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BIOMEDICAL

Predictive Value of CAR for In-Hospital Mortality in Patients with COVID-19 Pneumonia: A Retrospective Cohort Study

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Background. In the current literature, there is a growing evidence that supports the significant role of inflammation in the progression of viral pneumonia, including patients with coronavirus disease 2019 (COVID-19).

Aim. The present study aimed to investigate the predictive value of C-reactive protein/albumin ratio (CAR) for in-hospital mortality in patients with COVID-19.

Material and Methods. This retrospective study included the data of 275 consecutive COVID-19 patients who were hospitalized in a referral pandemic center. The CAR ratio was obtained by dividing the CRP level with albumin level. The study population was divided into tertiles (T1, T2, and T3) according to their admission CAR values. The endpoint of the study was a composite outcome of in-hospital mortality.

Results. During the in-hospital course, 33 (12%) patients died. The patients classified into T3 group had significantly higher CAR compared those classified into T2 and T1 groups. After the adjustment for the confounders, T3 group had 8.2 (95% CI: 4.2–48.1) times higher rates of in-hospital mortality compared to T1 group (the reference group) in a logistic regression model using CAR values.

Conclusion. To the best of our knowledge, this is the first study to demonstrate the predictive value of CAR for in-hospital mortality in COVID-19 patients. © 2021 Instituto Mexicano del Seguro Social (IMSS). Published by Elsevier Inc. All rights reserved.

Key Words: COVID-19, C-reactive protein/albumin, In-hospital mortality, Predictive value.

Introduction

The coronaviruses are single-chain, positive polarity, and enveloped RNA viruses. The newly identified coronavirus, named as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is responsible for coronavirus disease 2019 (COVID-19), which also shares sim-

ilar genomic features with SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) (1). The SARS-CoV-2 was first identified in patients with unknown etiology of viral pneumonia in the Wuhan region of China on December 31, 2019 (2). After that, the virus spreads all over the world, and on 11 March 2020, the World Health Organization (WHO) officially declared COVID-19 as an ongoing global pandemic.

In most cases, the COVID-19 is usually mild. However, the patients with moderate and severe COVID-19 illness can rapidly progress to acute respiratory failure and

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develop multiple organ failure leading to disseminated intravascular coagulopathy, septic shock, and event death (3). Hence, early identification of a prognostic biomarker is crucial to distinguish the patients in whom the risk of developing more severe forms of illness and to better manage the limited medical resources.

In the current literature, there is growing evidence that supports the significant role of inflammation in the progression of viral pneumonia, including patients with COVID-19. Therefore, systemic inflammatory biomarkers, which represent the inflammation status of patients, are possible predictors of poor outcomes in COVID-19 cases. The C-reactive protein/albumin ratio (CAR) is a newly defined systemic inflammatory marker that combines both CRP (positive acute phase reactant) and albumin (positive acute phase reactant) level (4). Several previous studies have demonstrated the prognostic value of CAR in patients with various solid tumors, coronary artery disease, and acute coronary syndrome (5–7). Considering this data, the objective of the present study was to examine the predictive value of CAR for in-hospital mortality in patients with COVID-19 pneumonia.

Material and Methods

Study Population

In this retrospective cohort study, we collected the clinical data of consecutive patients who were diagnosed and hospitalized with COVID-19 pneumonia in our institution. In the present study, the patients who were pregnant, who had an end-stage liver and renal failure, undergoing dialysis, and with known hematologic disease (for example, pancytopenia, aplastic anemia) were not included. In addition, the patients whose CRP and albumin levels were not measured upon admission or during the in-hospital course were excluded (Figure 1). Baseline demographic features, including hypertension, diabetes, coronary artery disease, chronic renal failure, cancer as well as laboratory and imaging findings were retrieved from hospital's electronic database. In all patients, the COVID-19 infection was confirmed by the real-time reverse transcriptase polymerase chain reaction (RT-PCR) test in addition to specific signs and symptoms and computerized thoracic tomography findings. Our institution was accepted as a referral pandemic center by the Ministry of Health, in where moderate and severe COVID-19 cases were hospitalized. In all the patients, the standard medical treatment was planned in accordance with the Ministry of Health COVID-19 pandemic guidelines. The design of the present study was reviewed and approved by both the Ministry of Health Scientific Research Committee and the Local Ethics Committee (approval number: 2020.07.10-52). After that, the study was conducted in accordance with the "Good Clinical Practice" guidelines of the Declaration of Helsinki. Due to the

retrospective design of the study, informed consent was not needed.

