J Surg Med. 2021;5(6):623-627.
DOI: 10.28982/josam.930254

Journal of Surgery and Medicine
e-ISSN=2602-2079

Neutrophil-to-lymphocyte and fibrinogen-to-albumin ratios may be indicators of worse outcomes in ICU patients with COVID-19

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Ethics Committee Approval
Harran University Clinical Research Ethics Committee; Document Date and Number: 28/09/2020-E.37467.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 June 25

Abstract

Background/Aim: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a pandemic. Early diagnosis of complications and mortality caused by this disease will guide the treatment process in patients with COVID-19. We aimed to investigate whether the neutrophil/lymphocyte and fibrinogen/albumin ratios can predict mortality in COVID-19 patients.

Methods: A total of 102 adult patients (≥18 years) who were followed up in the intensive care unit (ICU) between May and August 2020 because of COVID-19 were included in this retrospective cohort study. Demographic data, comorbid diseases, and hematological parameters of the patients during admission to the ICU were examined. Hematological parameters such as leukocyte, neutrophil, lymphocyte, platelet counts, C-reactive protein (CRP), D-dimer, and lactate data were recorded. The neutrophil-to-lymphocyte ratio (NLR) and fibrinogen-to-albumin ratio (FAR) were calculated, and their effects on mortality were examined.

Results: Of the patients, 71 (69.6%) were male and the mean age of all patients was 69.1 (14.3) (24–103) years. Comorbid diseases of the patients were as follows: Hypertension (n=40, 39.2%), diabetes mellitus (n=28, 27.4%), chronic obstructive pulmonary disease (n=20, 19.6%), coronary artery disease (n=14, 13.7%), heart failure (n=4, 3.9%), and cerebrovascular disease (n=3, 2.9%). Mortality was higher in older patients (median age = 72; range = 62–80 years) (P=0.043), and bilateral infiltration was observed in lung computed tomography images of all patients who died. Mortality was higher in patients with NLR>9.16, FAR>0.15, D-dimer>2.01 mg/L, CRP >11.6 mg/dL, lactate >2.3 mmol/L.

Conclusion: Elevated levels of neutrophil-to-lymphocyte Ratio, fibrinogen-to-albumin ratio, D-dimer, CRP, and lactate were associated with worse outcomes among COVID-19 patients in the ICU.

Keywords: COVID-19, Mortality, Neutrophil-to-lymphocyte ratio

How to cite: Atlas A, Altay N, Karahan MA, Pehlivan V, Pehlivan B, Duran E, Erol MK. Neutrophil-to-lymphocyte and fibrinogen-to-albumin ratios may be indicators of worse outcomes in ICU patients with COVID-19. J Surg Med. 2021;5(6):623-627.

Introduction

A novel coronavirus called "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" causes COVID-19 disease, which is highly contagious and progresses to pneumonia. Although COVID-19 has been documented to occur primarily as a respiratory infection, emerging data have suggested that it should be considered a systemic disease involving multiple systems, including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems [1-3]. Although death rates of COVID-19 are lower than SARS and Middle East respiratory syndrome, COVID-19 is more lethal than seasonal flu [4]. Elderly people and those with comorbid diseases are at increased risk of death from COVID-19, but young individuals without underlying major diseases can also experience potentially fatal complications such as fulminant myocarditis and disseminated intravascular coagulation [5, 6].

In most severe COVID-19 cases, several abnormal hematological parameters such as lymphopenia, neutrophilia, high D-dimer and fibrinogen levels, increased leukocyte count, and neutrophil-to-lymphocyte ratio (NLR) have been reported, as well as low percentages of monocytes, eosinophils, and basophils [7-9].

The fibrinogen-to-albumin ratio (FAR) is widely used as an effective marker of inflammation and tends to be highly elevated in various conditions, such as severe infection and malignant disorders [10]. An increased FAR level may be associated with cytokine storms induced by virus invasion [11].

NLR is a convenient index that can be calculated from a complete blood count, and numerous studies have shown that the NLR has a prognostic value in a variety of conditions such as sepsis, cardiovascular disease, and malignant tumors [12-15]. Normal NLR value ranges between 0.78 and 3.53 and is a simple parameter to easily assess a patient's inflammatory status [16].

In our study, we examined the correlation between hematological parameters and the severity of COVID-19 disease. We aimed to predict mortality and detect possible complications in the early period of the disease by examining the hematological parameters during admission to the intensive care unit (ICU).

