published up to 30 September 2020; mortality rates varied from 10.6% to 61.9% depending on the geographical region [10]. It is important to predict the mortality of patients with COVID-19 requiring ICU treatment. Therefore, this study investigated the potential association between the FAR and in-hospital mortality in patients with SARS-CoV-2 pneumonia requiring intensive care.

Material and methods

Study population

We retrospectively analyzed the data of patients with COVID-19 treated in the Adiyaman University Education and Research Hospital ICU between 1 August and 30 November, 2020. Patients attending the hospital who presented with cough, dyspnea, myalgia, malaise, weight loss, sore throat, headache, fever, loss of appetite, diarrhea, nausea, vomiting, rhinitis, and/or loss of smell received the polymerase chain reaction (PCR) test for SARS-CoV-2 using nasopharyngeal swab specimens. Those with positive PCR results and with severe SARS-CoV-2 pneumonia were included in the study. Patients with a negative PCR result, lack of appropriate laboratory test parameters, terminal malignancy, or who were < 18 years of age were excluded.

The diagnosis of SARS-CoV-2 pneumonia was made according to the World Health Organization interim guidelines. Patients with COVID-19 who had dyspnea, respiratory rate > 30/min, tachycardia > 100/min, blood oxygen saturation level < 90% despite 5 L/min oxygen treatment, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of < 300 mm Hg, infiltrates in > 50% of the lung fields on X-rays, need for mechanical ventilation, development of acute organ dysfunction, sepsis, septic shock, immunosuppression, acute bleeding diathesis, arrhythmia, or increased troponin level were admitted to the ICU [11, 12].

Demographic characteristics, laboratory parameters, comorbidities (cardiovascular diseases, cerebrovascular diseases, hypertension, diabetes mellitus [DM], chronic obstructive lung disease, chronic kidney disease, or prior malignancy), epidemiologic features, and treatment protocols of patients were collected from the electronic medical records of our hospital. The endpoints of the study were discharge from the ICU and/or in-hospital mortality. Patients were divided into two groups according to in-hospital mortality: survivors and non-survivors. The patients discharged from the hospital were followed-up with until 15 December 2020 to determine mortality.

Collection of blood samples and biochemical analysis

Blood samples were collected for hematological and biochemical testing within 24 h after admission to the ICU. Complete white blood cell counts, including neutrophil and lymphocyte counts, were measured using an automated hematologic analyzer (CELL-DYN Ruby, Abbott Diagnostics, Abbott Park, IL, USA) and are expressed as × 1,000 cells/mm^3. The hemoglobin level and platelet count were also measured. Glucose, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, albumin, sodium, potassium, calcium, ferritin, and C-reactive protein (CRP) levels were analyzed by the Architect c8000 Chemistry System (Abbott Diagnostics) using commercial kits (Abbott Diagnostics).

Troponin I and D-dimer levels were analyzed using an immunoassay analyzer (Radiometer AQT90 FLEX, Radiometer Medical ApS, Brønshøj, Denmark). The activated partial thromboplastin time (aPTT), prothrombin time, international standardized ratio, and plasma fibrinogen concentration were measured using an automatic coagulation analyzer (STA Compact, Diagnostica Stago, Parsippany, NJ, USA). FAR was calculated using the SPSS statistical program by dividing the fibrinogen concentration by the albumin concentration. Myocardial injury was diagnosed if the serum concentration of troponin I was > 99th percentile of the upper reference limit (> 0.023 ng/mL), as measured by our hospital laboratory.

The study procedures complied with the Declaration of Helsinki. The Ministry of Health and Adiyaman University Ethics Committee on Human Research approved the study protocol.

Table 1. Demographic features and comorbidities of the study population (n=386)

	Survivors (n = 188)	Non-survivors (n = 198)	P-value
Male, n (%)	94 (50)	115 (58)	0.111[a]
Age [years]	70.7 ± 13.8	71.7 ± 13.8	0.439[b]
Smoking, n (%)	72 (38)	85 (42)	0.355[a]
Heart failure, n (%)	21 (11)	30 (15)	0.240[a]
Hypertension, n (%)	101 (53)	122 (62)	0.117[a]
Coronary artery disease, n (%)	84 (44)	85 (43)	0.546[a]
Cerebrovascular disease, n (%)	20 (11)	19 (8)	0.388[a]
Diabetes mellitus, n (%)	58 (31)	75 (46)	0.003[a]
Chronic lung disease, n (%)*	61 (32)	59 (30)	0.574[a]
Malignancy, n (%)	12 (6)	10 (5)	0.572[a]
Chronic kidney disease, n (%)	14 (7)	31 (16)	0.012[a]
Length of intensive care unit stay [days]	4 (2.3–7.7)	8 (3–14)	< 0.001[c]

