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Research Article

Evaluation of the relationship between C-reactive protein/albumin ratio and hospitalization in novel coronavirus disease 2019

Cigdem Damla Deniz[1], Nahide Baran[2], Ayse Ruveyda Ugur[3], Ahmet Guneyk[1], Mehmet Ozcan[4], Ismail Hakkı Tuncez[5], Mehmet Koc[6]

[1]Department of Medical Biochemistry, Konya City Hospital, Konya, Turkey
[2]Department of Radiology, Cihanbeyli State Hospital, Konya, Turkey
[3]Department of Microbiology, Konya City Hospital, Konya, Turkey
[4]Department of Infectious Diseases and Clinical Microbiology, Konya State Hospital, Konya, Turkey
[5]Department of Public Health, Konya Provincial Health Directorate, Konya, Turkey
[6]Department of Radiation Oncology, Necmettin Erbakan University, Meram Faculty of Medicine, Konya, Turkey

Abstract

Objectives: Coronavirus disease 2019 (COVID-19), a global pandemic with catastrophic consequences for healthcare systems causing serious respiratory illness, was first reported in China. Early identification of severe illness is critical for controlling it and improving the prognosis of patients. In this study, we aimed to evaluate the prognostic value of C-reactive protein (CRP)/albumin ratio and to investigate the usability of this ratio in COVID-19.

Methods: This was a retrospective cohort study of 1077 patients. The statistical significance was calculated using Mann-Whitney U test. The correlations between CRP/albumin ratio and other datas were evaluated by Spearman's rho test. We evaluated the prognostic value of CRP/albumin ratio using the Chi-Square test and Cox regression analysis.

Results: Higher CRP/albumin ratio levels were associated with long-term hospitalization in COVID-19. When the results of the receiver operating characteristic analysis were examined for all laboratory parameters, the area under the curve value of the CRP/albumin ratio, procalcitonin, CRP, and albumin were 0.85, 0.64, 0.86, and 0.81, respectively. The survival mortality cut-off value for CRP/albumin ratio was determined as 1.895. When evaluated by Cox regression analysis (cut-off value: 1.895, $p<0.0001$), the CRP/albumin ratio was found to be independently associated with in-hospital mortality.

Conclusion: We showed that the CRP/albumin ratio is a useful prognostic marker this marker can be used in predicting the severity of COVID-19.

Keywords: Albumin, COVID-19, C-reactive protein, C-reactive protein/albumin ratio, hospitalization

In December 2019, Wuhan city, the capital of Hubei province in China, became the center of an outbreak of pneumonia of unknown cause. A novel virus named 2019 novel coronavirus (2019-nCoV/SARS-CoV-2) is the cause of a syndrome of symptoms that are classified as coronavirus disease 2019 (COVID-19). The COVID-19 pandemic has rapidly propagated through person-to-person transmission [1-3]. It is important to predict the prognosis of patients to determine the direction of treatment. A simple, quick, and accessible parameter is needed to confirm treatment response and predict mortality in COVID-19.

Several classes of inflammation markers have been described: cytokines/chemokines, reactive oxygen and nitrogen species, prostaglandins and cyclooxygenase-related factors, and mediators such as transcription factors and growth factors. Among all these markers, the techniques currently available for C-reactive protein (CRP) are easy to perform and present low cost

Address for correspondence: Cigdem Damla Deniz, MD. Department of Medical Biochemistry, Konya City Hospital, Konya, Turkey
Phone: +90 553 422 68 21 **E-mail:** c.d.cetinkaya@gmail.com **ORCID:** 0000-0002-6052-4645
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and high analytical sensitivity [4]. CRP is an acute-phase protein that circulates as a disk-shaped pentamer consisting of five identical subunits. It is produced following stimulation by various cytokines in response to inflammatory conditions. As the exact function of CRP is not fully understood yet, it is believed that it functions as part of the innate immune system [5]. CRP levels have been studied in relation to prognosis and mortality in critically ill patients [6].

On the other hand, low serum albumin is known to be associated with poor prognosis and mortality [7]. Based on this knowledge, we speculated that the CRP/albumin ratio could be used as a predictive marker for COVID-19.

The CRP/albumin ratio, a novel inflammation-based prognostic indicator, has been extensively studied as an independent prognostic marker in patients with infection and malignancy [8, 9]. In this retrospective study, we aimed to evaluate the potential of CRP/albumin ratio in the outcome prediction of patients with COVID-19.

