Kritik COVID-19 Hasta Prognozunun Değerlendirilmesinde Akut Faz Proteinlerinin Önemi

The Importance of Acute Phase Proteins in the Evaluation of Critical COVID-19 Patient Prognosis

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ÖZET

Amaç: Yoğun bakım ünitesine ilk kabulde kötü prognoz riskine sahip COVID-19 hastalarını belirlemenin çeşitli tanısal zorlukları vardır. Karaciğer tarafından sentezlenen akut faz proteinlerinin konsantrasyonu inflamasyon ve enfeksiyonu takiben serumda artar veya azalır. Bu çalışmada, kritik COVID-19 hastalarında akut faz proteinlerinin prediktif değerini belirleme ve yoğun bakım ünitesinde mortalite riskini öngörmede inflamatuar belirteçlerin etkinliğini değerlendirme amaçlanmaktadır.

Gereç ve Yöntem: Retrospektif olarak tasarlanan bu çalışma yoğun bakım ünitesinde tedavi gören kritik COVID-19 hastalarında yapıldı. Çalışmaya yoğun bakım ünitesine kabulün ilk 24 saatinde ARDS ve/veya çoklu organ disfonksiyonu olan 123 hasta dahil edildi. Yoğun bakım ünitesindeki 28 günün sonunda sağ kalan (n=54) ve ölen (n=69) hasta grupları veya invaziv mekanik ventilasyon (n=83) uygulanan ve uygulanmayan (n =40) hasta grupları oluşturuldu. Gruplar arasında akut faz proteinleri olan serum amiloid A, C-reaktif protein, albümin ve prealbüminin yoğun bakım ünitesine kabulün ilk 24 saat içerisindeki değerleri karşılaştırıldı.

Bulgular: Albümin ve prealbümin düzeyleri ölen (sırasıyla $p=0.011$, $p<0.001$) ve mekanik ventilasyon uygulanan (sırasıyla $p=0.010$, $p=0.006$) hastalarda anlamlı olarak azaldı. Mekanik ventilasyonlu hastalarda serum amiloid A düzeyleri anlamlı olarak arttı ($p=0.022$).

Sonuç: Yoğun bakım ünitesine kabul sırasında düşük prealbümin ve albümin seviyeleri ve yüksek serum amiloid A seviyeleri, hastalık şiddeti ve mortalitenin prognostik bir belirteci olarak kullanılabilir.

Anahtar Kelimeler: Akut faz proteinleri; COVID-19; mekanik ventilasyon; mortalite

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ABSTRACT

Objectives: Identifying COVID-19 patients with risk of adverse outcomes at first admission to the intensive care unit has several diagnostic challenges. The concentration of acute phase proteins synthesized by the liver increases or decreases markedly in the serum following inflammation and infection. This study aimed to investigate the predictive value of acute phase proteins in critically ill COVID-19 patients and to evaluate the efficacy of inflammatory markers in predicting mortality risk in the intensive care unit.

Methods: A retrospective study was conducted in critically ill COVID-19 patients treated in the intensive care unit. Overall, 123 patients with ARDS and/or multi-organ dysfunction were included in the first 24 hours of admission to intensive care unit. After 28 days, groups of survived (n=54) and dead patient (n=69) or groups of patient with (n=83) and without (n=40) invasive mechanical ventilation were formed. Serum amyloid A, C-reactive protein, albumin, and prealbumin values considered as acute phase proteins within the first 24 hours of admission to the intensive care unit were compared between groups.

Results: Albumin and prealbumin levels significantly decreased in dead patients ($p=0.011$, $p<0.001$, respectively) and were mechanically ventilated patients ($p=0.010$, $p=0.006$, respectively). The Serum amyloid A levels in mechanically ventilated patients significantly increased ($p=0.022$).

Conclusion: Low prealbumin and albumin levels and high serum amyloid A levels during admission to ICU can be used as a prognostic marker of disease severity and mortality.

Keywords: Acute-phase proteins; COVID-19; mechanical ventilation; mortality

INTRODUCTION

Chinese scientists defined a new pathogen termed Severe Acute Respiratory Tract Syndrome Coronavirus 2 (SARS-CoV-2) in January 2020. Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 with rapid contamination, was firstly declared as an epidemic then pandemic by WHO (1). Even though vaccination seems to be the best way of controlling pandemic, new mutations occurring within the virus genome, and the progression of the disease, indicate that we need more information about the pathophysiology of this disease.