[a]Depending on the Expected count, Pearson Chi-Square or Fisher Exact test was used. Descriptive statistics were presented as a number (%).
[b]Student's unpaired t-test was used. Descriptive statistics were presented as mean ± standard deviation.
[c]Mann–Whitney U test was used. Descriptive statistics were presented as median [IQR].
IQR — Interquartile range.
*Chronic lung disease was defined as chronic obstructive pulmonary disease, asthma, or chronic bronchitis

Statistical analysis

Data were examined using SPSS software 17.0 for Windows (Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the presence of a normal distribution of continuous variables. Variables with a normal distribution are expressed as means ± standard deviation, whereas those with a non-normal distribution are expressed as medians with interquartile ranges. Categorical variables are expressed as percentages. Group differences were assessed using the Student's unpaired *t*-test or the Mann–Whitney U test. Differences in categorical variables were assessed using the Pearson chi-square and Fisher exact tests, depending on the sample size. Pearson's and Spearman's tests were used for correlation analyses. Forward variable selection was applied to the binary logistic regression analysis to eliminate statistically non-significant predictors. The Hosmer-Lemeshow test was used to evaluate model fit. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each independent variable. A p-value < 0.05 was considered significant.

Results

The data of 838 COVID-19 patients treated in the ICU were analyzed retrospectively. Those with a negative PCR test (n = 320), a lack of appropriate laboratory parameters (n = 122), or terminal malignancy (n = 10) were excluded from the study. After exclusion, 386 patients (209 [54%] males, aged 71.2 ± 12.9 years) were included in this retrospective cohort study. The in-hospital mortality rate was 51.3%.

The demographic characteristics and comorbid conditions are shown in Table 1. The study groups included surviving (n = 188) and non-surviving (n = 198) COVID-19 patients. There were no significant differences between the groups in terms of age or sex. The rate of DM (p = 0.003), chronic kidney disease (p = 0.012), and duration of hospital stay (p < 0.001) were higher in the non-survivor group compared with the survivors.

The laboratory parameters and treatments are shown in Table 2 according to the study groups. White blood cell and neutrophil counts were higher, while the lymphocyte count was lower in the non-survivor group when compared with the survivors; however, these differences were not statistically significant. The FAR, neutrophil-to-lymphocyte ratio, prothrombin time, international standardized ratio, levels of CRP, glucose, creatine, urea, aspartate aminotransferase, lactate dehydrogenase, fibrinogen, procalcitonin, ferritin, D-dimer, and troponin I were higher in the non-surviving group when compared with surviving COVID-19 patients (all, p < 0.05). In contrast, the platelet count (p = 0.047) and albumin level (p = 0.004) were higher in the survivor

Table 2. Laboratory findings and treatments of patients with SARS-CoV-2 pneumonia on admission to the intensive care unit (n = 386)

