Turk J Intensive Care
DOI: 10.4274/tybd.galenos.2023.82621

ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

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The Role of Inflammatory Indices in Predicting Intensive Care Unit Mortalıty in Critically Ill COVID-19 Patients

COVİD-19 Kritik Hastalarında Yoğun Bakım Mortalitesini Öngörmede Enflamasyon İndekslerinin Rolü

Received/Geliş Tarihi : 23.06.2023
Accepted/Kabul Tarihi : 02.10.2023

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ABSTRACT *Objective:* The estimation of disease severity based on early biomarkers may facilitate treatment and reduce mortality in patients with COVID-19. The present retrospective, observational study evaluates the role of different inflammatory indices in predicting mortality in COVID-19 patients.

Materials and Methods: The prognostic value for the prediction of 30-day mortality of inflammatory parameters [C-reactive protein (CRP), ferritin, procalcitonin (PCT)] and [neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), derived NLR (dNLR), systemic inflammation index (SII), C-reactive protein-to-lymphocyte ratio (CRP/L), C-reactive protein-to-albumin ratio, and neutrophil-to-lymphocyte and platelet ratio (N/LP)] were evaluated upon the initial admission of 305 COVID-19 patients to the intensive care unit.

Results: In this study, APACHE score, ferritin, PCT and CRP/L were significantly higher in the non-survivors than in survivors. No significant differences were found in the other inflammatory indices. High ferritin ($p<0.001$) and high APACHE scores ($p<0.001$) were identified as predictors of in-hospital mortality in a ROC curve analysis. Only a high ferritin level was identified as an independent risk factor for mortality in a multivariate regression analysis ($p=0.002$).

Conclusion: Inflammatory indices were not identified as predictors of mortality in critically ill COVID-19 patients admitted to the intensive care unit in the present study; and only high ferritin levels among the parameters related to inflammation were identified as an independent risk factor for mortality.

Keywords: COVID-19, biomarker, inflammatory indices, ferritin, mortality

ÖZ *Amaç:* Kritik COVID hastalarında hastalığın şiddetinin erken biyobelirteçler ile belirlenmesi tedaviyi kolaylaştırabilir ve mortaliteyi azaltabilir. Bu retrospektif gözlemsel çalışmada, farklı inflamatuar indekslerin COVID-19 hastalarında mortaliteyi tahmin etmedeki rollerini belirlemek amaçlandı.

Gereç ve Yöntem: Yoğun bakım ünitesine kabul edilen 305 COVID-19 hastasında, başvuru sırasındaki enflamatuvar parametrelerin [C-reaktif protein (CRP), ferritin, prokalsitonin (PCT)] ve enflamatuvar indekslerin [nötrofil lenfosit oranı (NLO), trombosit lenfosit oranı (TLO), derive edilmiş NLO (dNLO), sistemik enflamasyon indeksi (SII), C-reaktif protein/lenfosit oranı (CRP/L), C-reaktif protein/albumin oranı ve nötrofil/(lenfositXtrombosit) oranı (NLTO)] 30 günlük yoğun bakım mortalitesi üzerine prognostik etkileri incelendi.

Bulgular: Yoğun bakım ünitesine kabul edilen 305 COVID-19 hastasında, başvuru sırasındaki enflamatuvar parametrelerin [C-reaktif protein (CRP), ferritin, prokalsitonin (PCT)] ve enflamatuvar indekslerin [nötrofil lenfosit oranı (NLO), trombosit lenfosit oranı (TLO), derive edilmiş NLO (dNLO), sistemik enflamasyon indeksi (SII), C-reaktif protein/lenfosit oranı (CRP/L), C-reaktif protein/albumin oranı ve nötrofil/(lenfositXtrombosit) oranı (NLTO)] 30 günlük yoğun bakım mortalitesi üzerine prognostik etkileri incelendi.

Sonuç: Yoğun bakımda yatan kritik COVID-19 hastalarında mortaliteyi öngörmede, çalışmamızda incelediğimiz inflamasyon indekslerinin prediktör olmadıkları, enflamasyon ile ilgili olarak sadece yüksek ferritin düzeylerinin mortalite için bağımsız risk faktörü olduğu saptandı.