The clinical manifestations of symptomatic COVID-19 develop as mild (40%-symptomatic patients), moderate (40%-pneumonia), severe (15%-severe pneumonia), and critical (5%-acute respiratory distress syndrome -ARDS, sepsis, septic shock, and multi-organ dysfunction) illness (1). Especially, in the high-risk patients associated with older age (>60 years), smoking, and comorbidity (diabetes, hypertension, obesity, etc.), there's a rapid progression. Cytokine storm plays a crucial role in the development of critical disease. ARDS, sepsis, and multiple organ failure are the most frequent causes of mortality. Most COVID-19 patients requires mechanical ventilation (2). Laboratory tests performed in COVID-19 patients are important in staging, prognosis of disease and monitorization of treatment (3). In patients requiring critical care and mechanical ventilation, the recognition of markers associated with mortality is highly important. A predictive biomarker with high sensitivity could also be very useful in clinical practice and it can help the regulation of treatment by yielding information on the severity of the disease.

In viral or bacterial infections, inflammation, or tissue injury, pro-inflammatory cytokines released from macrophages such as IL-6, IL-1β, and TNF-α cause to the release of acute phase proteins (APPs) from the liver (4). APPs, which are one of the first responses of the body to stress and they play an important role in suppressing inflammation and regulating immunity (5). Serum APP levels increase significantly in infective and inflammatory conditions and they are sensitive markers and a nonspecific indicators of inflammation. Serum APP levels may give information on the immune

system's competence, state of disease, prognosis, and response to treatment in diagnosed patients (5).

This study aims to evaluate whether acute inflammatory proteins, particularly serum amyloid A (SAA), C-reactive protein (CRP), albumin, and prealbumin, can be utilized in clinical practice to predict mechanical ventilation need or mortality in critical COVID-19 patients.

METHODS

Patient selection and data analysis

Critical COVID-19 patients who were admitted to the anaesthesia department intensive care unit (ICU) before the national vaccination program were included in this study. In acceptance to ICU, criteria in national guides were taken into consideration: respiratory rate≥30/min and arterial partial pressure of oxygen (PaO2)/fraction inspiratory O2 (FiO2)<300, increase in oxygen need during monitorization (despite 5 L/min oxygen treatment, oxygen saturation of (SpO2)<90% or PaO2<70 mmHg), hypoxia along with hypotension during monitorization (systolic blood pressure (SBB)<90 mmHg and over 40 mmHg fall in usual SBP and mean artery pressure <65 mmHg, tachycardia>100/min), as well as acute renal injury, acute liver function failure, confusion, acute organ dysfunction such as acute bleeding diathesis, immune suppression, high troponin levels and presence of an arrhythmia. Daily clinical monitorization in ICU was evaluated and patients who have criteria of critical disease according to the WHO guideline was included in the study (1). The patients who were younger than 18 years-old, pregnant, and who has insufficient data were excluded from the study, overall, 123 patients were included.

Two main outcomes were evaluated: 1) use of invasive mechanical ventilation (MV) and 2) survival status. Patients were divided into survived and non-survived patients and those who undergo invasive mechanical ventilation and those who do not undergo invasive mechanical ventilation (non-MV). Patients are intubated when the following conditions occur: Alteration of consciousness, severe decompensated acidosis (pH<7.2), severe hypoxemia (PaO2<50 mmHg or SaO2<90%); despite maximal noninvasive support, signs or symptoms of significant respiratory distress or tissue hypoxia (eg, respiratory rate above 25-30 per minute, use of accessory respiratory muscles, sweating, dyspnea, tachycardia, increased blood lactate levels, etc.). This retrospectively designed study was conducted under the principles of the World Medical Association Declaration of Helsinki and it was approved by the local ethics committee (No. 2020/13-38). Written consent was obtained from all participants or their legal surrogates.