	Survivors (n = 188)	Non-survivors (n = 198)	P-value
Haemoglobin, [g/dL]	12.1 ± 2.1	12.1 ± 2.3	0.569[b]
Platelet count (× $10_3/\mu$L)	233 (172–303)	207 (158–273)	0.047[c]
White blood cell count (× $10_3/\mu$L)	9.5 (6.3–14)	10 (7.1–14)	0.089[c]
Neutrophil count (× $10_3/\mu$L)	7.5 (4.7–11.6)	8.3 (5.6–11.7)	0.072[c]
Lymphocyte count (× $10_3/\mu$L)	1.0 (0.6–1.4)	0.9 (0.7–1.4)	0.725[c]
NLR	7.1 (4.5–12)	8.6 (6.1–12.4)	0.014[c]
Glucose [mg/dL]	141 (106–195)	166 (117–234)	0.009[c]
Serum creatinine [mg/dL]	0.8 (1.1–0.7)	1.1 (0.8–1.8)	< 0.001[c]
Urea [mg/dL]	46 (36–70)	63 (43–106)	< 0.001[c]
Alanine aminotransferase [U/L]	24 (16–37)	24 (17–42)	0.498[c]
Aspartate aminotransferase [U/L]	35 (23–54)	43 (27–65)	0.005[c]
Lactate dehydrogenase [U/L]	408 (324–483)	532 (418–678)	< 0.001[c]
Albumin [g/dL]	2.8 ± 0.5	2.6 ± 0.5	0.004[b]
Fibrinogen [g/L]	543.3 ± 164.8	595.6 ± 164.6	0.002[b]
FAR	206.8 ± 83.4	244.2 ± 98.1	< 0.001[b]
Serum potassium [mmol/L]	4.5 ± 0.7	4.6 ± 0.9	0.059[b]
Serum sodium [mmol/L]	136.1 ± 10.1	136.9 ± 7.7	0.446[b]
CRP [mg/dL]	9 (5–15)	14 (8–20)	< 0.001[c]
Ferritin [ng/mL]	389 (234–604)	456 (286–729)	0.021[c]
Procalcitonin [ug/L]	0.21 (0.12–0.69)	0.64 (0.21–1.62)	< 0.001[c]
D-dimer [μg/L]	1340 (784–2100)	1485 (911–3027)	0.017[c]
Troponin I [μg/L]	0.01(0.01–0.03)	0.01(0.01–0.22)	< 0.001[c]
Activated partial thromboplastin time [s]	32 (28–36)	33 (28–38)	0.543[a]
Prothrombin time [s]	16 (14–18)	17 (15–19)	0.008[c]
International standardized ratio	1.2 (1.1–1.3)	1.2 (1.1–1.4)	0.036[c]
Mechanical ventilation, n (%)	15 (8)	165 (83)	< 0.001[a]
Treatments, n (%)			
Antiviral agents	178 (95)	184 (93)	0.476[a]
Antibacterial agents	187 (99)	195 (98)	0.328[a]
Glucocorticoids	182 (97)	190 (96)	0.656[a]
Anticoagulants	180 (96)	188 (95)	0.711[a]
Antiplatelets	105 (56)	130 (66)	0.048[a]
Convalescent plasma	85 (45)	95 (52)	0.586[a]

[a]Depending on the Expected count, Pearson Chi-Square or Fisher Exact test was used. Descriptive statistics were presented as a number (%).
[b]Student's unpaired t-test was used. Descriptive statistics were presented as mean ± standard deviation.
[c]Mann–Whitney U test was used. Descriptive statistics were presented as median [IQR].
CRP — C-reactive protein; FAR — fibrinogen-to-albumin ratio; IQR — interquartile range; NLR — neutrophil-to-lymphocyte ratio

group. The use of antiplatelet medications was greater in the non-survivor group.

The correlation analyses between the FAR and laboratory parameters is shown in Table 3. The FAR was positively correlated with the levels of CRP (r = 0.447; p < 0.001), procalcitonin (r = 0.195; p < 0.001) and troponin I (r = 0.204; p < 0.001) (Figure 1). Logistic regression analysis was performed to determine the independent predictors of in-hospital mortality. The analysis demonstrated that DM (OR: 1.806; 95% CI: 1.142–2.856; p = 0.011), troponin I level (OR:

1.776; 95% CI: 1.031–3.061; p = 0.038), and FAR (OR: 1.004; 95% CI: 1.004–1.007; p = 0.010) at ICU admission were independent predictors of in-hospital mortality in patients with severe COVID-19 (Table 4).

Discussion

We evaluated the association between in-hospital mortality and the FAR, calculated based on the laboratory parameters obtained from blood samples collected within 24 h of ICU admission. The FAR was higher in the non-survivor group and was an independent predictor of in-hospital mortality. Similar to other studies investigating the prognostic risk factors for COVID-19, our results showed that DM and an increased troponin I level were also independent predictors of in-hospital mortality.

Fibrinogen, also known as Factor I, is a glycopeptide composed of three pairs of polypeptides covalently linked by disulfide bonds. Fibrinogen plays a major role in platelet aggregation via enzymatic conversion to fibrin and is also the main determinant of plasma viscosity and erythrocyte aggregation [13]. Several studies and meta-analyses have investigated the association between the fibrinogen level and cardiovascular diseases [14, 15]. Fibrinogen was found to be an independent risk factor for cardiovascular disease in these studies.