Anahtar Kelimeler: COVİD-19, biyobelirteç, enflamatuvar indeksler, ferritin, mortalite

Introduction

The first case of coronavirus disease 2019 was reported in the city of Wuhan (Hubei, China), and waslater named COVID-19 by the World Health Organization. It is a contagious disease that continues to threatenglobal public health. The causative agent is referred to as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) due to its similarity with SARS-CoV (1).

COVID-19 manifests with mild symptoms in the majority of patients, although a considerable number of patients suffer from severe rapidly-progressing pneumonia leading to multi-organ failure, acute respiratory distress syndrome (ARDS), septic shock and death (2). It is important to identify the prognostic factors if COVID-19-related mortality is to be reduced in high-risk patients followed up in the intensive care unit (ICU). There is still a need for clinical studies on this subject (3,4,5).

There is accumulating evidence in literature suggesting that increased inflammatory response is responsible for fatal complications in critically ill COVID-19 patients (3). Hyperinflammation plays an important role in viral pathogenesis. Microvascular endothelial dysfunction occurring as a result of hyperinflammatory response and severe cytokine stormleadsto multi-organ failure and death in patients (6). Significant increases in the levels of serum ferritin, procalcitonin, C-reactive protein (CRP), interleukin-6 and other acute phase reactants have been associated with mortality and prognosis in COVID-19 patients (6).

Peripheral white blood cell count (WBC) and differential WBC counts (neutrophil, lymphocyte, platelet, monocyte) obtained by complete blood count (CBC) can be considered good biomarkers of systemic inflammatory response in critically ill patients. In recent studies in literature, various inflammatory indices (i.e. NLR, LMR, PLR, dNLR, SII, AISI, SIRI and CRP/L) have been investigated for their use as predictors of poor prognosis in COVID-19 patients, althoughthese studies have yielded inconsistent results regarding the relationship between these biomarkers and prognosis (7). It is hypothesized in the present study that all these indices in broad terms could serve as independent predictors of prognosis inCOVID-19 patients.

The present study thus evaluates the value of inflammatory indices and inflammatory parameters in predicting prognosis in critically ill COVID-19 patients.

Materials and Methods

Ethical Statement

The study was conducted in a tertiary intensive care unit in Yozgat City Hospital between May 2020 and May 2021. The study was granted approval by the Ethics Committee of Yozgat Bozok University (protocol number 2017-KAEK-189_2021.09.27_03) and was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design

For this single-center retrospective study, clinical, demographic and laboratory data were retrieved from the hospital's information management system and from patient charts.

Included in the study were adult intensive care unit patients aged 18 years and older with a positive PCR test for COVID-19. After reviewing the patients' records, those with hematological disorders, those with a history of severe liver disease and malignancy, those younger than 18 years of age and those with missing laboratory data were excluded from the study.

Study Participants

The age, sex, Acute Physiology and Chronic Health Evaluation (APACHE 2) score, comorbidities, length of ICU stay, 30-day intensive care unit mortality, the need for mechanical ventilation in the first 24 hours, and the need for inotropic support and renal placement therapy while in the ICU were recorded.Patients requiring mechanical ventilatory support were defined as those undergoing resuscitation and endotracheal intubation due to cardiac or respiratory arrest. Patients were evaluated in two groups: survivors (dischargedto home or transfer to the ward) and non-survivors (death during the ICU stay). The laboratory parameters measured upon admission to the ICU, including C-reactive protein, procalcitonin, ferritin, white blood cell count, differential neutrophil, platelet and lymphocyte counts, and mean platelet volume, were retrieved from the hospital's information management system.

Laboratory Measurements

The laboratory parameters measured in each patient from venous blood samples collected upon admission to the ICU were retrieved from the hospital's information management system. Inflammatory indices were calculated as follows using the complete blood count parameters:

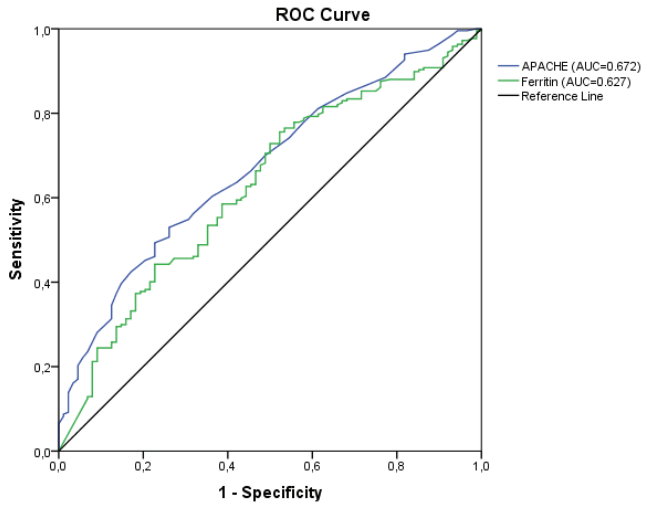

Figure 1. ROC curve

• Systemic immune-inflammation index (SII)=(neutrophil count×platelet count)/lymphocyte count;

• dNLR=neutrphil count/(white blood cell count-neutrophil count);

• NLPR=(neutrophil count/lymphocyte count)×platelet count;

• CRP/Albumin ratio=C-reactive protein/albumin, CRP/L=CRP/lymphocyte count;

• PLR=platelet/lymphocyte.

Statistical Analysis

The data was analyzed with IBM SPSS Statistics Standard Concurrent User V 25 (IBM Corp., Armonk, NY USA). Categorical data were presented in n and frequency, while continuous data were presented in mean ± standard deviation (SD) and median [interquartile range; 25th-75th percentile]. The normality of distribution was checked using the Kolmogorov–Smirnov test and histograms. The significance of differences between groups in terms of averages were assessed with chi-square test, independent samples t test and Mann Whitney U test. In cross tables, the Fisher's exact test was performed, if more than 20% of the expected values were smaller than 5 or at least one of the values was smaller than 2. All significant variables were included in the multivariate logistic analysis after the univariate analysis. The factors that predict the mortality of COVID-19 patients were investigated using a backward stepwise multivariate logistic regression analysis. The Hosmer and Lemeshow test for goodness-of-fit statistics was used to determine the calibration validation and discrimination of this regression analysis. The receiver operating characteristic (ROC) curve analysis was used to determine the parameters that had the greatest predictive value for mortality of COVID-19 patients, and the areas under the curve (AUC) were calculated.

Results

Demographic and Clinical Characteristics

A total of 305 COVID-19 patients (184 male; 121 female) were included in the study (Table 1). The median age was 72 years (IQR: 65–80 years). Of the total, 88 patients (28.9%) were discharged (survivors) and the remaining 217 patients (71.1%) died (non-survivors). Comorbidities included hypertension (48.2%), chronic obstructive pulmonary disease (COPD) (31.5%) and coronary artery disease (CAD) (25.6%). The median length of ICU stay was 9 days (IQR: 4–15 days).

As shown in Table 1, the APACHE score (27, IQR 18–37 vs. 19, IQR 14–27; p < 0.001) was significantly higher, the length of ICU stay was longer (median:10.0 days, IQR 5–17 days vs. 7.5 days, IQR 4–10 days; p= 0.002), chronic kidney disease (CKD) (79% vs. 51%, p = 0.002) was more common and COPD was less common (27.6% vs. 40.9%, p = 0.024) in the non-survivors than in the survivors. The need for MV in the first 24 hours (89.9% vs. 57.7%, p <0.001), the need for vasoactive agents (19.4% vs. 3.4%, p = 0.001) and the need for renal replacement therapy (38.2% vs. 21.8%, p = 0.006) were higher in the non-survivors than in the survivors.

Laboratory Parameters and Inflammatory Indices

An analysis of the laboratory parameters revealed (Table 2) significantly higher ferritin (median: 458; IQR: 237–787 vs. 257, IQR: 125.5–506; p <0.001) and PCT (median: 0.44; IQR: 0.13–1.68 vs. 0.175 IQR: 0.09–0.52, p <0.001) values among the inflammatory parameters; significantly higher urea (median: 63; IQR: 44–106 vs. 52 IQR: 33.5–80, p= 0.003) and creatinine (median: 1.17; IQR: 0.87–1.83 vs. 0.99 IQR: 0.76–1.21, p= 0.001) among the biochemical parameters; and significantly higher CRP/L (median: 19.75; IQR: 8.30–44.50 vs. 13.3 IQR: 3.7–30.2, p= 0.028) values among the inflammatory indices in the non-survivors than in the survivors. On the other hand, there were no significant differences in the CRP, albumin, complete blood count parameters and other (SII, NLR, dNLR, NLPR, CRP/Alb, CRP/L, PRL,) inflammatory indices of the survivors and non-survivors (Table 2).

