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Predictive value of C-reactive protein/albumin ratio in predicting poor outcome of hospitalized patients with COVID-19

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ABSTRACT

Introduction: For more than a year, COVID-19 has caused a high number of mortality and morbidity, and negatively affects life all over the world. Early detection tools that can be used to predict prognosis are particularly important in patients who need critical care. Among the acute phase reactants, CRP can be higher without any other findings. Otherwise, the cytokine storm that occurs in hospitalized COVID-19 cases can cause critical hypoalbuminemia, and low albumin levels can predict the course of the disease independently of other indicators. Our aim in this study is to determine the relationship between CRP / albumin ratio (CAR) and prognosis of COVID-19 patients.

Material and Method: In this study, from February 1, 2021 to April 30, 2021, patients who visited to the emergency department, diagnosed with COVID-19 and hospitalized, were selected to examine retrospectively.

Results: The study was completed with total of 273 patients. We divided the patients into two groups as those who require ICU and those who do not. The CAR was found to be more than 2 times higher in the ICU required group than the non-ICU need group (1.43 - 0.61, respectively). The area under the curve (AUC) of CRP, albumin and CAR were 0.708, 0.321 and 0.729 for the prediction of ICU admissions, respectively. In terms of mortality, AUC values were calculated as 0.660, 0.304 and 0.725, in the same order, and the predictive power of CAR was higher than CRP and albumin alone in both outcomes.

Conclusion: We found that the patients with high CAR values had further ICU requirements and further mortality rates. CAR is a simple, convenient and inexpensive prognostic marker that can be used in predicting the severity of COVID-19.

Keywords C-reactive protein, albümin, COVID-19, intensive care

INTRODUCTION

In late 2019, many pneumonia cases of unknown origin were detected in Wuhan, China (1). The pathogen that caused the cases was later identified as a novel enveloped RNA betacoronavirus and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) has declared coronavirus disease (COVID-19) as an internationally considerable public health emergency (2). For more than a year, COVID-19 has caused a high number of mortality and morbidity, and negatively affects life all over the world.

Early diagnosis tools that can be used to predict prognosis are crucial for the functioning of health systems, especially in patients who require critical care.

Inflammation is triggered the liver to synthesize a large number of the acute phase reactants. One of these such reactant is C-reactive protein (CRP), which can be used as a biomarker in the presence of rheumatoid arthritis, cardiovascular disease, and infection (3). It has been reported that in severe COVID-19 cases, CRP levels can be high without any findings observed on computed tomography, therefore, CRP can be used to determine the severe cases at an early stage (4).

Otherwise, cytokine storm induced in hospitalized COVID-19 cases, may cause critical hypoalbuminemia, increase the risk of death, and low albumin levels at the time of admission stage can predict the course of the disease independently than other indicators (5).

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Recently, the CRP/albumin ratio (CAR), that a combination of markers for systemic inflammation and nutritional status, has been extensively studied as an independent prognostic marker in patients with infection, malignancy, and other diseases (6). Our aim in this study is to determine the relationship between the CAR and the prognosis of COVID-19 patients.

MATERIAL AND METHOD

The study was approved by the ethics committee of Istanbul Education and Research Hospital (Date: 31.04.2021 Decision No: 2817), and conducted in accordance with the Declaration of Helsinki, the ethical principles.

Study Design

In this study, from February 1, 2021 to April 30, 2021, patients visited to the ED who diagnosed with COVID-19 and hospitalized, were selected to examine retrospectively.

All COVID-19 patients over the age of 18 who were visited to the ED, had oropharyngeal/nasopharyngeal swabs and hospitalized between February 1, 2021 and April 31, 2021 were included the study. Patients whose reverse transcriptase polymerase chain reaction (RT-PCR) test results were negative and whose CRP and/or albumin levels were not measured at the time of admission were not included in the study. Additionally, patients who visited to the ED due to cardiac arrest and who were received inotropic support at the time of admission were not included in the study.

Data were collected from electronic medical hospital records. All of the patients were recorded in a form, with their age, gender, CRP, albumin levels. After recording the CRP and albumin levels, the ratio of CRP/albumin was measured.