COVID-19 is characterized by respiratory failure, endothelial dysfunction, and activation of the coagulation pathway [16]. Patients with severe COVID-19 are susceptible to coagulation as a result of increased levels of coagulation factors

Table 3. Correlation between the FAR and laboratory parameters

	R	P-value
CRP	0.447	< 0.001
Lactate dehydrogenase	0.052	0.277
Procalcitonin	0.195	< 0.001
Troponin I	0.204	< 0.001
NLR	0.098	0.054

CRP — C-reactive protein; FAR — fibrinogen-to-albumin ratio; NLR — neutrophil-to-lymphocyte ratio

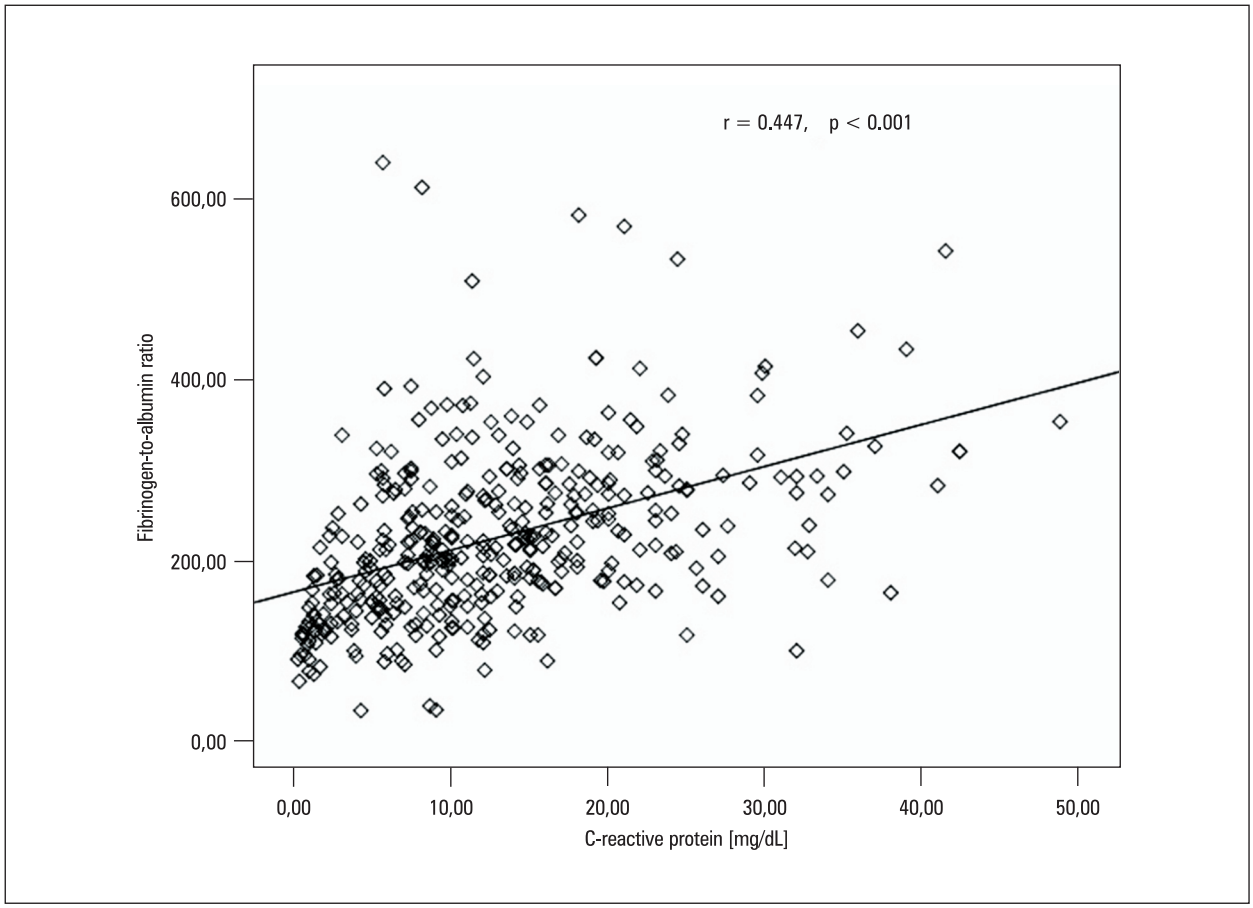

Figure 1. Scatter plot image of the correlation between fibrinogen-to-albumin ratio and C-reactive protein in patients with COVID-19 (n = 386)

Table 4. Multivariate logistic regression analyses of in-hospital mortality

	Odds ratio	95% CI	P-value
NLR	0.986	0.960–1.012	0.293
FAR	1.004	1.001–1.007	0.010
Age [years]	0.999	0.982–1.017	0.943
Sex, male	1.311	0.799–1.000	0.285
Diabetes mellitus	1.806	1.142–2.856	0.011
Hypertension	1.282	0.808–2.035	0.292
Procalcitonin [μg/L]	1.087	0.982–1.202	0.740
Smoking	1.017	0.623–1.660	0.946
D-dimer [μg/L]	1.000	1.000–1.000	0.968
Chronic kidney disease	1.364	0.644–2.889	0.448
Troponin I [μg/L]	1.776	1.031–3.061	0.038
Platelet counts ($\times$103/μL)	0.998	0.996–1.000	0.093