Materials and methods

In this retrospective cohort study, 102 adult patients aged ≥18 years and hospitalized in the third-level ICU with the diagnosis of COVID-19 between May and August 2020 were included. After obtaining permission from the Ethics Committee for Clinical Research of the Harran University (Document Date and Number: 19.02.2021-12864), patient files were reviewed retrospectively. The data of patients diagnosed with COVID-19 were accessed and evaluated via the hospital information processing system, ICU nurse observations, and patient files.

Demographic data, comorbid diseases, and hematological parameters, complete blood count, coagulation profile, arterial blood gas analysis, blood biochemistry, and inflammation biomarkers of the patients at admission to the ICU were examined. Hematological parameters such as leukocyte, neutrophil, lymphocyte, platelet counts, C-reactive protein (CRP), D-dimer, and lactate data were recorded. NLR and FAR values were calculated. The length of stay in the ICU, duration of mechanical ventilator use, and the length of hospitalization of the patients were analyzed retrospectively.

The COVID-19 treatment protocol in our center comprised pharmacotherapy and respiratory support modalities. Based on the protocol published by the Ministry of Health, pharmacotherapy included antiviral drugs, antibiotics, corticosteroids, and anticoagulants. The patients were administered hydroxychloroquine. Among antiviral drugs, they were prescribed Favipiravir. Corticosteroids (1–2 mg/kg methylprednisolone for 5–7 days) were prescribed to patients with widespread lung infiltration or rapid progression and antibiotics, to those with a secondary bacterial infection. Low-molecular-weight heparin was administered to the patients with high thrombosis risk along with hyperfibrinogenemia.

Patients who met the criteria for admission to the ICU (dyspnea, tachypnea, respiratory rate>30/min, oxygen saturation below 93%, PaO2/FiO2 <300, and/or >50% increase in lung infiltration within 24–48 hours) were admitted to the ICU. Discharge criteria were as follows: Patients with no respiratory failure, oxygen saturation of 94% while receiving 2 L/min nasal oxygen, oxygen saturation of 92% at room air, no need for mechanical ventilation, and having passed 48 hours after extubation, no need for vasopressors, and clinically stability. These patients were transported from the ICU to the wards.

Statistical analysis

The distribution of continuous variables was evaluated by Shapiro–Wilk test. Mann–Whitney U test was used to compare two independent groups of non-normally distributed data, and Cohen's d effect size was calculated for numerical variables. Binary logistic regression analysis was performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was performed to determine diagnostic values of some numerical measurements. Statistical analysis was performed with SPSS for Windows version 24.0, and a *P*-value <0.05 was considered statistically significant.

Results

In our hospital, 732 patients diagnosed with COVID-19 were treated between May and August 2020. A total of 35 patients aged <18 years and 595 patients treated in the normal wards were excluded from the study. In total, 102 COVID-19 patients who were followed up in the ICU were included in our study (Figure 1). The mean age of the patients was 69.1 (14.3) (24–103) years, and 71 (69.6%) were male. Comorbid diseases of these patients were as follows: Hypertension (HT) (n=40, 39.2%), diabetes mellitus (DM) (n=28, 27.4%), chronic obstructive pulmonary disease (COPD) (n=20, 19.6%), coronary artery disease (CAD) (n=14, 13.7%), heart failure (n=4, 3.9%), and cerebrovascular disease (CVD) (n=3, 2.9%) (Table 1). More than one comorbid disease was found in 30 patients (29.4%). The number of patients without a comorbid disease was 19 (18.6%). The most common comorbid disease was hypertension. Of the patients, 80.7% received mechanical ventilation support. Bilateral pneumonia proven by chest computed tomography (CT) was reported in 91.2% of the patients.