Table 1. Comparison of demographic and clinical characteristics of survivors and non-survivors				
Variables	**Overall (n=305)**	**Non-survivors (n=217)**	**Survivors (n=88)**	**p-value**
Age (years)	72 [65 to 80]	73 [66 to 81]	71.5 [59.5 to 79]	0.560
APACHE score	23 [17 to 35]	27 [18 to 37]	19 [14 to 27]	**0.000**
Length of ICU stay (days)	9 [4 to 15]	10 [5 to 17]	7.5 [4 to 10]	**0.002**
Sex, Female/Male	121/184 (39.7/60.3)	79/138 (36.4/63.6)	42/46 (47.7/52.3)	0.067#
Comorbidities, n (%)				
Hypertension	147 (48.2)	106 (48.8)	41 (46.6)	0.721#
CHF	39 (12.8)	26 (12.0)	13 (14.8)	0.647*
Diabetes mellitus	55 (18.0)	40 (18.4)	15 (17.0)	0.903*
Neurologic disease	54 (17.7)	40 (18.4)	14 (15.9)	0.721*
Arrhythmia	20 (6.6)	15 (6.9)	5 (5.7)	0.890*
CAD	78 (25.6)	57 (26.3)	21 (23.9)	0.771*
CKD	72 (23.6)	62 (28.6)	10 (11.4)	**0.002***
COPD	96 (31.5)	60 (27.6)	36 (40.9)	0.024#
Other	75 (24.7)	57 (26.4)	18 (20.5)	0.346*
Need for MV in the first 24 hours	244 (80.0)	195 (89.9)	49 (55.7)	**<0.001***
Need for vasoactive agent	45 (14.8)	42 (19.4)	3 (3.4)	**0.001***
Renal replacement therapy	102 (33.6)	83 (38.2)	19 (21.8)	0.006#

Data are presented as medians [interquartile range] for continuous variables and as numbers and percentages for categorical variables. Continuous variables were compared with a Mann-Whitney U test. Compared by the #Chi square test and Yates's correction for continuity. The level of statistical significance was set at 0.05. All statistically significant values are indicated in bold.
APACHE: Acute Physiology and Chronic Health Evaluation, ICU: intensive care unit, CHF: chronic heart failure, CAD: coronary artery disease, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, MV: mechanical ventilation

Predictive Accuracy of Laboratory Parameters for Mortality

In a ROC curve analysis for mortality in COVID-19 patients, the optimal cut-off value was 19.5 (AUC=0.672, 95% CI 0.607-0.736, p <0.001) for the APACHE score and 263.0 ng/dL (AUC=0.627, 95% CI 0.559-0.696, p <0.001) for ferritin (Table 3). Among the other inflammatory parameters, the ROC curve analysis for CRP/L did not show a significant level for the prediction of mortality in COVID-19 patients (p <0.05).

Risk Factors for COVID-19 Mortality in Univariate and Multivariate Analyses

ICU mortality in the entire study population was 71.1%. The results of univariate and multivariate logistic regression analyses for mortality in COVID-19 patients are presented in Table 4.

In a univariate analysis, APACHE score, ferritin, urea and creatinine were identified as significant predictors of mortality, whilein a multivariate analysis, high ferritin level (OR = 0.999; %95 CI 0.998–1.000; P=0.002) and APACHE score (OR = 0.947; %95 CI 0.923–0.972; p<0.001) were identified as independent predictors of mortality

Discussion

The present study evaluating the relationship between inflammatory indices, based on the laboratory parameters measured upon initial admission, and mortality in critically ill COVID-19 patients, has produced several important results. Ferritin, urea and creatinine were higher in the non-survivors than in the survivors. Among the inflammatory indices, CRP/L was higher among the non-survivors. High ferritin levels and APACHE scores were identified as independent predictors of mortality.

