Original Article

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The Predictive Ability of the C-reactive Protein to Albumin Ratio As A Mortality Predictor in Hospitalized Severe SARS-CoV-2 Infected Patients with Cardiovascular Diseases

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Abstract

Aim: Although there are few studies on the predictive value of C-reactive protein-to-albumin ratio (CAR) in coronavirus disease-2019 (COVID-19) patients, to the best of our knowledge, there are no studies specifically conducted in COVID-19 patients with cardiovascular disease (CVD). This study assessed the use of baseline CAR levels to predict death in hospitalized COVID-19 patients with CVD.

Methods: This study was designed as a single-center cross-sectional study. Patients diagnosed with COVID-19 who were admitted to the University of Health Sciences Turkey, Bagcilar Training and Research Hospital between April 16 and May 20, 2020 were analyzed retrospectively. The patients were divided into 2 groups: those who died and those who survived, considering the follow-up period. The CAR values of the study population, as well as patients with CVD, were calculated, and the association of CAR with in-hospital mortality was evaluated.

Results: The in-hospital mortality rate was 11.1% (49/442 pts) in all populations. Deceased patients had significantly more frequent CVD ($p < 0.001$) and the mortality rate was 34.4% (30/96 pts) in those patients. Median CAR values were higher in nonsurvivors than among survivors ($p<0.001$). Multivariate analysis demonstrated that CAR was an independent predictor of mortality in patients with CVD [hazard ratio 1.013 (95% confidence interval: 1.002-1.022), $p=0.018$].

Conclusion: CAR is an inflammatory risk marker that independently predicts mortality in all COVID-19 hospitalized patients and patients with CVD.

Keywords: C-reactive protein, albumin, cardiovascular disease, SARS-CoV-2, COVID-19

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Introduction

A series of pneumonia cases caused by a novel coronavirus were first identified in China in late 2019 (1). The outbreak of this virus, labeled as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and capable of causing coronavirus disease-2019 (COVID-19), was eventually awarded pandemic status by the World Health Organization in March 2020 (2). In just the short time since, many inflammatory markers such as interleukin-6, cardiac troponin, serum amyloid A, lactate dehydrogenase, D-dimer, ferritin, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio have been studied in an attempt to understand COVID-19, and researchers have discovered some to be related to COVID-19 severity (1). Identifying the risk factors for COVID-19-related mortality is critical because it allows for earlier interventions to prevent deaths during the pandemic (3,4). C-reactive protein (CRP) is a well-known positive acute-phase reactant, whereas albumin is a negative acute-phase reactant (5). Both are valuable markers, associated with systemic inflammation and poor outcome in critically ill patients (5-7). CRP-to-albumin ratio (CAR) is a novel inflammatory indicator, assumed to be more reliable than CRP or albumin alone in determining a patient's inflammatory status and predicting morbidity and mortality (5,8). Accumulating evidence supports the significance of CAR in determining prognosis in various clinical situations such as sepsis, diabetes, coronary artery disease, cancer, and vasculitis (5,8-12).

C- reactive protein is positive and albumin negative is affected in COVID-19 patients. It is prognostic for more severe disease and higher mortality if the CAR rate is elevated in COVID-19 patients (13). Many recent studies have suggested that cardiovascular disease (CVD) in particular is a risk factor for experiencing a more severe COVID-19 disease course. The China Disease Control and Prevention Center reported a mortality rate of 10.5% among those with comorbid CVD disease compared with the overall case fatality rate of 2.4% (14).

Although there are few studies on the predictive value of CAR in COVID-19 patients, to the best of our knowledge, there are no studies specifically conducted in COVID-19 patients with CVD disease. Hence, in this study, we determined the predictive role of baseline CAR values in the determination of death in hospitalized COVID-19 patients, especially patients with CVD.