Laboratory Analysis

The blood samples of all patients were collected following admission to the emergency department. The standard laboratory methods were used to analyze blood samples for glucose, hemoglobin, white blood cell (WBC) count, creatinine, lactate dehydrogenase (LDH), alanine aminotransferase, aspartate aminotransferase, etc. CRP levels were measured using nephelometry method. Albumin levels were determined using the bromocresolgreen method. The CAR ratio was obtained by dividing the CRP level with albumin level.

Endpoint

The endpoint of the study was a composite outcome of in-hospital mortality, which was considered death from any cause during hospitalization. All in-hospital deaths were evaluated and confirmed by a trained study coordinator who examined the patients' medical records.

Statistical Analysis

In a first step, our study population was divided into tertiles according to their admission CAR values. Tertile 1 (T1) and tertile 2 (T2) included 92 patients, tertile 3 (T3) included 91 patients. In a second step, baseline characteristics, admission symptoms, laboratory parameters and pneumonia regions in the lungs were compared between these tertiles. Kolmogorov-Smirnov test was used for evaluation of normality. All continuous variables were presented as median and interquartile range (IQ) and were compared using Kruskal-Wallis test. Categorical variables were presented as numbers and percentages. Analyses of categorical variables were performed by Pearson's χ^2 test. Univariate and multivariate logistic regression analyses were performed to determine the independent predictors of in-hospital mortality other than CAR. Variables that could be a predictor of in-hospital mortality and with a significant p value in Table 1 and Table 2 were entered into univariate analysis. Variables with a p value <0.05 in univariate regression were included into the binary logistic regression analysis. The results of regression analysis were presented as odds ratio (OR) with 95% confidence interval (CI). Two multivariate models were used: model I; unadjusted and model II; adjusted. The variables co-variated in the model II were: age, WBC, LDH, and D-dimer. Hosmer–Lemeshow statistic of multivariate analysis did not suggest a lack of fit ($\chi^2=9.78$, $p=0.18$). Analyses were performed using Statistical Package for Social Sciences software, version 20.0 (SPSS; IBM, Armonk, New York, USA).