Materials and Methods

Patients and study design

This study was conducted at the Konya Education Research Hospital. The study was retrospectively planned in patients diagnosed with COVID-19 between March 1, 2020 and June 29, 2020. We excluded patients under 19 years and patients with clinically suspected COVID-19 but negative polymerase chain reaction (PCR) testing. Patients whose CRP and/or albumin levels were not measured at the time of admission were not included in the study.

The biochemical and radiological evaluation results of the patients were collected from electronic medical hospital records. Other clinics such as Pulmonary Medicine, Internal Medicine and Infectious Diseases are defined as non-intensive care unit (non-ICU). The protocol was approved by Necmettin Erbakan University, Meram Faculty of Medicine Ethics Committee (Decision Number: 2020-2681). All participants submitted written informed consent prior to the examination.

Image acquisition

Low-dose chest computed tomography (CT) was performed using a second-generation dual-source MDCT scanner (Somatom Definition Flash, Siemens Healthcare). Scanning was performed from the thoracic inlet to the middle portion of the kidneys, and the scanning parameters are as follows: 20 effective mAs, 120 kVp, collimation of 1.5 mm, scanning range 35 cm, pitch 0.75, gantry rotation time 330 ms, and high spatial resolution algorithm. All patients were examined without injection of contrast media. Images were obtained with mediastinal (width 350-450 HU, level 20-40 HU) and parenchymal (width 1200-1600 HU, level-500 to-700 HU) window settings.

Image interpretation

CT images were evaluated by a thoracic radiologist with 4 years of experience. CT images of each patient were assessed for the presence and distribution of parenchymal abnormalities, including (1) no sign of lung involvement; (2) pure ground-glass opacity (GGO), which was defined as a hazy increase in lung attenuation with no obscuration of the underlying vessels; (3) GGO with consolidation, which was defined as an area of opacification obscuring the underlying vessels in GGO; and (4) consolidation without GGO. In addition, it was determined how many lobes in total were affected.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows 21.0 (IBM Corp., Armonk, NY, USA). The statistical significance was calculated using the Mann-Whitney test. The correlation between CRP/albumin ratio and other data was evaluated by Spearman's rho. We evaluated the predictive value of CRP/albumin ratio using receiver operating characteristic (ROC) analysis. Cox regression analysis was performed for survival analysis of the CRP/albumin ratio. A value of $p<0.05$ was considered statistically significant. The results were expressed as median value and standard deviation (median±SD).

Results

From March 1, 2020 to June 30, 2020, 57 patients admitted to the medical ICU and 1020 patients admitted to the other departments of the hospital were included in the study. The median (IQR) age of the ICU and non-ICU patients were 69 (58.5-78.5) and 46 (32-59), respectively. ICU patients were significantly older than non-ICU patients, ($p<0.0001$) (Table 1). Of the 29 patients who died, 51.7% were male and 48.3% were female. No sign of lung involvement was found in 307 non-ICU patients and 2 intensive care patients. ICU patients had a higher prevalence of lung involvement ($p<0.0001$) and numbers of lobes affected ($p<0.0001$). Furthermore, in laboratory findings, serum CRP ($p<0.0001$), CRP/albumin ratio ($p<0.0001$), and procalcitonin ($p<0.0001$) were lower in non-ICU than in ICU patients. Albumin level ($p=0.045$) was significantly higher in non-ICU than in ICU patients (Table 1).

High levels of CRP/albumin ratio were associated with length of stay in hospital and numbers of lobes affected of COVID-19 patients (correlation coefficients 0.249 and 0.488, respectively, $p<0.001$) (Fig. 1). Differences were evident between CRP/albumin ratio and procalcitonin as determined by Spearman's rho test ($p<0.001$, correlation coefficient 0.635) (Fig. 1).

Figure 2 shows the ROC curve of CRP/albumin ratio. The cut-off point of CRP/albumin ratio was 1.895, and the sensitivity and specificity were 81% and 86%, respectively. The positive predictive value was 42%, and the negative predictive value was 97%.

Figure 2 also shows the ROC curve of procalcitonin, which is widely used in viral infections and has proven clinical value.