Materials and Methods

Compliance with Ethical Standards

A written informed consent form was signed by each patient or by a first-degree relative of those patients who died. This study was conducted in accordance with the Declaration of Helsinki. The local institutional ethics committee of University of Health Sciences Turkey, Bagcilar Training and Research Hospital approved the study (protocol no. 2020.09.1.04.121).

Study Design

This study was designed as a single-center cross-sectional study. COVID-19 patients who were hospitalized between April 16 and May 20, 2020 and who were recorded as having either died in the hospital or survived hospital discharge as of June 1, 2020, were consecutively included. Patients under the age of 18 years old, pregnant, who died at admission, were transferred to another hospital, or who lacked baseline data were excluded. Finally, 442 of 475 admitted patients were included in the study cohort. A flow diagram of the study enrollment process is shown in Figure 1.

Patients were divided into two groups: group 1, those who lost their lives in the hospital, and group 2, those who were discharged after recovery. Clinical, demographic, comorbidity, and laboratory data of the study population were obtained by accessing the patient files and the electronic information system of the hospital. A positive laboratory finding for SARS-CoV-2 infection was defined as a positive result on high-throughput sequencing or a real-time reverse-transcriptase polymerase chain reaction assay of nasal or pharyngeal swab specimens. Acute respiratory distress syndrome was defined using the Berlin criteria (15). CVD was defined as any cardiovascular pathology, including coronary heart disease, cerebrovascular disease (stroke), peripheral vascular disease, heart failure, rheumatic heart disease, congenital heart disease, and cardiomyopathies (16).

Laboratory Assessment

Laboratory data collected within the first 24 hours of hospitalization were considered. Fluorescence flow cytometry was used to analyze complete blood count data using the Sysymex XN-2000 hematology analyzer (Sysmex Corporation, Kobe, Japan). CRP, albumin, and uric acid data were analyzed by photometry using the AU 5800 chemistry analyser (Beckman Coulter, Brea, CA, USA). High-sensitivity troponin I (hs-TnI) and ferritin levels were analyzed by a chemiluminescent assay using a UniCel DxI 800 immunoassay analyzer (Beckman Coulter). D-dimer levels were recorded by photometry using the Succeeded SF-8200 fully automated coagulation analyzer (Beijing Succeeder Technology Inc., Beijing, China). A COVID-19 diagnosis was established by real-time polymerase chain reaction (Bio-Speedy COVID-19 RT-qPCR kit; Bioeksen R&D Technologies Ltd., Istanbul, Turkey) of viral nucleic acids from throat swab samples. All patients underwent simultaneous testing for CRP and albumin levels. CAR

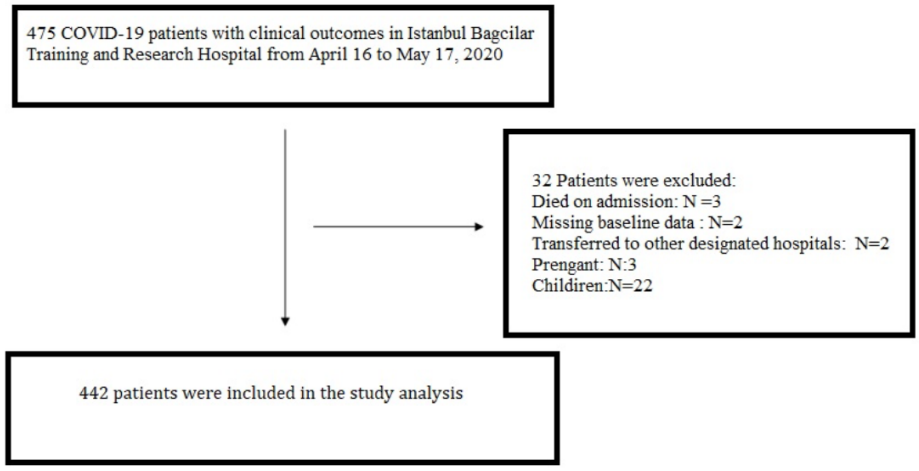


Figure 1. Study population chart
COVID-19: Coronavirus disease-2019

values were calculated by dividing the CRP level by the serum albumin level. Estimated glomerular filtration rates were measured using the Modification of Diet in Renal Disease study equation.