Figure 1: The patient inclusion and exclusion diagram

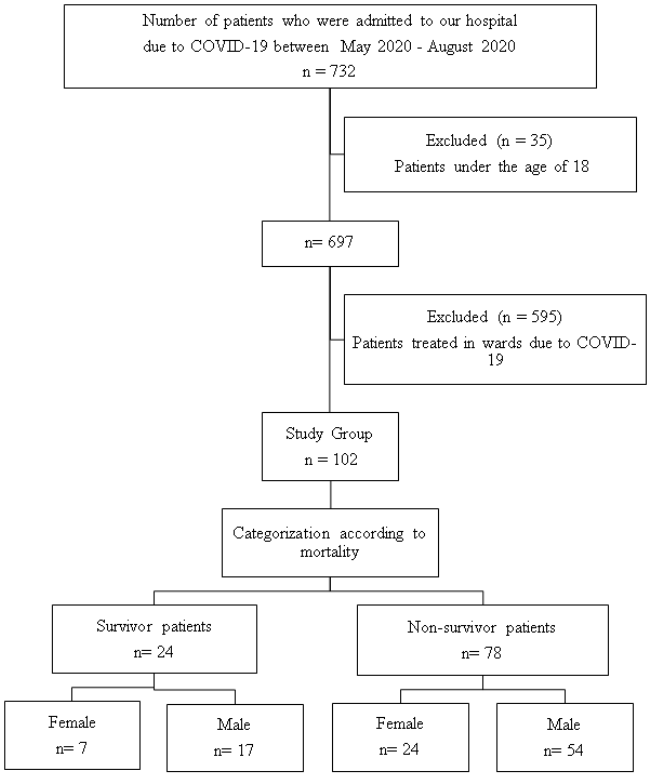


Table 1: Demographic data

Variables		Patient (n = 102)
Age (mean (SD))		69.1 (14.3)
Gender, n (%)		
Male		71 (69.6)
Female		31 (30.4)
Comorbid disease, n (%)		
DM	Yes	28 (27.5)
	No	74 (72.5)
HT	Yes	40 (39.2)
	No	62 (60.8)
COPD	Yes	20 (19.6)
	No	82 (80.4)
CAH	Yes	14 (13.7)
	No	88 (86.3)
Heart failure	Yes	4 (3.9)
	No	98 (96.1)
CVD	Yes	3 (2.9)
	No	99 (97.1)
CT findings	Bilateral	93 (91.2)
	Unilateral	9 (8.8)

SD: Standard deviation, DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CAH: Coronary artery disease, CVD: Cerebrovascular disease, CT: Computed tomography

Laboratory examination during admission to the ICU revealed abnormalities, particularly in the peripheral blood cell and coagulation profile. The mean hemoglobin level, neutrophil, lymphocyte, and platelet counts of the patients were 12.8 (1.9) g/dl, 10.3 (3.6) $\times 10^3$/L, and 0.74 (0.3) $\times 10^3$/L, and 272 (117)$\times 10^3$/L, respectively. The mean NLR, FAR, D-dimer, CRP, lactate levels of the patients were 16.1(8.2), 0.19 (0.04), 10.5 (15.5) mg/L, 15.2 (8.5) mg/dl, and 2.9 (1.9) mmol/L, respectively. The mean length of stay in the ICU was 8.8 (8.9) days, the mean duration of mechanical ventilation, 5.5 (8.8) days, and the mean length of hospital stay, 12.7 (10.5) days (Table 2).

The demographic and hematological parameters of the non-surviving and surviving patients were compared. Twenty-four patients (23.5%) survived their stay in the ICU and were transported to the normal wards, while 78 patients (76.5%) died. The two groups were similar in terms of gender, comorbid diseases, and hemoglobin levels. Results indicated that mortality was higher in older patients (median = 72 years; range = 62–80 years), and lung CTs of all the non-survivors showed bilateral infiltration (P=0.043; P=0.004). DM was detected in 29.5%, HT in 37.2%, and COPD in 20.5% of the non-survivors (Table 3). Among them, the median neutrophil and lymphocyte counts were 10.8 (8.76–13.2) × 109/L, and 0.55 (0.48–0.75) × 109/L, respectively (P=0.001). Their NLR and FAR values were 18.25 (14–22.3) and 0.2 (0.18–0.23), respectively (P=0.001). Median CRP, D-dimer and lactate values of the non-survivors were 15.85 (12.4–21.1) mg/dL, 7.03 (3.36–17.7) mg/L, and 2.9 (2.2–3.9) mmol/L, respectively (P=0.001; Table 4). The neutrophil, NLR, FAR, CRP, D-dimer, and lactate levels of the non-survivors were significantly higher, while their lymphocyte levels were significantly lower compared with the survivors ($p < 0.05$). ROC and area under the curve (AUC) values of hematological and inflammatory indices were calculated between the two groups (Figure 2). According to ROC curve analysis, we observed that NLR, FAR, D-dimer, CRP, and lactate data were successful in predicting mortality in patients with COVID-19. The AUCs for NLR, FAR, D-dimer, CRP, and lactate were 0.969, 0.989, 0.927, 0.913, and 0.893, respectively. We found that mortality increased in patients with NLR>9.16, FAR>0.15, D-dimer >2.01 mg/L, CRP >11.6 mg/dL, and lactate >2.3 mmol/L.