The primary outcome was to determine the relationship between CAR and ICU requirement. The secondary outcome was to determine the in-hospital mortality. Outcomes were retrospectively assessed by reviewing of the hospital medical database.

Statistical Analysis

Categorical variables were presented as frequency and percentage. Continuous variables were tested for distribution using the Kolmogorov–Smirnov and Shapiro-Wilk tests. The asymmetrically distributed variables were expressed as the median interquartile range (25%-75%). All variables were compared for ICU admission and mortality outcomes using Pearson's chi-squared, and Mann–Whitney U tests as appropriate. Receiver operating characteristic (ROC) analyses were performed to determine the predictive power of the variables in terms of both outcomes. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of all cutpoints were calculated. The cut-off point that achieves the maximum Youden's index is referred to as the optimal cut-off. A 2-sided P-value of 0.05 was regarded as statistically significant. All data analyses were performed using SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The study was completed with total of 273 patients after the inclusion and exclusion criteria were performed. The median (IQR) age of the patients was 52.0 (39.0–66.0), which 126 (46.2) were female. When our study sample was examined in terms of comorbid diseases, first three places were hypertension (HT), cardiovascular disease and pulmonary disease with 38.8%, 36.2%, 33.7%, respectively. ICU admission was required in 53 (19.4%) of all patients and 28 (10.3%) of them died. The baseline characteristics of the patients were shown in **Table 1**.

We divided the patients into two groups as those who require ICU and those who do not. Then we compared the variables in these two groups of age, gender, vital signs, comorbid diseases, laboratory findings, and mortality (**Table 1**). The median (IQR) age in the group with ICU requirement was 76.0 (67.0–79.0), and it was 47.0 (36.5–58.0) in the other group (non-ICU) and the difference was statistically significant ($p<0.001$). No significant difference was found in gender variable in the groups according to ICU requirements ($p=0.171$).

When we examined the vital signs, while the body temperature, pulse and respiratory rate increased significantly in the ICU requirement group, the saturation O2 was decreased ($p<0.001$ for all). But there was no significant difference between the groups in systolic-diastolic blood pressure and mean arterial pressure ($p>0.05$ for all).

In comorbidities, pulmonary disease (83.0%), cardiovascular disease (77.4%) and hypertension (60.4%) were the most common in ICU required patients, and there was a significant difference compared to the group that non-ICU patient ($p <0.001$). All ICU required patients had at least one comorbidity. While the comorbidity median (IQR) of the ICU requirement group was 1.0 (0.0–2.0), the comorbidity median of the non-ICU patients was 3.0 (2.0–4.0) and this difference was statistically significant ($p <0.001$).

In the laboratory results, the median value of CRP was significantly higher (49.0 - 23.5, respectively) and albumin was lower (36.5 - 40.0, respectively) in the ICU requirement group. The CAR was found to be more

than 2 times higher in the ICU requirement group than the non-ICU group (1.43 - 0.61, respectively), and all these differences were statistically significant (p <0.001 for all).

The ROC analysis was performed to determine the predictive power of CRP, albumin and CAR in ICU admissions and mortality outcomes. The area under the curve (AUC) of CRP, albumin and CRP/albumin were 0.708, 0.321 and 0.729 for the prediction of ICU admissions, respectively. In terms of mortality, AUC values were calculated as 0.660, 0.304 and 0.725, in the same order, and the predictive power of CAR was higher than CRP and albumin alone in both outcomes (**Table 2**).

The optimum cut-off points for the relevant outcomes were determined using the Youden's Index. The cut-off value of CAR determined for ICU requirement was 0.74. At this cut-off value, sensitivity was calculated as 86.79%, specificity 56.82%, PPV 32.62% and NPV 94.70%. The cut-off value of CAR for mortality was calculated as 0.91 and for this cut-off value, sensitivity was 78.57%, specificity 61.22%, PPV 18.80% and NPV 96.15%. The cut-off points of CRP, albumin and CAR with sensitivity, specificity, PPV, NPV, AUC and Youden's Index values were shown in **Table 2**.