Statistical Analysis

Categorical variables are given as frequencies and percentages. Dichotomous variables were examined using chi-square tests or Fisher's exact tests as appropriate for categorical data, and continuous variables were examined with the Student's t-test or Mann-Whitney U test. The normality of distribution was assessed by the Kolmogorov-Smirnov test. To identify the independent risk factors for in-hospital mortality, univariate and multivariable Cox regression analyses were performed. Only variables with p-values of less than 0.05 in the univariate analysis were included in the multivariate Cox regression analysis. Results of the Cox regression analysis were reported with hazard ratios (HRs) and 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was performed to determine the discriminatory performance of parameters found to be independent predictors of mortality. Discriminatory power was classified as 'good' if the area under curve (AUC) was 0.70 or greater and as "inadequate" if the AUC was less than 0.70 (17). To compare the discriminatory performance of the parameters, a pairwise comparison of ROC curves using DeLong et al. (18) was performed. Survival evaluations were conducted by Kaplan-Meier and long-rank tests. Statistical significance was defined as $p<0.05$. All statistical analyses were conducted using IBM Corporation's Statistical Package for the Social Sciences version 24.0 software (IBM Corporation, Armonk, NY, USA). Moreover, the ROC curves of the models were compared using the MEDCALC software (Software bvba 13, Ostend, Belgium).

Results

A total of 442 of 475 admitted patients (n=247 men) were enrolled in this study. Forty-nine patients died in the hospital (n=29). Detailed demographic, clinical, and laboratory parameters of all study participants, as compared the survivors and non-survivors, are given in Table 1.

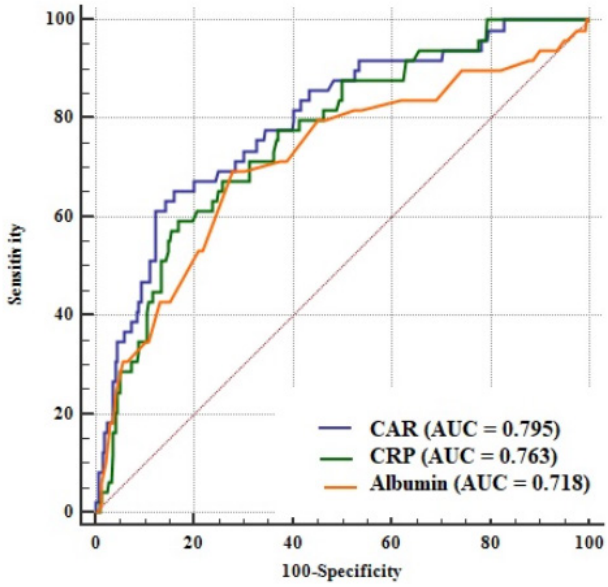
i) Parameters associated with the in-hospital mortality in all study population

In all multivariable analysis models, age, the presence of CVD, a lower estimated glomerular filtration rate, and a higher uric acid level independently predicted mortality (Tables 2 and 3). In the model 1 analysis, CRP was found to be an independent predictor of mortality. Additionally, model 2 cox regression analyses revealed that CAR was an independent predictor of mortality (HR: 1.017, 95% CI: 1.008-1.026; $p<0.003$).