CI — confidence interval; CRP — C-reactive protein; FAR — fibrinogen-to-albumin ratio; NLR — neutrophil-to-lymphocyte ratio

including fibrinogen, tissue factor, and Factor 7, a decrease in tissue plasminogen activator activity, and inhibition of the fibrinolytic pathway due to hypoxia, endothelial dysfunction, and hyperinflammation [17]. This leads to major venous thromboembolic events and arterial thrombosis [18] and is associated with a poor prognosis [19]. Thromboembolic events and in-situ thrombosis seem to contribute to multisystem injury, multiorgan failure, and mortality in patients with SARS-CoV-2 infection [20]. Increased D-dimer and fibrinogen levels together with prolongation of the aPTT promote coagulopathy in COVID-19 patients [21]. Increased levels of D-dimer, aPTT, and fibrinogen were associated with a poor prognosis in hospitalized patients with COVID-19 [22]. In our study, we observed that fibrinogen and D-dimer levels were higher in the non-survivor group when compared with the survivor group.

Albumin has anticoagulant and antiplatelet activities, probably due to its antioxidant effect [23]. Albumin increases fibrinolysis and inhibites erythrocyte aggregation. In addition, albumin neutralizes fibrinogen binding to endothelial cells, thus antagonizing several prothrombotic effects of fibrinogen [24]. Also, endothelial dysfunction and blood viscosity are increased in hypoalbuminemia [25]. During inflammatory states, the coagulation cascade favors thrombus formation due to decreased synthesis and increased catabolism of albumin. Lower albumin levels were observed in patients with severe COVID-19 compared with non-severe COVID-19 in a meta-analysis [26]. A serum albumin level < 3.5 g/dL is associated with a higher mortality rate in COVID-19 patients [27]. In our study, the serum albumin level was < 3.5 g/dL in both groups but was significantly lower in the non-survivor group. In a study of 299 COVID-19 patients, Huang et al. [28] showed a lower albumin level in the non-survivor group compared with the survivors, and hypoalbuminemia was a predictor of mortality regardless of age and comorbidities. Violi et al. [29] suggested that hypoalbuminemia may be related to hypercoagulability in patients with severe SARS-CoV-2 infection and found lower serum albumin levels in patients with ischemic events compared with thrombotic event-free patients with COVID-19.

The FAR has been introduced as a new prognostic marker based on inflammation. The association between FAR and mortality has been investigated because inflammation has an important role in the pathogenesis of both malignancy and cardiovascular disease. FAR was shown to be associated with a poor prognosis in these diseases [7, 8]. There are limited data in the literature on the associations among the FAR, disease progression, and mortality in COVID-19 patients. Bi et al. [30] investigated the associations among the FAR, platelet count, and disease severity in 91 patients with non-severe COVID-19 and 21 patients with severe COVID-19. They suggested that the FAR and platelet count were independent predictors of the development of severe illness in SARS-CoV-2 infection. To date, no studies have investigated the association between the FAR and mortality in COVID-19 patients. In our study, we have proven that the FAR is an independent

predictor of mortality in patients with severe COVID-19 in the ICU. The significant association between elevated fibrinogen/low albumin levels and mortality in COVID-19 patients found in our study supports the role of the FAR in the pathophysiology of the disease and the intensity of the thromboembolic and thrombotic state. FAR may be a useful and cost-effective parameter to predict in-hospital mortality in patients with severe SARS-CoV-2 infection.

Study limitations

As this was a retrospective, observational, and single-center study, our findings may not be generalizable. There were no ischemic/embolic events recorded in our study population. Fibrinogen and albumin levels were measured within 24 h of hospitalization, and serial measurements were not performed. All patients were administered low-molecular-weight heparin as an anticoagulant. Unfortunately, we were not able to measure plasma antifactor Xa activity, which is deemed to be the most accurate marker for monitoring therapeutic dosing of low-molecular-weight heparin.

Conclusions

We showed that the FAR, a novel inflammation-based prognostic parameter, was higher in non-surviving patients when compared with surviving COVID-19 patients. In addition, the FAR was associated with mortality in patients infected with SARS-CoV-2 in the ICU. An increased FAR (as an indicator of the inflammatory and thrombotic burden) might allow for early identification of COVID-19 patients at severe risk, which could assist in immediate optimization of the medical management of this highly susceptible group.

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Conflicts of interest

The authors declare no potential conflict of interest.

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