Table 2. Optimum cut-off points* of CRP, albümin and CRP/albumin ratio in predicting ICU admissions and mortality

	Cut-off point	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUC	Youden's Index
ICU admissions							
CRP	27	84.91	55.91	31.69	93.89	0.708	0.408
Albumin	53	1.89	99.09	33.33	80.74	0.321	-0.143
CRP/albumin	0.74	86.79	56.82	32.62	94.70	0.729	0.436
Mortality							
CRP	27	82.14	51.43	16.20	96.18	0.660	0.336
Albumin	53	0	98.78	0	89.63	0.304	-0.122
CRP/albumin	0.91	78.57	61.22	18.80	96.15	0.725	0.398

*Cut-off points with the highest Youden's index value were shown
CRP: C-reactive protein, ICU: Intensive care unit, Sens: Sensitivity, Spec: Specificity, PPV: Positive predictive value, NPV: Negative predictive value AUC: Area under the curve

Table 1. Baseline characteristics of 273 patients

Variables Median (IQR), n(%)	All n=273	ICU (-) n=220	ICU (+) n=53	p
Age. years	52.0 (39.0–66.0)	47.0 (36.5–58.0)	76.0 (67.0–79.0)	<0.001*
Gender. n (%)				**0.171****
Female	126 (46.2)	106 (48.2)	20 (37.7)	
Male	147 (53.8)	114 (51.8)	33 (62.3)	
Vital Signs				
Body temperature	37.8 (37.2–38.2)	37.7 (37.2–38.0)	39.0 (38.0–39.2)	<0.001*
Saturation O_2	96.0 (93.0–98.0)	97.0 (95.0–98.0)	79.0 (74.0–90.0)	<0.001*
Pulse	83.0 (73.0–97.0)	80.5 (71.8–91.0)	108.0 (90.0–126.0)	<0.001*
Systolic blood pressure	124.0 (116.0–159.0)	124.0 (116.0–150.0)	136.0 (108.0–176.0)	0.337*
Diastolic blood pressure	82.0 (71.0–100.0)	81.0 (71.0–100.0)	83.0 (69.0–105.0)	0.780*
Mean arteriel pressure	95.7 (85.3–119.0)	95.0 (85.6–116.0)	101.0 (80.3–131.0)	0.529*
Respiratory rate	16.0 (14.0–18.0)	15.0 (13.0–16.0)	24.0 (21.0–27.0)	<0.001*
Comorbidities				
Diabetes	36 (13.2)	27 (12.3)	9 (17.0)	0.363**
Hypertension	106 (38.8)	74 (33.6)	32 (60.4)	<0.001**
Cardiovascular disease	99 (36.2)	58 (26.4)	41 (77.4)	<0.001**
Pulmonary disease	92 (33.7)	48 (21.8)	44 (83.0)	<0.001**
Hepatitis B	6 (2.2)	3 (1.4)	3 (5.7)	0.055**
Malignancy	36 (13.2)	16 (7.3)	20 (37.7)	<0.001**
Cerebrovascular disease	9 (3.3)	2 (0.9)	7 (13.2)	<0.001**
Chronic renal failure	18 (6.6)	8 (3.6)	10 (18.9)	<0.001**
Immunodeficiency	3 (1.1)	2 (0.9)	1 (1.9)	0.540**
Any comorbidities	203 (74.4)	150 (68.2)	53 (100.0)	<0.001**
Number of comorbidities	1.0 (0.0–2.0)	1.0 (0.0–2.0)	3.0 (2.0–4.0)	<0.001*
Laboratory				
CRP. mg/L	28.0 (14.0–56.0)	23.5 (12.0–48.5)	49.0 (34.0–67.0)	<0.001*
Albumin. g/L	39.1 (36.0–43.0)	40.0 (37.0–43.7)	36.5 (30.8–40.6)	<0.001*
CRP/albumin ratio	0.76 (0.35–1.56)	0.61 (0.31–1.25)	1.43 (0.91–1.84)	<0.001*
Mortality	28 (10.3)	1 (0.5)	27 (50.9)	<0.001**

*Mann-Whitney U test, **Pearson's chi-squared test
ICU: Intensive care unit, CRP: C-reactive protein

The AUC of CAR for ICU requirement was 0.729±0.034 (95% CI, 0.662–0.797), (**Figure 1**) and mortality was 0.725±0.046 (95% CI, 0.635–0.815), (**Figure 2**); (p <0.001 for both).