While the discriminatory power of CRP and albumin is similar ($p=0.191$), CAR was statistically superior to both, with P-values of 0.018 and 0.017, respectively. The CAR cut-off value was also determined to be >2.2 with 74% sensitivity and 70% specificity (Figure 2). Kaplan-Meier survival curve analysis revealed that low CAR scores (≤2.2) are associated with a greater chance for survival ($p<0.001$) (Figure 3).

ii) Parameters associated with the in-hospital mortality in patients with CVD

CVD was present in 21.7% of the study population, and nonsurviving patients had more frequent CVD than those who survived (61.2% vs. 16.8%, $p<0.001$). Moreover, patients with CVD had approximately a 3-fold greater mortality compared to the study population (34.4% vs. 11.1%). Compared to survivors those, deceased



	DBA	95 % CI	Z-statistic	*p*-Value
CAR vs. CRP	0.031	0.005 – 0.057	2.367	0.018
CAR vs. albumin	0.077	0.014 – 0.140	2.393	0.017
CRP vs. albumin	0.046	-0.023 – 0.114	1.308	0.191

Figure 2. Comparison of the ROC curves of the CAR (AUC: 0.795, CI 95% 0.754-0.831, p<0.001), CRP (AUC: 0.763, CI 95% 0.721-0.802, p<0.001), and albumin (AUC: 0.718, CI 95% 0.673-0.759, p<0.001) for detecting the in-hospital mortality

ROC: Receiver operating characteristic, CAR: C-reactive protein-to-albumin ratio, AUC: Area under curve, CI: Confidence interval, CRP: C-reactive protein

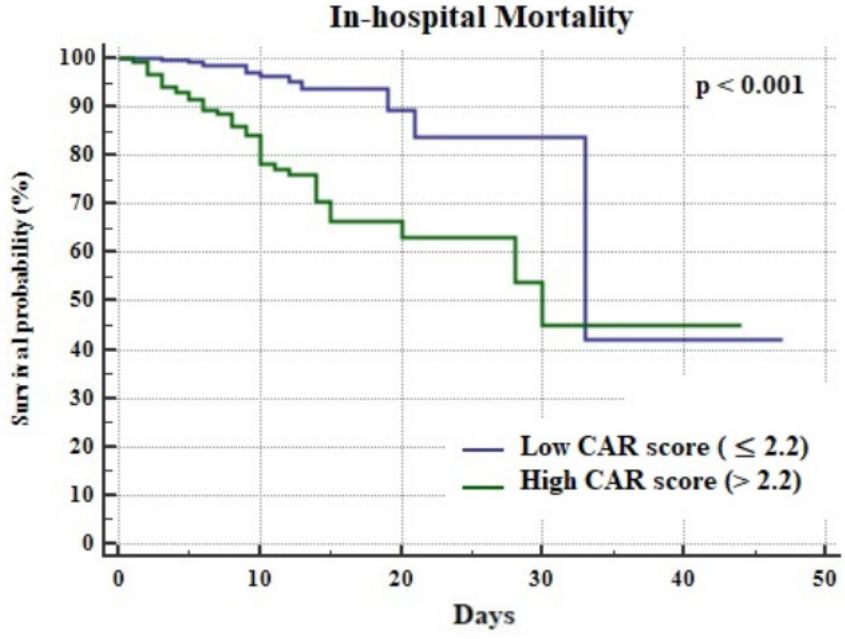


Figure 3. Kaplan-Meier plots of survival curves of patients with low (blue line) and high CAR (green line)

CAR: C-reactive protein-to-albumin ratio

Table 1. Demographic, admission clinical and laboratory parameters of the study cohort