Table 2: Clinical and laboratory data of the patients

Data (n:102)	Mean (SD)	Median (min–max)
Hb (g/dL)	12.85 (1.97)	12.95 (8.45–18.2)
WBC ($\times 10^3$/L)	11.72 (3.94)	11.6 (1.89–20.7)
Neutrophil ($\times 10^3$/L)	10.28 (3.63)	10.5 (1.14–18.1)
Lymphocyte ($\times 10^3$/L)	0.74 (0.33)	0.65 (0.21–1.75)
NLR	16.11 (8.19)	16.45 (2.47–50.9)
Platelet ($\times 10^3$/L)	272.1 (117.8)	255 (43–718)
Fibrinogen (g/L)	5.63 (1.18)	5.64 (3.2–8.47)
Albumin (g/L)	30.12 (2.69)	30 (22–36)
FAR	0.19 (0.04)	0.19 (0.11–0.29)
CRP (mg/L)	15.22 (8.59	14.55 (1.71–47.2)
D-dimer (mg/L)	10.47 (15.53)	3.74 (0.34–80)
Lactate (mmol/L)	2.91 (1.94)	2.4 (1.1–11.8)
Mechanical ventilator time/day	5.5 (8.8)	2 (0–60)
ICU stay/day	8.8 (8.9)	6 (1–60)
Hospital stay/day	12.7 (10.5)	10 (1–65)

SD: Standard deviation, min: Minimum, max: Maximum, Hb: Hemoglobin, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, FAR: Fibrinogen-to-albumin ratio, CRP: C-reactive protein, ICU: Intensive care unit

Table 3: Relationship between mortality and categorical variables

Variables		Non-survivor (n = 78) n (%)	Survivor (n = 24) n (%)	OR [95% CI]	*P*-value
Gender	Male	54 (69.2)	17 (70.8)	1.08 [0.39–2.94]	0.881
	Female	24 (30.8)	7 (29.2)	1 (reference)	
CT findings	Bilateral	78 (100)	15 (62.5)	46.8 [5.52–397.2]	*0.004**
	Unilateral	0 (0)	9 (37.5)	1 (reference)	
DM		23 (29.5)	5 (20.8)	1.59 [0.53–4.77]	0.409
HT		29 (37.2)	11 (45.8)	1.43 [0.57–3.61]	0.449
COPD		16 (20.5)	4 (16.7)	1.29 [0.39–4.31]	0.679

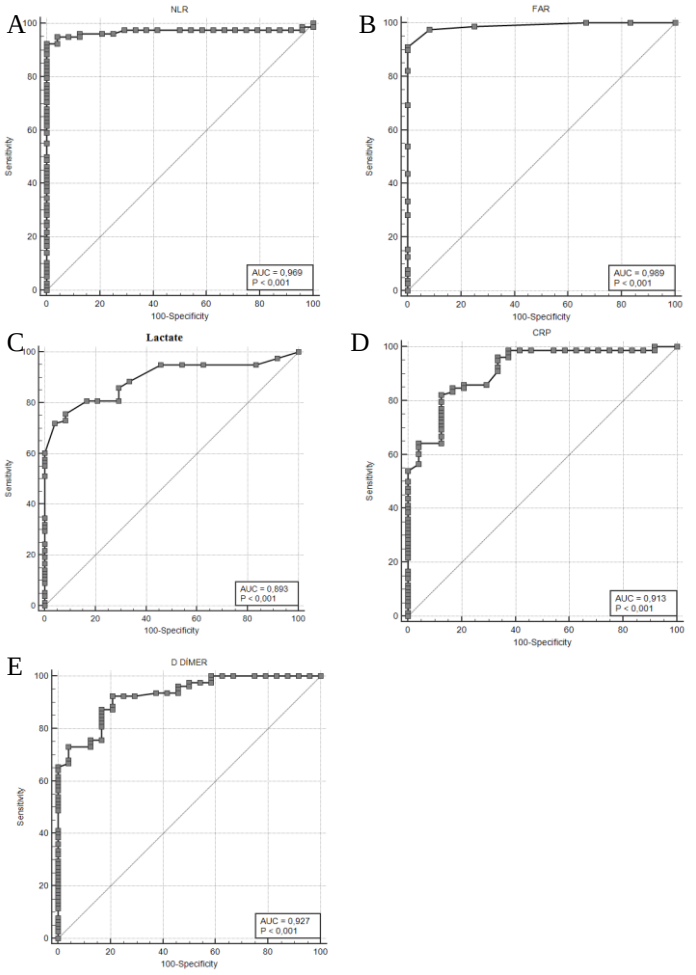
*significant at 0.05 level. Univariate binary logistic regression analysis. OR: Odds ratio, CI: Confidence interval, CT: Computed tomography, DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease

Table 4: Comparison of clinical and laboratory data of patients with and without mortality

Variables	Non-survivor (n = 78) Median (min–max)	Survivor (n = 24) Median (min–max)	Cohen's *d* effect size	*P*-value
Age (year)	72 (62–80)	66 (52–75.5)	0.55	0.043 *
Hb (g/dL)	13 (11.7–14)	12.85 (9.95–14.2)	0,30	0.435
WBC ($\times 10^3$/L)	12.2 (10.1–14.3)	9.67 (7.52–11.45)	0.66	0.004 *
Neutrophil ($\times 10^3$/L)	10.8 (8.76–13.2)	7.64 (6.36–10.03)	0.79	0.001 *
Lymphocyte ($\times 10^3$/L)	0.55 (0.48–0.75)	1.02 (0.95–1.32)	*1.89*	0.001 *
NLR	18.25 (14–22.3)	7.35 (6.52–7.82)	*1.78*	0.001 *
Platelet ($\times 10^3$/L)	247 (192– 354)	310 (234– 350)	0.37	0,193
Fibrinogen (g/L)	5.85 (5.46–6.67)	4.2 (4.1–4.4)	*2.28*	0.001 *
Albumin (g/L)	30 (28–31)	31 (30.5–32)	0.82	0.001 *
FAR	0.2 (0.18–0.23)	0.13 (0.12–0.14)	*2.43*	0.001 *
CRP (mg/L)	15.85 (12.4–21.1)	6.6 (4.55–9.4)	*1.40*	0.001 *
D-dimer (mg/L)	7.03 (3.36–17.7)	1.59 (0.82–2)	0.78	0.001 *
Lactate (mmol / L)	2.9 (2.2–3.9)	1.5 (1.3–1.9)	0.96	0.001 *
ICU hospitalization period/day	6 (3–13)	5 (3–9.5)	0,26	0.534
Mechanical ventilator time/day	4 (1–9)	0 (0–0)	0.76	0.001 *
Hospital stay/day	9 (5–16)	14.5 (9–18)	0.33	0.017 *

*significant at 0.05 level, Median [25%–75%], Mann–Whitney U test. Hb: Hemoglobin, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, FAR: Fibrinogen-to-albumin ratio, CRP: C-reactive protein, ICU: Intensive care unit.

Figure 2: Results of neutrophil-to-lymphocyte ratio (NLR), fibrinogen-to-albumin ratio (FAR), lactate, C-reactive protein (CRP), and D-dimer receiver operating characteristic (ROC) curve analyses in patients with COVID 19. A: NLR ROC curve analysis; B: FAR ROC curve analysis; C: Lactate ROC curve analysis; D: CRP ROC curve analysis; E: D-dimer ROC curve analysis



Discussion

In this study, we found that older age, high neutrophil count, NLR, FAR, D-dimer, CRP, and lactate successfully predicted mortality. FAR (AUC=0.989) and NLR (AUC = 0.969) had the highest AUC values. A previous study reported that the mean age of patients hospitalized because of COVID-19 was 46.6 (12) (22–77) years, 60% were male, and 17.3% had underlying comorbidities. A bilateral ground-glass image was observed in the lung CT of 76% of these patients. Moreover, 21.3% of the patients were followed up in the ICU [17]. In their study examining 245 patients diagnosed with COVID-19, Liu et al. reported that the mean age was 53.95 (16.90) years and 46.53% of the patients were male. They stated that 3.2% of patients had COPD, 21.22% had HT, and 9.39% had DM and the in-hospital mortality rate was 13.47% [18]. In our study, we found that gender was not significant in terms of mortality; however, mortality increased with older age.