Analysis of biochemical and hematological parameters

Laboratory data within the first 24 hours of admission to ICU and demographic data were retrieved from the hospital information system. SAA, prealbumin, CRP, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), glucose, creatinine, and urea levels in serum were measured on an AU 5800 chemistry analyzer (Beckman Coulter, High Wycombe, UK). ADVIA Centaur XP immunoassay analyzer (Siemens Healthineers, Erlangen, Germany) was used for serum high sensitive troponin I (hs-TNI) and procalcitonin (PCT) analyses. CS 2500 automated coagulation analyzer (Sysmex Corporation, Kobe, Japan) was used for plasma fibrinogen and D-dimer analyses. White blood cell (WBC), leukocyte formula, platelet, red blood cell (RBC), hemoglobin (Hgb), hematocrit (Hct) were measured on UniCel DxH 800 hematology analyzer (Beckman Coulter, Miami, FL, USA). The detection of SARS-CoV-2 in nasopharyngeal swabs specimens were made by rRT-PCR (Biospeedy® SARS CoV-2 Triple Gene RT-qPCR kit, Bioeksen R&D Technologies Ltd, Istanbul, Turkey).

Statistical analysis

Data were analyzed in IBM SPSS Statistics 25.0 and the normal distribution of data was analyzed by Shapiro Wilk Test. The data with normal distribution were presented as the mean ± standard deviation and the parameters between groups were compared using an independent t-test. The data with skewed distribution were presented as the median and interquartile range (IQR) and the parameters between groups were compared using a Mann Whitney U test. Categorical values were expressed as frequencies, and the differences were analyzed using the Chi-Square test. The receiver operator characteristic (ROC) curve was used for predicting patients who were mechanically ventilated or had a mortality of COVID-19. The cut-off points of parameters, that have a significant difference between groups, and areas under the curve (AUC) were estimated for these predictions. According to APP cut-off values, binary logistic regression analysis was carried out and odds ratio (OR) was estimated to determine the prediction of mechanical ventilation and mortality risk. $P<0.05$ was considered statistically significant.

RESULTS

Survival and mechanical ventilation status after 28 days of monitorization in ICU

Mean age of the patients was 67.2±14.1 years and 59.3% (n=73) was male and 40.7% (n=50) female. The median duration of admission to ICU was 11 (6-19) days. After 28 days of follow up, 44.7% (n=55) of patients survived, while 56.1% (n=69) died. The mean age of patients who died was significantly higher than that of the patients who survived ($p<0.004$) (Table 1). During the 28-day follow-up of patients, 67.5% (n=83) of patients underwent invasive mechanical ventilation. The ratio of MV in dead patients was significantly higher than those of non-MV ($p<0.002$).

Biochemical and hematological parameters at admission to ICU

Laboratory results of all patients at admission to ICU were demonstrated in Table 1. In the survived group, urea and creatinine levels were significantly lower ($p=0.009$, $p=0.029$, respectively) and the number of lymphocytes significantly higher ($p=0.001$) compared to the non-survived group. In the MV group, the number of lymphocytes and RBCs were found to be significantly lower than that in the non-MV group ($p=0.012$, $p=0.033$, respectively). Among APPs, prealbumin and albumin were significantly lower in both non-survived and MV groups ($p<0.001$, $p=0.011$, $p=0.006$, $p=0.010$, respectively). SAA increased significantly ($p=0.022$) only in the MV group. No significant difference was found between the two groups for CRP values ($p=0.078$, $p=0.178$).

Predictive value of SAA, CRP, Albumin, and Prealbumin for survival and mechanical ventilation status in critical COVID-19 patients

To determine the predictive power of inflammatory proteins for both mortality and MV, ROC AUC, optimal cut-off, sensitivity, and specificity values were demonstrated in Tables 2 and 3. The AUC of albumin and SAA parameters were found to be weak and significant in the prediction of mortality and MV. While the AUC of prealbumin was moderate for the prediction of mortality, was weak for the prediction of MV. In the ROC curve analysis (Figure 1 and 2), while albumin and prealbumin had significant cut-off values for mortality and MV prediction, SAA had significant cut-off values only for mortality prediction.

In patients with prealbumin≤0.09 g/L and albumin≤29.0 g/L, sensitivity for mortality was 54.8%, and specificity was 76%. As to patients with prealbumin≤0.1 g/L and albumin≤30.0 g/L, sensitivity for MV was found to be 50.6%, and specificity was 80%.