Variables	All population (n=442)	Survivors (n=393)	Non-survivors (n=49)	P
Male gender, n (%)	247 (55.9)	218 (55.6)	29 (59.2)	0.622
Age, year, median (max-min)	58 (18-99)	56 (18-92)	79 (46-99)	<0.001
CVD, n (%)	96 (21.7)	66 (16.8)	30 (61.2)	<0.001
Hypertension, n (%)	204 (46.2)	168 (42.7)	36 (73.5)	<0.001
Diabetes mellitus, n (%)	146 (33)	124 (31.6)	22 (44.9)	0.061
Current smoking, n (%)	128 (29)	113 (28.8)	15 (30.6)	0.787
COPD, n (%)	50 (11.3)	41 (1048)	9 (18.4)	0.098
Cancer, n (%)	26 (5.9)	19 (4.8)	7 (14.3)	0.008
CVA, n (%)	18 (4.1)	11 (2.8)	7 (14.3)	<0.001
Needing ICU, n (%)	90 (20.4)	51 (11.7)	39 (79.6)	<0.001
ARDS, n (%)	70 (15.8)	36 (9.2)	34 (69.4)	<0.001
Hospitalization period, days, median, [IQR]	9 [5-12]	9 [5-12]	9 [4-13]	0.802
Uric acid, mg/dL	5.1±2.1	4.8±1.8	7.3±2.9	<0.001
eGFR, mL/min/1.73m^2, median, [IQR]	94 [67-105]	97 [78-106]	45 [30-70]	<0.001
WBC, 10^9/L, median, [IQR]	6.2 [4.8-8.6]	6.0 [4.5-7.8]	9.9 [7.1-13.7]	<0.001
Neutrophil, 10^9/L, median, [IQR]	4.4 [3.0 -6.7]	4.1 [2.8-6.0]	8.4 [5.8-11.9]	<0.001
Lymphocyte, 10^9/L, median, [IQR]	1.1 [0.8-1.5]	1.2 [0.9-1.5]	0.8 [0.6-1.1]	<0.001
Haemoglobin, g/L	126±19	127±18	112±24	<0.001
Platelet, 10^9/L	231±95	232±95	223±95	0.514
D-Dimer, µg FEU/L, median, [IQR]	400 [200-900]	300 [200-700]	1200 [800-2100]	<0.001
Ferritin, µg/L, median, [IQR]	213 [98-406]	198 [95-385]	360 [148-638]	<0.001
CRP, mg/L, median, [IQR]	37 [15-104]	32 [15-104]	134 [61-215]	<0.001
Albumin, g/L	34.9±5.1	35.2±4.8	31.6±5.5	<0.001
CAR, median, [IQR]	1.08 [0.42-3.0]	0.95 [0.36-2.58]	4.4 [1.9-7.0]	<0.001
hs-TnI, pg/mL, median, [IQR]	3.1 [1.3-8.0]	2.9 [1.1 -6.9]	5.5 [3.2-17.5]	0.364

CVD: Cardiovascular disease, COPD: Chronic obstructive pulmonary disease, CVA: Cerebrovascular accident, ARDS: Acute respiratory distress syndrome; eGFR: Estimated glomerular filtration rate, WBC: White blood count, CRP: C-reactive protein, CAR: CRP to albumin ratio, hs-TnI: High-sensitivity troponin I, IQR: Interquartile range

patients were older (mean 77.9±11.2 years vs. 66.8±11.5 years; p<0.001) and had lower eGFR (median 48 mL/min/1.73m^2 vs. 80 mL/min/1.73m^2; p<0.001), lower hemoglobin (mean 113±17 g/L vs. 127±19 g/L; p=0.003), higher white blood cell (median 9.9 10^9/L vs. 7.2 10^9/L; p< 0.001), lower albumin (mean 31.5±5.5 g/L vs. 34.3±4.8 g/L; p=0.013), higher CRP (median 130 mg/L vs. 37 mg/L; p<0.001), higher D-dimer (median 1.0 µg FEU/L vs. 0.4 µg FEU/L; p=0.037), higher ferritin (median 336 µg/L vs. 231 µg/L; p=0.017), and higher hs-TnI levels (median 9.8 pg/mL vs. 143 pg/mL; p<0.001) at admission.

Multivariate analysis revealed that, anemia, high admission hs-TnI values, high admission CRP levels, and high admission CAR values were independent predictors of mortality in COVID-19 patients with CVD (Table 4). Moreover, ROC analysis showed that CAR had a better AUC than CRP (AUC: 0.809 (95% CI=0.712- 0.905; p<0.001 vs. AUC: 0.763 (95% CI=0.695-0.831; p<0.001) and adequate discrimination ability to predict in-hospital mortality with 76% sensitivity and 75% specificity for >2.2 cut-off value (Figure 4).