In their study investigating 1,099 COVID-19 cases, Guan et al [7] reported that most patients presented with lymphocytopenia (83.2%), 36.2% had thrombocytopenia and 33.7% had leukopenia. Huang et al. [8] and Wang et al. [11] emphasized the relationship between lymphopenia and admission to the ICU. Wu et al. [19] demonstrated a relationship between lymphopenia and the development of acute respiratory distress syndrome (ARDS). In their study, they retrospectively analyzed the risk factors for ARDS and mortality in 201 patients with COVID-19 pneumonia and found that increased risk of ARDS during the disease was associated with increased neutrophil and decreased lymphocyte count by bivariate Cox regression analysis. They reported a positive correlation between increased neutrophil count and mortality rate. In our study, consistent with the literature, we found a strong correlation between increased neutrophil count and mortality.

Fan et al. [20] found that patients needing ICU support initially had significantly lower lymphocyte levels. Lymphopenia was reported in 85% of patients in another retrospective study involving 52 critically ill patients in Wuhan, China [21]. Other studies have also shown that lymphopenia was prominent in critically ill patients with COVID-19 [22, 23]. The mortality rate was higher in patients with lymphopenia during hospitalization [11]. Patients with severe diseases and fatal outcomes have been reported to have a decreased lymphocyte/white blood cell ratio both at admission and during hospitalization [9, 24]. Tan et al. [25] reported that patients with lymphocytes <20% on days 10–12 and <5% on days 17– 19 from the onset of symptoms had a poor prognosis. In our study, similar to the literature, we found that mortality was higher in patients with lymphopenia.

The hyperactivity of fibrinolysis usually results in increased platelet consumption. Although widely used to treat patients with severe COVID-19, corticosteroids can also cause thrombocytopenia [26]. Lippi et al. [27] reported that thrombocytopenia was associated with an increased risk of serious illness and death in patients with COVID-19. In our study, there was no significant relationship between the decrease in platelet count and mortality.

NLR was proposed as a new biomarker for systemic inflammation in which both neutrophil and lymphocyte count are considered [28]. High NLR occurs due to increased neutrophil and decreased lymphocyte counts. The inflammatory response can stimulate neutrophil production and accelerate the apoptosis of lymphocytes [29]. Qin et al. [9] reported that severe cases of COVID-19 had higher neutrophil, but lower lymphocyte counts than non-severe cases; therefore, NLR was higher in patients with severe infection. In their study examining 155 patients with COVID-19, Mo et al. [30] found that patients who did not respond to treatment had higher neutrophil levels. In our study, there was a direct relationship between increased NLR and mortality.

FAR is widely used as an effective marker of inflammation, and it tends to be elevated in various conditions, such as severe infection and malignant disorders [10]. An increased FAR level may be associated with cytokine storms induced by virus invasion [11]. In our study, the median FAR values of the non-survivors and survivors were 0.2 (0.18–0.23) and 0.13 (0.12–0.14), respectively. We found that the mortality rate was high in patients with high FAR.

Studies have reported that high CRP is an indicator of poor prognosis. Guan et al. [7] reported that CRP increased in 60.7% of the patients. The severity of the disease was associated with high CRP, and they detected high CRP levels in 81.5% (110 / 135) of the severe cases. Wu et al. [19] found a relationship between high CRP and the development of ARDS. Deng et al. [24] reported that the mortality rate was high in patients with high CRP levels at the time of admission. Consistent with the

literature, we found that mortality increased in patients with high CRP values during hospitalization.

In patients with COVID-19, the incidence of coagulation disorders increases with the severity of the disease [24, 31]. A multicenter retrospective study showed that 46.4% of 560 patients with laboratory-confirmed COVID-19 infection had high D-dimer levels [7]. It has been reported that high D-dimer levels were associated with poor prognosis in patients with community-acquired pneumonia [32]. High D-dimer (>1.5 mg/L) was detected in 36% of the patients in a study of 99 COVID-19 cases in Wuhan, China [26]. Another retrospective study on 41 patients in China reported that D-dimer and prothrombin time levels were higher at admission among patients requiring ICU support (median D-dimer was 2.4 mg/L within the ICU and 0.5 mg/L outside the ICU) [8]. Wang et al. [11] reported that the patients needing ICU support had high D-dimer levels. In accordance with the literature, we found a relationship between high D-dimer levels and mortality.

Limitations

The single-center retrospective design of our study is its major limitation.

Conclusion

Elevated levels of neutrophil-to-lymphocyte ratio, fibrinogen-to-albumin ratio, D-dimer, CRP, and lactate were associated with worse outcomes among COVID-19 patients in the ICU. These parameters should be closely monitored in hospitalized COVID-19 patients. Morbidity and mortality can be prevented with early interventions by evaluating these parameters. More studies are needed to confirm these findings.

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