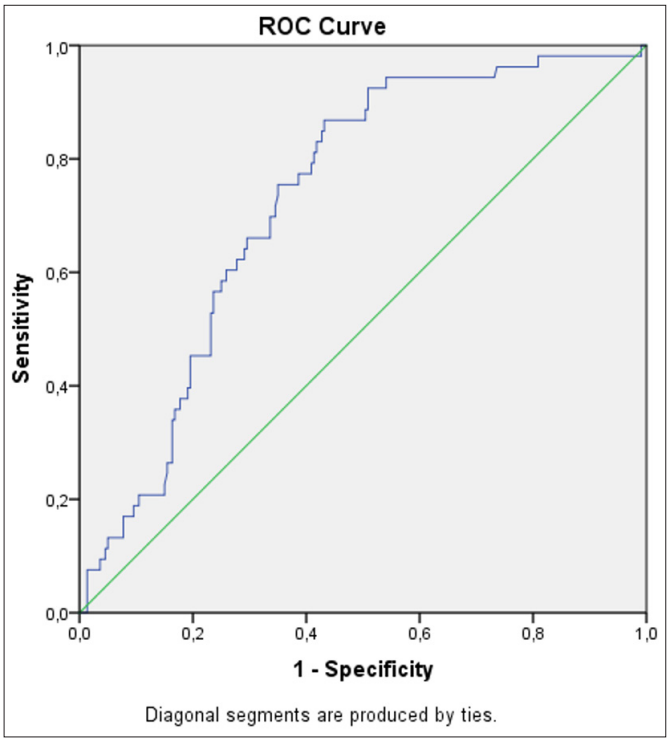

Figure 1. The ROC curve of CRP/albumin ratio for ICU admissions.
AUC: 0.729±0.034 (95% CI, 0.662 – 0.797), (p<0.001).

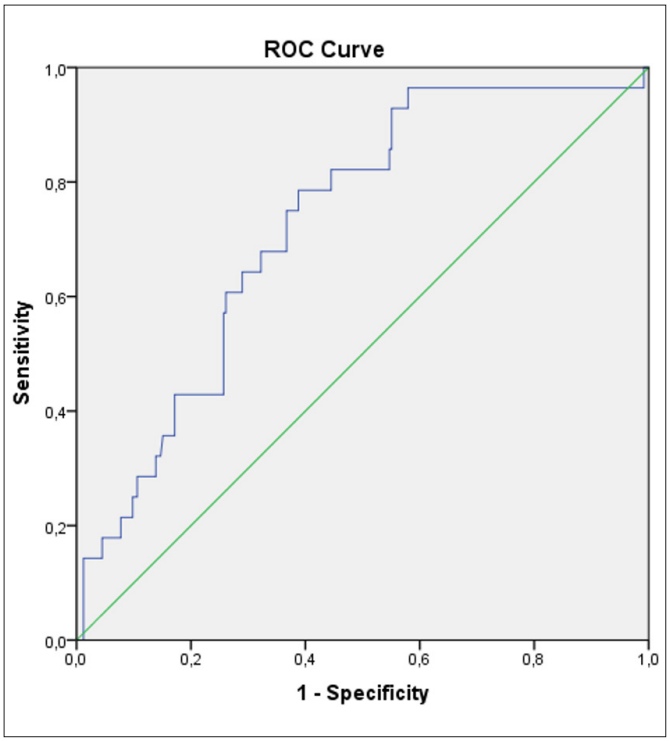

Figure 1. The ROC curve of CRP/albumin ratio for mortality
AUC: 0.725±0.046 (95% CI, 0.635 – 0.815), (p<0.001).