Table 1. Baseline characteristics of COVID-19 patients*

Variable	Non-Intensive care unit (n=1020)	Intensive care unit (n=57)	p**
Age, years of age, Median (IQR)	46 (32-59)	69 (58.5-78.5)	<0.0001
Male, n (%)	53.33	56.14	0.673
Radiological findings			
Lung involvement, n (%)			<0.0001
No sign of lung involvement	307 (30.1)	2 (3.5)	
GGO	461 (45.2)	22 (38.6)	
GGO with consolidation	242 (23.7)	31 (54.4)	
Consolidation without GGO	10 (1)	2 (3.5)	
Numbers of lobes affected, n (%)			<0.0001
0	307 (30.1)	2 (3.5)	
1	131 (12.8)	4 (7)	
2	110 (10.8)	6 (10.5)	
3	107 (10.5)	4 (7)	
4	78 (7.6)	2 (3.5)	
5	287 (28.1)	39 (68.4)	
Laboratory parameters, median (IQR)			
CRP, mg/L	6.43 (3.11-22.2)	123 (64.1-179.5)	<0.0001
Albumin, g/dL	37.8 (34.06-40.22)	29.6 (27.9-33.1)	0.045
CRP/Albumin ratio	0.27 (0.08-0.94)	4.45 (2.1-6.3)	<0.0001
Procalcitonin, ng/mL	0.031 (0.02-0.057)	0.276 (0.1-1.4)	<0.0001

*: Data are presented as number (percentage) or median [interquartile range (IQR)], unless otherwise indicated. GGO: Ground-glass opacities; CRP: C-reactive protein, **statistically difference between two groups, p<0.05 statistically significance.

The cut-off point of procalcitonin was 0.63, and the sensitivity and specificity were 44% and 85%, respectively. The positive predictive value was 16%, and the negative predictive value was 95%.

The results of ROC analysis for all laboratory parameters are presented in Table 2. Area under the curve value (AUC) of the CRP/albumin ratio, procalcitonin, CRP, and albumin were 0.85, 0.64, 0.86, and 0.81, respectively (Table 2).

The survival cut-off value for CRP/albumin ratio was determined to be 1.895. When evaluated by Cox regression analysis (hazard ratio (HR)=1.53; 95% confidence interval (CI)=1.38-1.68; p<0.0001), the CRP/albumin ratio was found to be independently associated with survival (Fig. 3).

Discussion

Many studies have evaluated biomarkers used for the prediction of prognosis in critically ill patients. However, these factors are difficult to determine, and the immediate application of such prognostic information is complicated when dealing with unstable patients. The most important finding of our study is the clinical value of CRP/albumin ratio in predicting poor outcome of COVID-19 patients.

CRP is a type of protein produced by the liver that is elevated in response to inflammation [10]. CRP levels are associated with various conditions, including severe sepsis, heart failure, and other inflammatory diseases [11, 12]. The inflammatory response also plays a serious role in COVID-19. Generally, CRP level is much higher in bacterial infections than in viral infections [13]. In a study by Wang et al. [14], many COVID-19 patients showed elevated CRP levels, which is in agreement with other studies. Moreover, aggravated cases in the study showed significantly higher levels of CRP than nonsevere patients, which suggested that CRP may be a serum marker of disease aggravation in COVID-19 patients. Liu et al. [15] studied that the serum levels of IL-6 and CRP had a significant correlation with the severity of COVID-19 and suggested that these parameters can be used as independent factors to predict the risk of the disease. Changes in the CRP levels have been previously reported in COVID-19 patients, but little is known about their correlation with disease severity. In an earlier study, it was found that CRP in severe COVID-19 patients increased significantly at the initial stage, before CT findings, and importantly, CRP, which was associated with disease development, predicted early severe COVID-19 [16]. Luo et al. [17] study suggested that admission serum CRP level performed well in discriminating disease severity and predicting adverse outcomes in patients with COVID-19, and patients with high CRP should be provided more attention and strengthened treatment.