In the designed model for MV and mortality risk, the results of binary logistic regression analysis were demonstrated (Table 4). In patients with prealbumin≤0.1 g/L or albumin ≤30 g/L, the risk for MV was significantly increased (respectively, OR=3.551, $p=0.005$ and OR=2.752, $p=0.027$). The risk for mortality was found statistically significant (OR=0.310, $p=0.007$) in patients with albumin≤29 g/L.

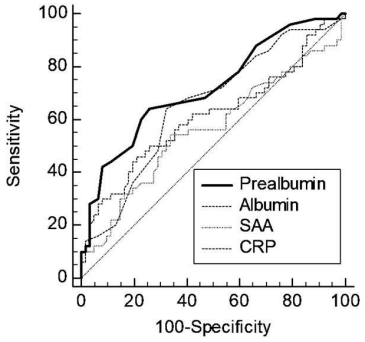

Figure 1. ROC curve of Prealbumin, Albumin, SAA and CRP to predict mortality of critic COVID-19 patients.

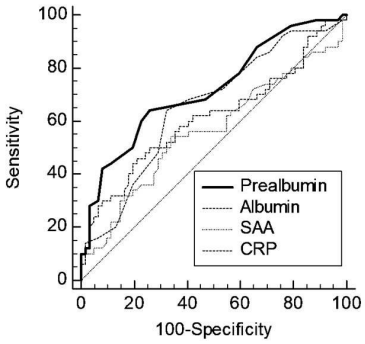

Figure 2. ROC curve of Prealbumin, Albumin, SAA and CRP to predict invasive MV among critic COVID-19 patients.

Table 1. Laboratory data of patients with critical COVID-19 at admission to ICU.