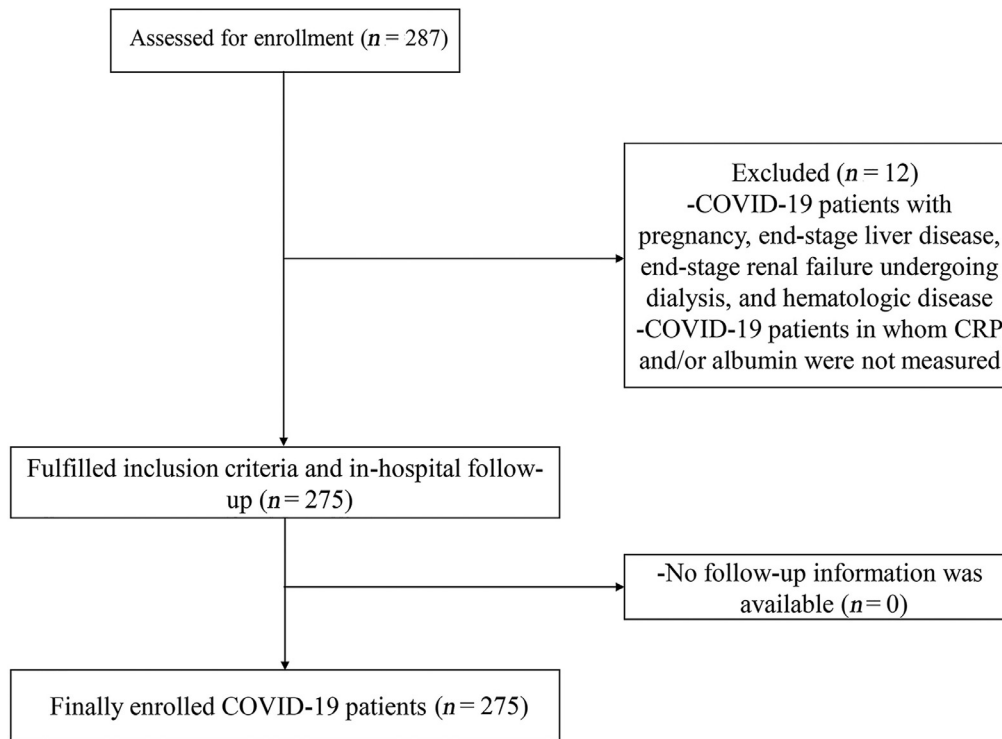


Figure 1. Flow chart of the enrolled cases.

Table 1. Baseline clinical characteristics and admission symptoms of all cases.

	CAR			p
	T1 <0.29, (n=92)	T2 ≥0.29 and <1.56, (n=92)	T3 ≥1.59 and <11.19, (n=91)	
Baseline characteristics				
Age, years	48 (42–56)	52 (44–62)	60 (54–66)	<0.001
Male gender, n (%)	37 (40.2)	46 (50.0)	68 (74.7)	<0.001
Hypertension, n (%)	28 (30.4)	27 (29.3)	48 (52.7)	0.001
Diabetes mellitus, n (%)	17 (18.5)	20 (21.7)	28 (30.8)	0.128
Insulin dependency, n (%)	4 (4.3)	4 (4.3)	4 (4.4)	1.000
Hyperlipidemia, n (%)	3 (3.3)	4 (4.3)	7 (7.7)	0.365
COPD, n (%)	6 (6.5)	8 (8.7)	16 (18.2)	0.036
CAD, n (%)	3 (3.3)	5 (5.4)	19 (20.9)	<0.001
CRF, n (%)	5 (5.4)	1 (1.1)	6 (6.6)	0.157
Atrial fibrillation, n (%)	0 (0.0)	2 (2.2)	2 (2.2)	0.364
Cerebrovascular disease, n (%)	1 (1.1)	1 (1.1)	3 (3.3)	0.435
Dementia, n (%)	0 (0.0)	2 (2.2)	1 (1.1)	0.366
Cancer, n (%)	1 (1.1)	5 (5.5)	2 (2.2)	0.186
Congestive heart failure, n (%)	1 (1.1)	4 (4.3)	3 (3.3)	0.412
Smoking, n (%)	15 (16.5)	8 (8.9)	9 (9.9)	0.226
Alcohol, n (%)	12 (13.0)	12 (13.0)	19 (20.9)	0.242
Admission symptoms				
Fever, n (%)	37 (40.2)	51 (56.0)	58 (63.7)	0.005
Cough, n (%)	52 (56.5)	55 (60.4)	48 (52.7)	0.578
Dyspnea, n (%)	14 (15.2)	18 (19.6)	23 (25.3)	0.234
Diarrhea, n (%)	2 (2.2)	7 (7.6)	3 (3.3)	0.163
Myalgia, n (%)	34 (37.4)	31 (33.7)	28 (30.8)	0.642
Weakness, n (%)	28 (30.4)	36 (39.1)	23 (25.3)	0.125
Asymptomatic, n (%)	10 (10.9)	4 (4.3)	6 (6.6)	0.224

Continuous variables are presented median and IQ (interquartile) range, nominal variables presented as frequency (%).

CAR indicates C-reactive/albumin ratio, COPD indicates chronic obstructive pulmonary disease, CAD indicates coronary artery disease, CRF indicates chronic renal failure.

Table 2. Laboratory parameters and pneumonia regions in the lungs of all cases.