DISCUSSION

In this study, it is concluded that the elevation of CAR was successful in determining the ICU requirement and mortality rate of COVID-19 patients. Additionally, it was observed that the advanced age, high CRP, low albumin and the presence of comorbidity was to accompany CAR in predicting poor outcome.

It is known that systemic inflammatory response plays an important role in infections. With the release of proinflammatory cytokines and the formation of an inflammatory microenvironment, the immune system protects metabolism against existing pathogens. Recent studies have shown that many important inflammation-based prognostic scores are associated with survival outcomes in various infections (7).

It has been previously reported in the literature that high markers of inflammation at the time of admission and advanced age are significantly associated with the severity of COVID-19 (8,9). In particular, it has been reported that comorbidities such as hypertension, coronary artery disease, diabetes mellitus and the presence of malignancy are another indicator for the severity of COVID-19. Metabolic disturbances in the pathway of glycolipid can affect the severity of COVID-19 by creating an imbalance between angiotensin converting enzyme-2, causing a cytokine storm (10). The results of our study are consistent with the literature on this topic.

CRP is an acute phase protein and is produced in hepatocytes. When bound to macromolecular ligands, CRP, strongly activates the classical complement pathway and can regulate alternative pathway amplification as well as C5 transformers (11). CRP levels are known to be associated with severe sepsis, heart failure, and other inflammatory diseases (9). In a study comparing the prognosis and CRP levels of COVID-19 patients, it was observed that CRP values were significantly higher in patients with poor prognosis (12).

Albumin is a main protein synthesized in the liver, with a normal serum albumin concentration of approximately 35 to 50 g/L in healthy adults. There are many physiological functions defined for albumin. The primary ones of these defines are, the binging and transport, colloid-osmotic pressure effect, free radical scavenging, anticoagulant effect and increasing capillary membrane permeability (13). However, it can be significantly adversely affected by factors such as inflammation, which can cause a decrease in serum albumin levels by downregulating albumin synthesis through IL-6 and TNF-α or by increasing the catabolism (10). On the other hand, in the literature, there are studies include many desease which hypoalbuninemia is associated with poor outcome (14,15). Low serum albumin levels have also been reported in these studies, to be indicator of poor prognosis in COVID-19 patients (5).

This study showed that the diagnostic value of albumin and CRP in COVID-19 patients is not as good as CAR. Also, hypoalbuminemia can be caused by previous diseases or nutritional disorders, therefore, using CRP or albumin alone as a biomarker could be difficult.

In a study conducted on patients with sepsis, it was stated that CAR is an independent marker for mortality and it is provides a higher accuracy than the CRP values alone (16). In a study examining community-acquired pneumonia (CAP) patients, it was stated that CAR could be used effectively to predict the severity of pneumonia (17). In another study, in the preoperative prognosis study of ovarian cancers, it was reported that CAR may be a new independent marker of poor prognosis (18).

In the literature, there are only a few studies evaluating the efficacy of CAR in COVID-19 patients. In a retrospective study on 1077 patients, conducted by Canan D. it was stated that CAR was more successful than isolated CRP and albumin in predicting poor outcome. In another study, Xiaoyue W et al. reported that the height of CAR and age can be an early warning for severe COVID-19 disease. Another study conducted in Turkey, Faysal S. et al. reported that increased CAR could be used as an independent predictor of in-hospital mortality in hypertensive COVID-19 patients. (19–21). Studies in the current literature are consistent with our study.

Limitations

As with any retrospective study, there are some limitations in this study. Limitation of this study was the small sample size. Therefore, more studies with a larger sample size are required to confirm these results.

CONCLUSION

The COVID-19 pandemic has caused a serious death and morbidity problem worldwide. In this study, we found that the patients with high CAR values had further ICU requirements and further mortality rates. We are defending the idea of that the CAR is a simple, convenient and inexpensive prognostic marker that can be used in predicting the severity of COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the ethics committee of Istanbul Education and Research Hospital (Date: 31.04.2021, Decision No: 2817).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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