Variables (referance range)	Non-Survival n=69	Survival n=54	p value	MV n=83	Non-MV n=40	p value
Age (years)	70.0 (64.5-78.0)	65.5 (56.0-75.0)	**0.004**	69.0 (63.0-76.0)	68.5 (56.3-77.5)	0.335
Female n (%)	24 (34.8%)	26 (48.1%)	0.134	18 (45.0%)	32 (38.6%)	0.627
Prealbumin (0.2-0.4 gr/L)	0.08 (0.06-0.10)	0.12 (0.08-0.16)	**<0.001**	0.08 (0.06-0.11)	0.12 (0.08-0.15)	**0.006**
Albumin (35-52 g/L)	27.8 ±4.4	30.0±5.4	**0.011**	28 (25-31)	31 (27-33)	**0.010**
SAA (0.6-5.0 mg/L)	923 (496-1220)	681 (227-1173)	0.118	946±608	721±637	**0.022**
CRP (0-5 mg/L)	165 (107-226)	119.2 (57.8-230.3)	0.078	160 (97.8-230)	120.5 (65.0-221.7)	0.178
PCT (0.04-0.10 μg/L)	0.35 (0.14-1.70)	0.24 (0.09-0.88)	0.109	0.43 (0.14-1.38)	0.20 (0.07-0.98)	0.101
hs-TNI (2.5-46.0 ng/L)	41.2 (15.4-352.8)	30.6 (7.5-134.8)	0.055	41.2 (14.2-367.8)	27.6 (8.82-71.9)	0.123
Fibrinojen (1.7-4.2 g/L)	6.10 (4.76-7.72)	5.88 (4.30-7.32)	0.304	6.19 (4.68-7.68)	6.01 (4.34-7.60)	0.787
D-dimer (0-0.4 mg/L)	1.90 (0.99-5.56)	1.76 (0.81-5.00)	0.591	1.99 (1.04-5.69)	1.44 (0.76-4.87)	0.167
Glucose (4.1-5.9 mmol/L)	9.05 (6.77-12.29)	8.19 (6.52- 12.68)	0.708	8.05 (6.55-11.4)	8.96 (6.9-13.7)	0.332
Ure (17-43 mg/dL)	72.0 (50.5-100)	51.0 (37.8-76.0)	**0.009**	61.0 (46.0-95.0)	59.0 (40.8-99.8)	0.837
Creatinine (0.8-1.4 mg/dL)	1.20 (0.90-1.80)	1.00 (0.80-1.30)	**0.029**	1.10 (0.80-1.50)	1.10 (0.93-1.75)	0.240
AST (0-50 U/L)	41.0 (28.5-64.5)	35.0 (28.0-57.8)	0.366	41.0 (29.0-66.0)	37.5 (26.5-48.8)	0.259
ALT (0-50 U/L)	30.0 (16.0-41.0)	29.0 (18.8-47.5)	0.594	30.0 (17.0-43.0)	28.0 (17.3-44.3)	0.991
LDH (0-278 U/L)	609 (395-815)	499 (320-768)	0.223	587 (388-828)	512 (323-719)	0.195
WBC (4.2-10.6x10^9/L)	11.2 (7.7-14.9)	11.0 (8.8-15.7)	0.541	11.20 (7.90-15.70)	10.80 (8.23-14.30)	0.972
NEU (2-6.9x10^9/L)	9.90 (6.30-13.50)	9.40 (6.55-13.75)	0.913	9.90 (6.50-13.90)	9.25 (6.40-13.00)	0.718
LYM (0.6-3.4x 10^9/L)	0.50 (0.30-0.80)	0.70 (0.50-1.00)	**0.001**	0.55 (0.30-0.80)	0.70 (0.50-1.00)	**0.012**
MON (0-0.9 x 10^9/L)	0.50 (0.30-0.90)	0.60 (0.40-1.00)	0.069	0.60 (0.30-0.90)	0.65 (0.30-1.15)	0.483
RBC (4.04-5.48x 10^{12}/L)	4.11 (3.44-4.50)	4.24 (3.74-4.71)	0.430	3.95±0.87	4.31±0.81	**0.033**
Hgb (12.2-16.2 gr/dL)	11.7±2.4	11.7±2.2	0.996	11.6±2.4	12.0±2.3	0.339
Hct (%)	37.8 ±24.0	35.0 ±6.4	0.404	36.8±22.0	3.0±6.4	0.224
PLT (140-400x10^9/L)	228 (172-317)	203.5 (162.25-274.25)	0.600	228 (169-275)	216 (169-371)	0.709
Length of ICU stay (day)	11.0 (6.0-18.0)	11.0 (5.8-20.3)	0.719	12.0 (6.0-19.0)	10.5 (6.3-16.8)	0.482

ICU- intensive care unit, MV- invasive mechanically ventilated, SAA- serum amyloid A, CRP- C-reactive protein, PCT- procalcitonin, hs-TNI- high sensitive troponin I AST- aspartate aminotransferase, ALT- alanine aminotransferase, LDH- lactate dehydrogenase, WBC- white blood cell count, NEU- neutrophil count, LYM- lymphocyte count, MON- monocyte count, RBC- red blood cell count, Hgb- hemoglobin, Hct- hemotocrit, PLT- platelet count, n- number. Albumin, Hgb and Hct (%) parameters were presented as "mean±standard deviation (SD)" and other parameters as "median (IQR-interquartile range)".
p value < 0.05 was considered statistically significant and are shown in bold.

Table 2. Analysis of the effectiveness of laboratory data to predict mortality occurrence in critical COVID-19 patients.

Parameters	Cut-off	AUC (95% CI)	p value	Sensitivity (95% CI)	Specificity (95% CI)
Albumin (g/L)	≤29.0	0.632 (0.541-0.718)	**0.010**	63.0 (48.7- 75.7)	66.7 (54.3- 77.6)
Prealbumin (gr/L)	≤0.09	0.718 (0.625-0.799)	**<0.001**	64.0 (49.2- 77.1)	74.2 (61.5- 84.5)
SAA (mg/L)	>717	0.582 (0.490- 0.671)	0.126	55.6 (41.4- 69.1)	66.7 (54.3-77.6)
CRP (mg/L)	>97.7	0.593 (0.501- 0.681)	0.089	42.6 (29.2- 56.8)	82.6 (71.6-90.7)

COVID-19- coronavirus disease 2019, AUC- the areas under the curve, CI- confidence interval, SAA- serum amyloid A, CRP- C-reactive protein. p value < 0.05 was considered statistically significant and are shown in bold.