	CAR			p
	T1 <0.29, (n=92)	T2 ≥0.29 and <1.56, (n=92)	T3 ≥1.59 and <11.19, (n=91)	
Laboratory parameters				
WBC, cells/μL	4.8 (3.8–6.6)	5.1 (4.0–6.9)	6.4 (4.5–8.5)	<0.001
Lymphocytes, cells/μL	1.6 (1.2–2.2)	1.4 (0.9–1.9)	1.1 (0.8–1.5)	<0.001
Platelets, cells/μL	203 (159–236)	192 (157–229)	176 (144–269)	0.345
Hemoglobin, g/dL	13.3 (12.5–14.5)	13.1 (12.0–14.2)	13.5 (12.5–14.5)	0.279
Glucose, mg/dL	99 (87–114)	101 (89–129)	105 (88–136)	0.652
LDH, U/L	364 (288–444)	433 (329–542)	496 (389–658)	<0.001
ALT, U/L	22 (18–37)	25 (19–37)	26 (20–40)	0.324
AST, U/L	22 (17–29)	24 (18–30)	22 (18–31)	0.170
Creatinine, mg/dL	0.9 (0.7–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.117
Potassium, mEq/L	4.2 (4.0–4.5)	4.2 (4.0–4.4)	4.2 (3.9–4.5)	0.380
Sodium, mEq/L	138 (134–140)	137 (13–139)	137 (135–139)	0.943
D-dimer, μg/mL	373 (316–583)	498 (308–1294)	700 (310–1460)	<0.001
CRP, mg/dL	3.2 (2.5–4.8)	23.5 (14.8–32.5)	105 (75–156)	<0.001
Albumin, g/L	43 (40–46)	40 (36–44)	38 (34–41)	<0.001
CAR	0.078 (0.056–0.120)	0.568 (0.368–0.812)	2.971 (1.902–4.105)	<0.001
Pneumonia region				
Bilateral, n (%)	65 (70.6)	77 (83.7)	71 (78.0)	0.105
Left, n (%)	10 (10.8)	8 (8.8)	8 (8.8)	0.858
Right, n (%)	17 (18.4)	7 (7.6)	12 (13.2)	0.092

Continuous variables are presented median and IQ (interquartile) range, nominal variables presented as frequency (%). CAR indicates C-reactive/albumin ratio, WBC indicates white blood cells, LDH indicates lactate dehydrogenase, ALT indicates alanine aminotransferase, AST indicates aspartate aminotransferase, CRP indicates C-reactive protein.

Table 3. Univariate predictors and multivariate model for in-hospital mortality.

	Univariate Analysis			Multivariate analysis*		
	p	OR	95% CI	p	OR	95% CI
Age	<0.001	1.099	1.059–1.140	<0.001	1.089	1.041–1.139
Male gender	0.016	3.177	1.240–8.140	-	-	-
Hypertension	0.002	3.835	1.652–8.902	-	-	-
COPD	0.002	4.268	1.676 –10.871	-	-	-
CAD	<0.001	9.969	3.974 –25.009	-	-	-
White blood cells	<0.001	1.390	1.246–1.550	<0.001	1.232	1.118–1.358
Lymphocytes	0.019	0.389	0.177–0.858	-	-	-
LDH	0.001	1.002	1.001–1.004	0.002	1.003	1.002–1.005
D-dimer	<0.001	1.001	1.000–1.001	0.035	1.000	1.000–1.001

OR=odds ratio; CI=confidence interval. *All clinically relevant parameters were included in the model. Only parameters that reached statistical significance at univariate analysis were given in the left most columns. COPD indicates chronic obstructive pulmonary disease; CAD indicates coronary artery disease; LDH indicates lactate dehydrogenase.

Results

In total, 275 COVID-19 cases were included in this analysis (mean age was 53.9 ± 15.4 years and 151 (54.9%) cases were male). During the in-hospital course, 33 (12%) patients died. We divided the study population into three tertiles (T1, T2, and T3 groups) based on the CAR values; patients with CAR value of <0.29 formed the T1 group, patients with CAR value of ≥0.29 and <1.56 formed the T2 group, and patients with CAR value of ≥1.59 and <11.19 formed the T3 group.