Discussion

The main findings of this study are as follows: Patients who died had higher baseline CAR values, baseline CRP levels, and lower albumin levels compared with those who survived; (ii) while high CAR values and increased CRP levels were found to be independent predictors of mortality, the presence of hypoalbuminemia was not; (iii) the predictive ability of CAR was significantly better than that of both CRP and albumin; (iv) patients with CAR values of greater than 2.2 were at greater risk of in-hospital mortality; and (v) CAR was also found to be an independent predictor of in-hospital mortality in patients with CVD.

CRP is well-known today as a marker of systemic inflammation and severe infection. C- reactive protein is a non-specific acute-phase reactant classically related to

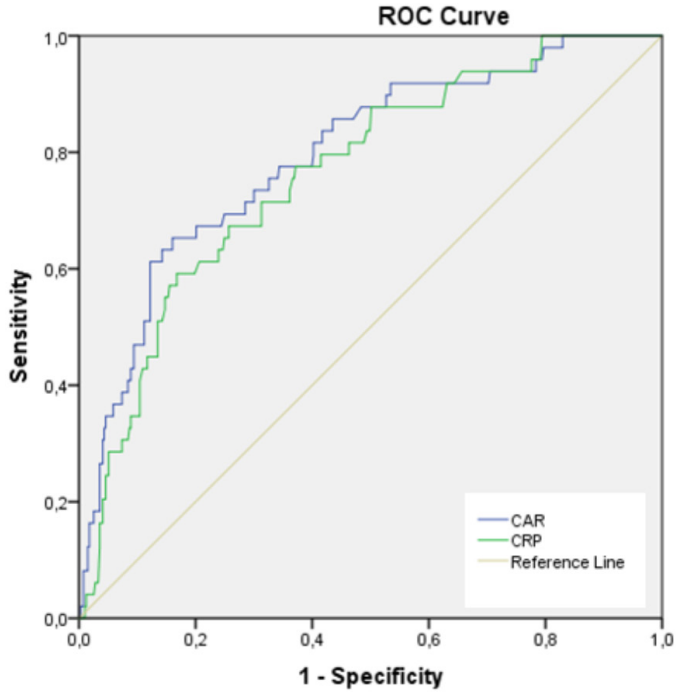


Figure 4. ROC curves of the CAR (AUC: 0.809 (95% CI=0.712- 0.905; p<0.001) and CRP (AUC: 0.763 (95% CI=0.695- 0.831; p<0.001) in patients with CVD for detecting the in-hospital mortality

ROC: Receiver operating characteristic, CAR: C-reactive protein-to-albumin ratio, AUC: Area under curve, CI: Confidence interval, CRP: C-reactive protein, CVD: Cardiovascular disease

inflammation (19). Additionally, in providing host defense against invading pathogens, CRP plays an important role by activating the complementary system (19). It has been suggested that CRP can be a marker in the early diagnosis of pneumonia and that patients with severe pneumonia have high CRP levels (20). Recently, CRP levels were found to be positively correlated with lung lesions and may reflect disease severity in the early stages of COVID-19 (21). In a large-scale study involving 2782 COVID-19 patients, CRP was strongly associated with venous thrombo-embolism, acute kidney injury, critical illness, and in-hospital mortality (22). In our study, in line with the available data, CRP independently predicted in-hospital mortality.