Serum albumin is a negative acute-phase maintenance protein that is rapidly downregulated by inflammatory processes, i.e., sepsis, trauma, and massive hemorrhage [18]. A reduction

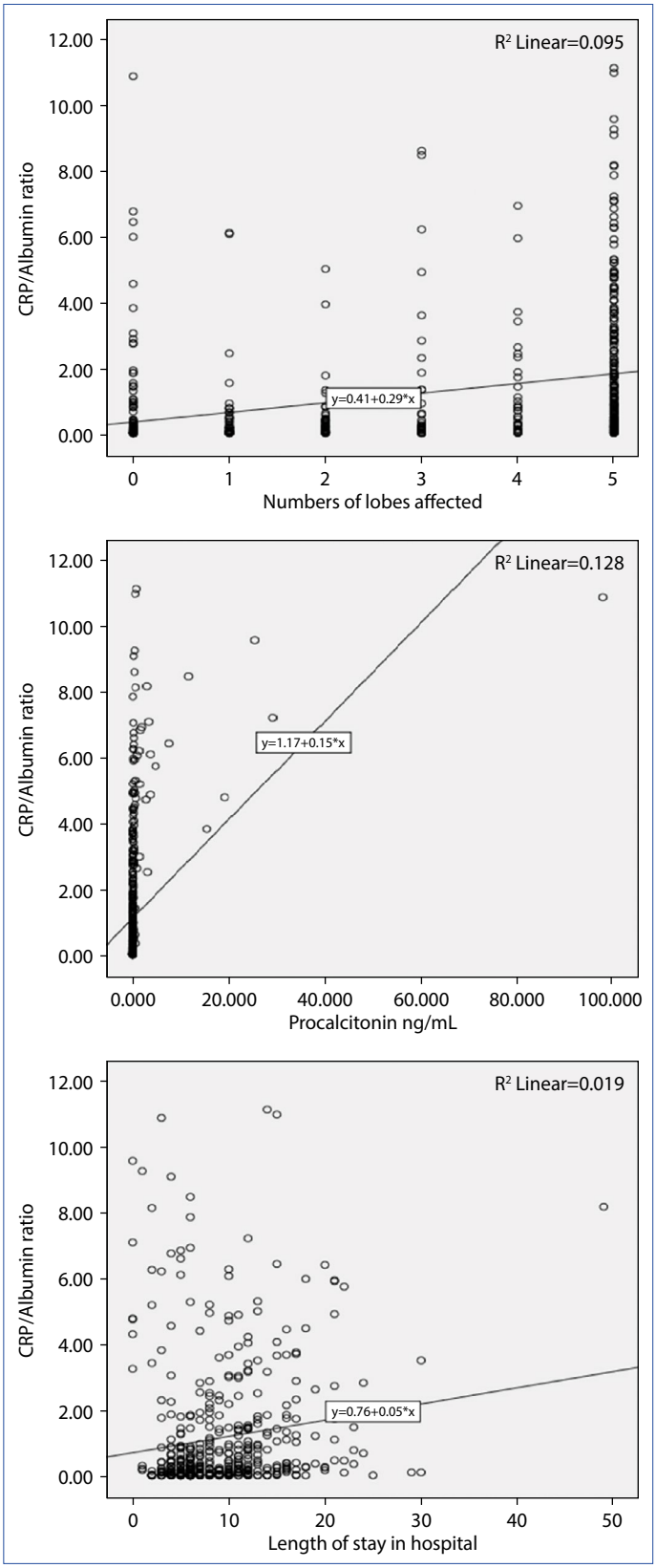


Figure 1. Graphs showing the correlation between CRP/albumin ratio and numbers of lobes affected, length of hospital stay, and procalcitonin (ng/mL), respectively, in COVID-19 patients.

CRP: C-reactive protein.