Table 3. Analysis of the effectiveness of laboratory data to predict mechanic ventilation in critical COVID-19 patients.

Parameters	Cut-off	AUC (95% CI)	p value	Sensitivity (95% CI)	Specificity (95% CI)
Albumin (g/L)	≤30.0	0.644 (0.552-0.728)	**0.007**	69.9 (58.8-79.5)	55.0 (38.5-70.7)
Prealbumin (gr/L)	≤0.1	0.661 (0.566-0.748)	**0.005**	71.4 (60.0-81.2)	62.9 (44.9-78.5)
SAA (mg/L)	>717	0.628 (0.536-0.713)	**0.018**	66.3 (55.1-76.3)	62.5 (45.8-77.3)
CRP (mg/L)	>107	0.575 (0.483-0.664)	0.185	69.9 (58.8-79.5)	45.0 (29.3-61.5)

COVID-19- coronavirus disease 2019, AUC- the areas under the curve, CI- confidence interval, SAA- Serum amyloid A, CRP- C-reactive protein. p value < 0.05 was considered statistically significant and are shown in bold.

Table 4. Logistic regression analysis of MV and mortality risk for acute phase proteins in critical COVID-19 patients.

Parameters	Groups	B	S.E.	OR	95% CI for Exp(B)	p value
Prealbumin	Non-survival	0.562	0.426	0.570	0.247-1.314	0.187
	MV	1.267	0.454	3.551	1.459-8.638	**0.005**
Albumin	Non-survival	1.170	0.434	0.310	0.133-0.727	**0.007**
	MV	1.012	0.457	2.752	1.125-6.735	**0.027**
SAA	Non-survival	0.633	0.474	0.531	0.210-1.344	0.181
	MV	0.875	0.500	2.398	0.900-6.388	0.080
CRP	Non-survival	0.651	0.502	0.521	0.195-1.395	0.195
	MV	0.057	0.511	1.058	0.389-2.882	0.912

B- Logistic regression coefficient, SE- standard error, OR- odds ratio, CI- confidence interval, SAA- serum amyloid A, CRP- C-reactive protein, MV- invasive mechanically ventilated.

Regression model was adjusted for APP's cut-off limits for AUC. Cut-off limits of non-survival group: prealbumin ≤0.09 gr/L, albumin ≤29 g/L, SAA >717 mg/L, CRP >97 mg/L. Cut-off limits of MV group: prealbumin ≤0.1 gr/L, albumin ≤30 g/L, SAA >717 mg/L, CRP >107 mg/L. p value <0.05 was considered statistically significant and are shown in bold.

DISCUSSION

In our study, biochemical and hematologic parameters were evaluated to predict MV need or mortality in critical COVID-19 patients. We found that especially prealbumin, albumin, SAA, urea, creatinine levels, LYM, and RBC count changed in critical COVID-19 patients who needed MV or died. These results were in keeping with those reported in other studies. An increase in CRP, PCT, LDH, SAA, urea, creatinine, blood glucose, D-dimer, fibrinogen, white blood cell, and neutrophil count, and a decrease in prealbumin, albumin, hemoglobin, and lymphocyte count was observed in other studies (3).

Of symptomatic COVID-19 patients, 5% are in critical condition and need treatment in

ICU (6). In COVID-19, death occurs most commonly in critical patients requiring ICU. Petrilli et al. reported that the mortality rate was 44.9% (292/650) and the rate of mechanical ventilation was 68.5% (445/650) among critical patients. They have found that the rate of mortality in mechanically ventilated patients was 36.4% (162/445) (7). Wu et al. reported mortality in 49.0% (1023/2087) of critical patients (6). Yang et al. reported mortality at the rate of 61.5% (32/52) and mechanical ventilation rate at 71.2 % (37/52), of critical patients. They have reported that, in the deceased group (32) mechanical ventilation (invasive and noninvasive) was used in 93.8% (30/32) of the patients (8). Similarly, in the present study, in critical COVID-19 patients monitored in ICU, the rate of mortality was found to be 56.1% (69/123), MV ratio was 67.5% (83/123), and MV ratio in dead patients was 79.7% (55/69).