The prediction of prognosis is of utmost importance in critically ill COVID-19 patients, who have a high rate of mortality. Clinical studies have generally reporteddecreased T lymphocytes and CD3, CD4 and CD8 levels together with an increase in proinflammatory cytokines. Cytokine storm has been linked to disease severity, leading to multi-organ failure

Table 2. Comparison of laboratory variables between survivors and non-survivors				
Variables	**Overall (n=305)**	**Non-survivors (n=217)**	**Survivors (n=88)**	**p-value**
Inflammatory parameters				
CRP (mg/dL)	11.2 [7.01 to 21.5]	11.6 [7.29 to 22.7]	10.2 [3.95 to 18.9]	0.053
Ferritin (ng/dL)	413 [182 to 709]	458 [237 to 787]	257 [125.5 to 506]	**<0.001**
PCT (ng/mL)	0.35 [0.12 to 1.21]	0.44 [0.13 to 1.68]	0.175 [0.09 to 0.52]	**<0.001**
Biochemical parameters				
Urea (mg/dL)	60 [42 to 93]	63 [44 to 106]	52 [33.5 to 80]	**0.003**
Creatinine (mg/dL)	1.09 [0.83 to 1.59]	1.17 [0.87 to 1.83]	0.99 [0.76 to 1.21]	**0.001**
Albumin (g/dL)	3.19 (0.48)	3.17 (0.44)	3.24 (0.56)	0.293†
Complete blood count				
WBC (×109 L)	8.6 [6.1 to 12.9]	8.4 [6.2 to 12.7]	9.05 [6.1 to 13.3]	0.850
Neutrophils (×10^9 L)	7.5 [4.7 to 11.6]	7.4 [4.8 to 11.3]	7.8 [4.3 to 11.9]	0.925
Lymphocytes (×10^9 L)	0.7 [0.4 to 1]	0.7 [0.4 to 1]	0.8 [0.45 to 1.1]	0.076
Platelets (×10^9 L)	202 [154 to 271]	200 [149 to 259]	209 [165 to 281.5]	0.134
MPV (fL)	8.4 [7.8 to 9.1]	8.4 [7.9 to 9.1]	8.4 [7.75 to 9.1]	0.922
Inflammatory indices				
SII	2079.75 [938 to 4566]	2120 [1001 to 4442]	2063 [899 to 4942]	0.879
NLR	10.8 [5.5 to 19.3]	10.8 [5.8 to 19.2]	9.56 [4.54 to 21.25]	0.328
dNLR	5.66 [3.35 to 10.33]	5.66 [3.4 to 10.42]	5.02 [2.84 to 10.1]	0.222
NLPR	5.08 [2.90 to 10.40]	5.16 [3.13 to 10.58]	4.71 [2.46 to 9.22]	0.139
CRP/alb	3.55 [2.03 to 7.08]	3.8 [2.2 to 7.5]	3.17 [1.12 to 6.22]	0.058
CRP/L	16.66 [6.95 to 41]	19.75 [8.30 to 44.66]	13.3 [3.7 to 30.2]	**0.028**
PLR	290 [174 to 503]	300 [180 to 498]	253.35 [163 to 540]	0.693

Values are quoted as mean (SD) and median [interquartile range]. †Compared by independent sample t-test. Other values were compared with a Mann-Whitney U test. The level of statistical significance was set at 0.05. All statistically significant values are indicated in bold.
CRP: C-reactive protein, PCT: procalcitonin, WBC: white blood cell, MPV: mean platelet volume, SII: systemic immune-inflammation index, NLR: neutrophil-to-lymphocyte ratio, dNLR: derived neutrophil-to-lymphocyte ratio, NLPR: neutrophil-to-lymphocyte, platelet ratio, CRP/alb: C-reactive protein-to-albumin ratio, CRP/L: C-reactive protein-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio

and death (8). In such cases, the increase in the number of inflammatory cells at the level of the endothelium is known to impair microcirculation and to cause systemic impairment in different organs in COVID-19 patients (6).Further studies have reported various laboratory abnormalities in response to an exaggerated inflammatory response in critically ill COVID-19 patients (9,10), and theseresults are important indicators of systemic inflammation and immune response (9,11). There have been many studies in literature evaluating the relationship between inflammatory biomarkers and poor outcomes in COVID-19 patients (10,11,12,13). The present study analyzes the predictive value of inflammatory indices derived from inflammatory markers on mortality in critically ill COVID-19 patients in whom an exaggerated immune response is observed.