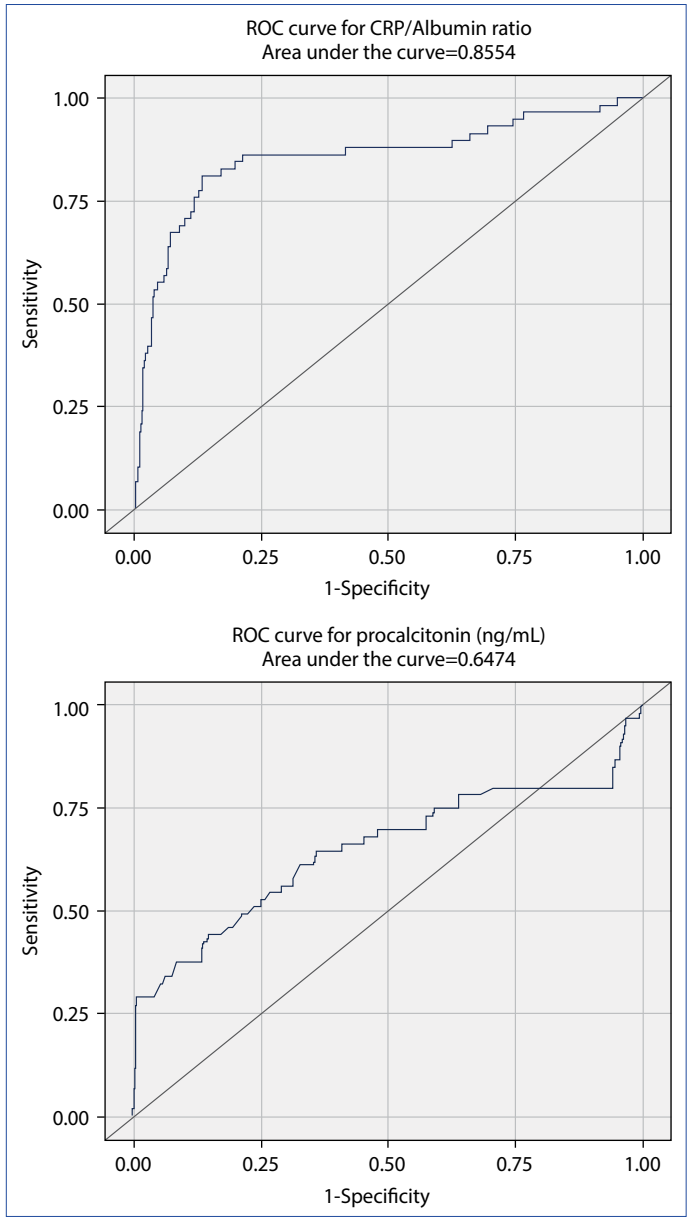


Figure 2. ROC curves of CRP/albumin ratio and procalcitonin in COVID-19 patients. The AUC value of procalcitonin is lower than that of the CRP/albumin ratio.

ROC: Receiver operating characteristic; AUC: Area under the curve; CRP: C-reactive protein.

of albumin concentration usually results in decreasing blood volume, which might even cause multiple organ dysfunction when serious. Furthermore, an essential function of albumin is to neutralize toxic compounds such as oxygen radicals and nitrite peroxides. Decreased albumin can make infection control more difficult [19]. Hypoalbuminemia is common in seriously ill patients, and serum albumin level has been associated with increased mortality in acutely ill patients in previous reports. Because of its value as an outcome predictor, serum albumin level has been added as one of the component parameters in the acute physiology and chronic health evaluation III score

Table 2. ROC analysis results of COVID-19 patients

Variable	Cut-off point	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	AUC
CRP/albumin ratio	1.89	81	86	42	97	0.85
Procalcitonin	0.63	44	85	16	95	0.64
Albumin	34.3	89	68	25	98	0.81
CRP	12	91	67	14	99	0.86

ROC: Receiver operating characteristic; AUC: Area under the curve; CRP: C-reactive protein.

[20]. In a meta-analysis of 90 cohort studies, hypoalbuminemia was a dose-dependent predictor of poor outcomes, such as mortality, morbidity, and prolonged intensive care unit and hospital stay. The association between hypoalbuminemia and poor clinical outcomes appeared to be independent of both nutritional status and inflammation in that study [21]. Our study demonstrated significantly lower albumin levels and higher CRP levels in ICU patients with COVID-19. However, hypoalbuminemia can also be caused by previous diseases or general conditions, and therefore it is difficult to use CRP or albumin as a biomarker alone [22].

The CRP/albumin ratio is being used as a prognostic score to assess outcomes in patients with cancer, inflammation, and sepsis [23]. The combination of albumin and CRP into a single index has been suggested previously, and subsequent studies have shown that the CRP/albumin ratio is more consistent with prognosis than CRP or albumin alone [24]. Kim et al. [25] reported that the CRP/albumin ratio at admission was positively correlated with prognosis in patients with severe sepsis or septic shock treated with early goal-directed therapy. In that study, the cut-off value for the CRP/albumin ratio as a predictor of mortality was 5.09 in patients with severe sepsis or septic shock [25]. In a study of elderly patients admitted via the emergency room, high-sensitivity-CRP/albumin ratio at admission to the emergency department was associated with all-cause in-hospital mortality among patients older than 65 years [26]. The CRP/albumin ratio has been shown as a predictor of mortality in acute pancreatitis patients [27]. Furthermore, the CRP/albumin ratio has predicted overall survival in various malignancies [28-32]. In our study, CRP/albumin ratio had greater accuracy than CRP in terms of prognostic value in COVID-19 patients.