APP's are used in laboratories as indicators of acute and chronic inflammation (5). There were significantly low albumin and prealbumin levels in both of our patient groups. While the AUC of albumin and prealbumin were found to be statistically significant in the prediction of mortality or mechanical ventilation, the highest AUC belonged to Prealbumin to predict mortality. In addition, MV risk increased 3.5 fold in patients with prealbumin value of ≤0.1 g/L and 2.8 fold in those with albumin value of ≤30 g/L, and mortality risk increased 0.3 fold in patients with albumin value of ≤29 g/L. These findings indicate that critical COVID-19 patients who have low prelbumin and albumin levels at first admission to ICU, have a poorer prognosis and we suggest that combined use of these parameters can be utilized for early treatment planning.

Patients with low plasma prealbumin levels have a higher risk of malnutrition and inflammatory conditions. Malnutrition occurs quite commonly in hospitalized patients, particularly in the elderly patients (9). However, prealbumin levels lower than the expected values are associated with an increased risk of mortality in elderly COVID-19 patients (9). It was reported that prealbumin decreased markedly in the early stage of COVID-19 (10), and furthermore it was considerably lower especially in patients with severe disease (11). Luo et al. evaluated prealbumin and most routine laboratory indicators together and stated that low prealbumin levels on admission were successful for predicting the prognosis of COVID-19 (12).

Prealbumin is a transporter protein and is commonly used as an indicator of liver protein synthesis in cases of malnutrition (13). In addition, many cytokines synthesized in response to inflammation, downregulates plasma concentrations of albumin and prealbumin. Therefore, they are accepted as a marker of both malnutrition and inflammation (13).

Albumin is the main blood protein synthesized in the liver. However, except for malnutrition, the decrease of serum albumin levels may cause by factors such as hemodilution, leak to extravascular space, increase in consumption by cells, and decrease due to increase in colloidal osmotic pressure caused by positive AFR's increasing in inflammation (5). Some studies stated that low serum albumin levels indicate a poor prognosis in COVID-19 patients (3,14). In addition, in many studies, it was shown that a decrease in albumin has a negative correlation with an increase in IL-6, and is associated with the severity of the disease (14). Because of normal transaminase values in our critical COVID-19 patients, the possible reason for the decrease in prealbumin and albumin may be a response to changes in pro-inflammatory cytokines rather than to liver injury.

Particularly SAA and CRP increase rapidly and significantly during the acute inflammatory response (15). CRP is a sensitive but not specific APP. It has a role in differentiating bacterial or viral infections by itself or in combination with other markers (16). It has been shown that in severe COVID-19 patients

that high CRP levels are associated with the high rate of ICU admission need, but not with mortality (17). Li et al. stated that CRP may yield information on the progression of COVID-19 in the early period (18). In the present study, although CRP increased in all critical COVID-19 patients, there was no significant difference between groups. Hence, a high CRP value maybe not be a specific marker for the prognosis of patients in ICU.

SAA plays an important role in the defense of the host against the various environmental agents and antiviral activity (19). It aids especially the determination of the presence of secondary infection that may develop in patients undergoing treatment in ICU. It has been demonstrated that alteration in SAA in the acute stage has prognostic value for COVID-19 (20-21). In the present study, an increase in SAA was significant only in MV group patients, but the AUC of SAA was weak in the prediction of mortality or mechanical ventilation.

In our retrospective study, laboratory data could not be completely obtained in some patients and were recorded only within the first 24 hours of admission to ICU. Therefore, the evaluation of clinical data together with laboratory data obtained at the end of 28 days in ICU will further elucidate the issue.

In conclusion, evaluation of APP levels, especially albumin and prealbumin in the early period of COVID 19 may be beneficial for the prediction of mortality and the need for MV. In the present study, a cut-off value we found for albumin (≤30 g/L) and prealbumin (≤0.1 g/L) decided to predict poor prognosis for ICU COVID-19 patients. Besides, it may assist early detection of patients that are most likely to need ICU treatment and improves the ability to make accurate decisions in conditions in which the health system is overwhelmed. Because our study was performed pre-vaccination period, our results may provide valuable information for understanding the pathophysiology of COVID-19.

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Conflicts of Interest: None

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