Serum albumin, as a negative acute-phase reactant, is a marker of systemic inflammation and hypoalbuminemia is common in many inflammatory diseases (23). There is ample evidence to address the importance of reduced albumin levels in severe COVID-19 (24). In parallel with the findings of previous studies, in our investigation, hypoalbuminemia was detected more frequently among patients who died. Although the exact mechanism of hypoalbuminemia in COVID-19 is not yet understood, systemic inflammation may be a reason. Moreover, The systemic inflammatory response that occurs because of SARS-CoV-2 infection may increase capillary permeability, causing serum albumin to escape into the interstitial space and thus increase the volume of albumin distribution. This may contribute to the development of hypoalbuminemia beyond the negative acute-phase response to the systemic inflammatory response. Serum albumin levels are affected by various factors, such as vascular injury, renal injury, various cytokine levels, free fatty acid concentrations, and steroid hormones (25). Therefore, it is difficult to establish a direct relationship between the serum albumin level and the mortality rate, and, hence, the exact mechanism of this relationship, beyond serum albumin being a marker associated with mortality, remains unknown. As such, albumin alone may not be a reliable prognostic marker in the context of a complex disease like COVID-19.

The CRP to albumin ratio, as a reflection of equilibrium between CRP and albumin, was first described by Fairclough et al. (26) and is an emerging inflammatory indicator suggested to be a better option than either the serum CRP or albumin level alone in predicting poor prognosis in patients with acute medical conditions (5,13). Several previous studies have emphasized the significance of taking pretreatment CAR measurements on clinical outcomes in patients severe inflammation (27,28). In a study by Sun et al. (27), CAR was revealed to be a better prognostic tool than just CRP or albumin level alone in

Table 2. Factors that were found to be independently associated with in-hospital mortality in unadjusted univariate cox regression analysis

Variables	Univariate HR (95% CI)	P
Age	1.090 (1.064-1.116)	<0.001
CVD	5.260 (2.891-9.572)	<0.001
Hypertension	2.517 (1.331-4.758)	0.005
Cancer	2.243 (1.003-5.016)	0.049
CVA	2.631 (1.165-5.016)	0.020
Uric acid	1.343 (1.219-1.480)	<0.001
eGFR	0.973 (0.965 - 0.981)	<0.001
Haemoglobin	0.743 (0.648-0.851)	<0.001
Neutrophil	1.132 (1.078-1.189)	<0.001
Lymhocyre	1.023 (1.017-1.030)	0.002
CRP	1.007 (1.004-1.010)	<0.001
Albumin	0.330 (0.176-0.619)	0.001
Ferritin	1.001 (1.000 -1.000	0.049
CAR	1.025 (1.016-1.034)	<0.001

CVD: Cardiovascular disease, CVA: Cerebrovascular accident, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, CAR: CRP to albumin ratio, CI: Confidence interval, HR: Hazard ratio

patients with sepsis. Furthermore, Karayiannis et al. (28) concluded that higher CAR values are positively correlated with an increased risk of postoperative complications, especially infections. Furthermore, the potential significance of CAR on long-term prognosis was also investigated recently. Park et al. (29) showed that higher CAR values were an independent predictor of 28-day mortality risk in critically ill patients. Similarly, Oh et al. (8) demonstrated the importance of calculating the CAR at the time of ICU admission for long-term mortality prediction in a mixed ICU patient population (8). Moreover, Kim et al. (30) cited CAR level at admission as an independent predictor of 180-day mortality in patients with severe sepsis or septic shock who received early goal-directed treatment.

In patients hospitalized with a diagnosis of COVID-19, high CAR levels were associated with disease severity, 30-day and postdischarge mortality (13). Additionally, in two other studies, a high CAR value was associated with prognosis in patients hospitalized with the diagnosis of hypertensive COVID-19 (31,32). Karakoyun et al. (33) reported that pretreatment CAR levels were statistically higher among those with severe disease than in those with non-severe disease, which is similar to what was reported by Wang et al. (34). In a single study by El-Shabrawy et al. (35) where prognostic importance was evaluated, CAR independently predicted the 30-day mortality rate in 116 patients with COVID-19. Our study, which has a relatively higher number of patients, supports the results of this previous study.

Moreover, CAR has been found to be a more valuable predictive biomarker than either CRP or albumin alone due to its incorporation of two measures (increased CRP and decreased albumin) to predict inflammatory status and prognosis in various CVDs such as coronary artery disease, carotid artery disease, heart failure, valvular heart disease (11,12,36-38). In this study, mortality was higher in COVID-19 patients with CVD, consistent with the literature. Additionally, high CAR levels were also found to be an independent predictor of death in this subset of patients with CVD and COVID-19. Considering literature data, this is the first study to examine the association of high CAR level and mortality in COVID-19 patients with CVD.