Viral infections do not usually affect the number of leukocytes, and therefore the use of acute-phase reactants, such as procalcitonin, as biomarkers may be of great help in reaching a diagnosis [33]. The production of procalcitonin depends on the presence of circulating tumor necrosis factor (TNF-α); in viral infections, macrophages produce interferon-α that can inhibit TNF-α, suppressing the elevation of procalcitonin, thus suggesting a viral origin [34]. We showed that the CRP/albumin ratio has much better sensitivity and specificity than procalcitonin in COVID-19 patients' follow-up.

In a meta-analysis in which 16 different studies were evaluated, the most common lung involvement pattern was found

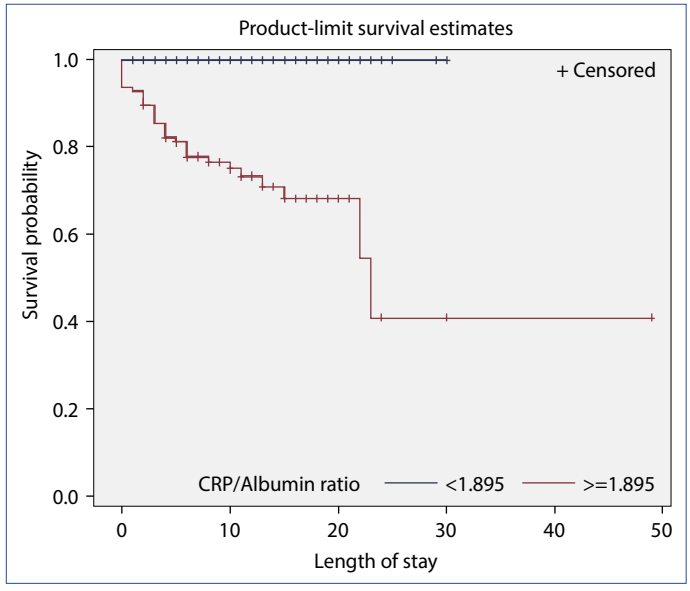


Figure 3. Survival analysis graph for CRP/albumin ratio.
CRP: C-reactive protein.

to be GGO, and the second was GGO with consolidation. In addition, the least common involvement pattern was found to be consolidation without GGO [35]. In this study, the most common lung involvement pattern was found to be GGO, and GGO with consolidation was the second in both intensive care patients and non-intensive care patients. Consolidation without GGO was the least common pattern of involvement in both groups. On the other hand, although the PCR test was positive in this study, lung involvement was not detected in 30% of the patients by tomography. This may indicate that some of the patients with positive PCR tests may not have lung involvement, or CT may be performed before lung involvement occurs in this patient group.

In one study, it was reported that 5 lobes of the lungs of 75% of the patients were affected. In another study, more than 2 lobes of the lungs of 77% of the patients were affected [36, 37]. In our study, it was determined that more than 2 lobes were involved in the majority of patients with pulmonary involvement. In addition, 5 lobes were affected in 68.4% of intensive care patients and 5 lobes in 28.1% of non-intensive care patients, and this finding was statistically significant.

In the light of the findings obtained as a result of our study, we

think that the high CRP/albumin ratio can be used as a prognostic marker in COVID-19 due to its easy measurement and clinical value. To our knowledge, in the literature, there are only a few studies concerning the usability of CRP/albumin ratios in COVID-19 patients. The limitation of this study was the small sample size, and further studies with larger sample sizes should be planned to confirm these results.

In conclusion, this study showed that the patients with high CRP/albumin ratio levels had further ICU requirements and further death rates. We support the idea of that the CRP/albumin ratio is a simple, inexpensive and useful prognostic marker that can be used in predicting the severity of COVID-19.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University Meram Faculty of Medicine Non-Pharmaceutical and Non-medical Research Ethics Committee (No: 2020-2681, Date: 03/07/2020).

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