Before the COVID-19 pandemic, a significant increase in CRP concentrations would mostfrequently be attributed to a condition caused by a bacterial pathogen (14), although elevated CRP levels have also been reported in severe viral infections, including pneumonia caused by H1N1 influenza, and particularly in COVID-19 patients in recent years (15,16). Furthermore, as a biomarker of inflammation, CRP has been strongly linked to disease severity, ARDS and mortality in such patients (17). Yang et al. reported CRP/L to be a highly sensitive indicator of disease severity in patients with early COVID-19 pneumonia, and while similar to the present study they reported a higher CRP/L ratio in non-survivors, CRP/L did not predict mortality in a univariate regression analysis (18). In contrast to the findings of the present study, Ullah et al. reported the lymphocyte-to-C-reactive protein ratio (LCR)

Table 3. ROC curve analysis predicting the mortality of COVID-19 patients							
Variables	AUC	Cut-off point	Sensitivity (%)	Specificity (%)	p-value	95% CI	
						Lower	Upper
APACHE score	0.672	19.5	70.0	51.1	**<0.001**	0.607	0.736
Ferritin	0.627	263.0	71.0	50.0	**<0.001**	0.559	0.696
The level of statistical significance was set at 0.05. All statistically significant values are indicated in bold. AUC: Area under the curve, APACHE: Acute Physiology and Chronic Health Evaluation, CI: confidence interval							

Table 4. Univariate and multivariate analysis for the mortality of COVID-19 patients						
Variables	Univariate analysis			Multivariate analysis		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
APACHE score	0.944	(0.921-0.964)	**<0.001**	0.947	(0.923-0.972)	**<0.001**
CRP	0.978	(0.955-1.001)	0.066			
Ferritin	0.999	(0.998-1.000)	**0.002**	0.999	(0.998-1.000)	**0.002**
PCT	0.963	(0.917-1.012)	0.140			
Urea	0.992	(0.986-0.998)	**0.007**	0.996	(0.990-1.002)	0.196
Creatinine	0.671	(0.499-0.903)	**0.008**			
CRP/L	0.993	(0.985-1.001)	0.098			
Multivariate Model's Adjusted R2= 0.183, p-value <0.001. The level of statistical significance was set at 0.05. All statistically significant values are indicated in bold. APACHE: Acute Physiology and Chronic Health Evaluation, CRP: C-reactive protein, CRP/L: CRP-to-lymphocyte ratio, CI: confidence interval						

to be a sensitive predictor of the inflammatory cascade, and should be considered as a potential new predictor of in-hospital mortality and poor outcomes in COVID-19 patients (19). The same study also reported an association between an increased risk of in-hospital mortality and low LCR (19). In another study, Acar et al. reported LCR to be a significant independent predictor of in-hospital mortality in their study of 148 patients (20). The LCR has high sensitivity in the acute phase of inflammation due to the fact that CRP levels increase early before the emergence of neutrophilia or lymphopenia, regardless of the reasons for the elevated levels (i.e. infections, cancer, autoimmune) (19). For this reason, elevated LCR may be regarded as an independent biomarker of the initial stages of inflammation. Although it is well established that the NLR correlates with the severity of COVID-19, it is important to know that the NLR can be affected in an immunosuppressed patient or in those receiving high-dose corticosteroid therapy(21). For this reason, the authors believe the lowCLR to be attributable to the fact that all patients were started on corticosteroid therapy upon admission to the ICU.

Ferritin, one of the inflammatory parameters, is known to play an important role in mortality in COVID-19 patients. Lu et al. reported elevated ferritin levels to be associated with a poorer prognosis and death in COVID-19 patients than in those with low ferritin levels (22). In their study, Hou et al. suggested the use of ferritin as a predictor of disease severity in critically ill COVID-19 patients based on their multivariate logistic regression analysis (23), while Cecconi et al. reported that ferritin could be useful for the early identification of a risk of deterioration in the clinical condition of hospitalized COVID-19 patients that may result in a transfer to the ICU or death, and in the determination of the treatment approach (24). Elevated ferritin levels, as a marker of inflammation, have been associated with increased mortality considering their contribution to the development of both cytokine storms and ARDS (25). Consistent with these studies, the multivariate logistic regression analysis in the present study found that only elevated ferritin levels could serve as an independent indicator of mortality.