Study Limitations

The current study has several limitations that should be mentioned. First, this study was unicentric and thus subject to bias. We only calculated CAR at admission. However, serial CAR measurements would facilitate more powerful analysis concerning mortality, as such would allow us to understand CAR kinetics in response to therapy. Additionally, we did not compare the CAR with well-established ICU prognostic scores such as the

Table 3. Factors that were found to be independently predicted the in-hospital mortality in model 1 and 2 multivariate cox regression analysis models

Variables	Multivariate 1* HR (95% CI)	P	Multivariate 2* HR (95% CI)	P
Age	1.060 (1.030-1.091)	<0.001	1.057 (1.027-1.087)	<0.001
CVD	2.097 (1.094-4.022)	0.026	2.122 (1.111-4.055)	0.023
Uric acid	1.156 (1.027-1.301)	0.016	1.151 (1.023-1.294)	0.017
eGFR	0.983 (0.971-0.995)	0.007	0.984 (0.972-0.996)	0.009
CRP	1.004 (1.001-1.007)	0.012	-	-
CAR	-	-	1.013 (1.005-1.022)	0.003

*T the variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Backward LR method. Parameters that are not found to be statistically significant by using the Backward-LR method are not included in the table.
CVD: Cardiovascular disease, CVA: Cerebrovascular accident, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, CAR: CRP to albumin ratio, CI: Confidence interval, HR: Hazard ratio

Table 4. Factors that were found to be independently predicted the in-hospital mortality in multivariate cox regression analysis in patients with CVD

Variables	Multivariate 1* HR (95% CI)	P	Multivariate 2* HR (95% CI)	P
Haemoglobin	0.742 (0.645-0.855)	<0.001	0.764 (0.663-0.880)	<0.001
hs-TnI	1.000 (1.000-1.001)	0.008	1.000 (1.000-1.001)	0.007
CRP	1.007 (1.004-1010)	<0.001	-	-
CAR	-	-	1.024 (1.015-1.033)	<0.001

*T the variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Backward LR method. Parameters that are not found to be statistically significant by using the Backward-LR method are not included in the table.
CVD: Cardiovascular disease, hs-TnI: High-sensitivity troponin I, CAR: C-reactive protein to albumin ratio, CI: Confidence interval, HR: Hazard ratio

Sequential Organ Failure Assessment or Acute Physiologic Assessment and Chronic Health Evaluation scores. The contribution of these scores should be evaluated on a larger scale. Multicentre prospective studies including more patients are still required to evaluate the predictive accuracy of CAR in determining mortality in the COVID-19 population.

Conclusion

Our study revealed that admission CAR levels independently predicted the in-hospital mortality in both the study population and the subgroup of patients with CVD. Therefore, we think that CAR, which is an inexpensive indicator, easily accessible and does not require any calculator to use, may allow for the identification of high-risk COVID-19 patients so that they may be stratified early on.

Ethics

Ethics Committee Approval: The local institutional ethics committee of University of Health Sciences Turkey, Bagcilar Training and Research Hospital approved the study (protocol no. 2020.09.1.04.121).

Informed Consent: A written informed consent form was signed by each patient or by a first-degree relative of those patients who died.

Authorship Contributions

Concept: F.K., M.K., F.N.T.C., E.O., Design: F.K., M.K., F.N.T.C., E.O., Data Collection and/or Processing: F.K., S.K., S.O., Z.A.T., S.H.K., Analysis and/or Interpretation: F.K., M.K., F.N.T.C., Literature Research: F.K., M.K., F.N.T.C., U.K., A.G., H.I.B., Writing: F.K., M.K., F.N.T.C., E.O.

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

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