Under normal circumstances, procalcitonin is produced and released into circulation by the parafollicular C cells in the thyroid gland, and is produced in substantial quantities in extrathyroidal tissues during severe infections (26)and maintained by increased interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6 concentrations. Procalcitonin has been reported to better differentiate between bacterial infections and other inflammatory processes than WBC count and CRP (27). While Lippi et al. found that bacterial co-infections resulted in elevated procalcitonin levels

(28), Kotula et al. reported elevated procalcitonin levels in patients with a confirmed viral infection but without bacterial infection (29). In another study, higher procalcitonin levels were identified in critically ill COVID-19 patients than in those without a critical illness (30). Similarly, procalcitonin levels were significantly higher in the non-survivors than in survivors. In a meta-analysis of four studies, Lippi et al. reported serial procalcitonin measurement to be useful for the prediction of prognosis in COVID-19 patients (28). The authors of the present study believe that although COVID-19 is a viral infection, PTC measurement could be useful in predicting prognosis and could support treatment decisions in COVID-19 patients.

There have been studies in literature investigating the relationship between various inflammatory indices, and prognosis and mortality in COVID-19. Ding reported a significant relationship between NLR after the fifth day of admission to the hospital and the length of hospital stay in 72 COVID-19 patients, and suggested that NLR measured after the fifth day of hospitalization could be used to predict prognosis in hospitalized COVID-19 patients (31). Seyit et al. reported that PRL upon initial admission to the emergency room showed a better correlation with disease severity than NLR in 110 COVID-19 patients (32).When the findings of the present study are examined in detail, inflammatory indices such as NLR, PLR, dNLR, SII, CRP/Alb and NPLR, whichare known to predict prognosis in COVID-19 patients, were found to be unrelated to mortality.

In a study of 114 patients with COVID-19, Xue et al. reported NLR, PLR, dNLR and SII, measured at the time of admission to the hospital, to be insufficient for the prediction of disease severity (33), althoughtheir study did not evaluate mortality rates. Similarly, in a study evaluating SII measured from blood tests performed within one hour of hospitalization in 285 patients, Kudlinski et al. identified no significant value of SII in predicting mortality (34).

In addition to this, Ullah et al. compared LCR and NLR in terms of their performance in predicting in-hospital mortality in the early period, and found that NLR could significantly predict mortality and the need for mechanical ventilation on day seven, whileNLR measured on day one had no significant predictive power. They also reported that the values may vary, with the potential to be increased in those receiving steroid therapy and to be decreased in those with bone marrow suppression due to cancer or chemotherapy (19). The authors of the present study believe the inflammatory indices of the study patients may have been affected considering the fact that all critically ill patients requiring oxygen supplementation due to respiratory distress, unlesscontraindicated, received dexamethasone 6 mg/day or prednisolone 0.5–1 mg/kg or its equivalent methylprednisolone for 10 days, as per the treatment guidelines published by the Ministry of Health of Türkiye (35).

The present study has some limitations, the first of whichis its retrospective and single-center study design. Multicenter studies would certainly contribute significantly to literature. The second limitation is that the administration of steroid therapy to patients without contraindications, as per the treatment protocols, may have affected the inflammatory indices, although the studied inflammatory markers were comparable, considering that these therapies have been standardized. The strengths of the present study include its sample of 305 ICU patients, and its ICU follow-up and treatment of these patients having been performed by the same team. An additional strength of the study to be considered is its simultaneous examination of multiple parameters in the same patient group, which have been evaluated in dispersed groups in previous studies in literature.

Conclusion

In the present study, inflammatory indices were not identified as a predictor of mortality in critically ill COVID-19 patients admitted to the ICU, and only high ferritin levels among the parameters related to inflammation were identified as an independent risk factor for mortality. Ferritin levels at the time of admission to the intensive care unit can be useful for the prediction of prognosis in critically ill ICU patients, including COVID-19 patients.

Ethics

Ethics Committee Approval: The study was granted approval by the Ethics Committee of Yozgat Bozok University (protocol number 2017-KAEK-189_2021.09.27_03) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.D., Concept: Ö.H.M., Design: A.D., Data Collection and Process: A.D., Analysis or Interpretation: Ö.H.M., Literature Search: A.D., Writing: A.D.

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

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

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