The clinical properties of the study groups are shown in Table 1. Patients in the T3 group was older compared to

those in the T2 and T1 group. The frequency of hypertension, chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD) were significantly higher in patients stratified into the T3 group (p <0.05 for each). The presenting symptoms, except fever, were not different between the tertiles groups (p >0.05 for each). Comparison of laboratory findings revealed that patients classified into T3 group had significantly higher WBC count, LDH, D-dimer, CRP, and CAR, while their lymphocytes and albumin level were lower compared those classified into T2 and T1 groups (p <0.05 for each) (Table 2). Imaging findings were indifferent between the groups (p >0.05 for each).

Table 4. Logistic regression models for in-hospital mortality by CAR tertiles.

	CAR		
	T1 <0.29, (n = 92)	T2 ≥0.29 and <1.56, (n = 92)	T3 ≥1.59 and <11.19, (n = 91)
In-hospital mortality			
Number of patients	1	5	27
Case rate, %	1.1	5.4	23.1
In-hospital mortality, OR (95%CI)			
Model 1: unadjusted	1 (Reference)	3.2 (1.6–7.4)	13.6 (5.2–36.9)
Model 2: adjusted for all covariates ^a	1 (Reference)	1.9 (1.1–5.8)	8.2 (4.2–48.1)

OR, odds ratio; CI, confidence interval.

CAR indicates C-reactive/albumin ratio.

^aOnly parameters that reached statistical significance at multivariate analysis were age, white blood cells count, lactate dehydrogenase, and D-dimer.

To determine independent predictors of in-hospital mortality, we first performed a univariate analysis. Then, the variables with a *p*-value of <0.05 (other CAR) were included in multivariate analysis. Age, male gender, hypertension, COPD, CAD, WBC count, lymphocytes, LDH, and D-dimer were predictor of in-hospital mortality according to univariate analysis. These parameters were included into multivariate analysis. In a multivariate analysis, age (OR: 1.089, 95% CI: 1.041–1.139, *p* <0.001), WBC count (OR: 1.232, 95% CI: 1.118–1.358, *p* <0.001), LDH (OR: 1.003, 95% CI: 1.002–1.005, *p* = 0.002), and D-dimer (OR: 1.000, 95% CI: 1.000–1.001, *p* = 0.035) were independently correlated with in-hospital mortality. Independent predictors of in-hospital mortality are depicted in Table 3.

In a different analysis using CAR, the in-hospital mortality had the higher rates at the T3 group, and that had 12.6 times higher than T1 group, which was used as the reference group. This relevance increased after the adjustment for the confounders demonstrated to independently predict the in-hospital mortality; T3 group had 8.2 times higher rates of in-hospital mortality compared to T1 group. The results of logistic regression models of in-hospital mortality based on the CAR are shown in Table 4.

Discussion

In the present research, we found that the CAR is an independent prognostic biomarker for in-hospital mortality in COVID-19 patients. We anticipate that the CAR might be used as an early-stage biomarker for a more extended treatment plan in patients with COVID-19 pneumonia.

The COVID-19 has become a global pandemic that affects the whole world. As the date of 3 July 2020, more than 10 million cases and more than 500,000 deaths have been reported (8). It has affected more people than recent coronavirus outbreaks caused by SARS-CoV-1 and MERS-CoV viruses (9). As a result, COVID-19 is the fastest growing infectious disease of the last century. Although the course of the disease differs from person to

person, clinical deterioration and mortality can occur quite rapidly. Therefore, designing an early treatment plan with a fast, inexpensive, repeatable test that can be take place in routine examinations is very important in terms of reducing in-hospital mortality as well as using limited medical resources.

The increases of acute phase proteins in the plasma are strong indicators of inflammation, and their release is triggered by various cytokines, primarily by interleukin -6 (IL-6), IL-1 β and IL-18 (10). CRP is the most important prototype among these proteins, which rises in any case with an acute and chronic inflammatory response (11). Recent studies have revealed that elevated CRP levels predict both the disease progression and mortality in COVID-19 cases (12,13). On the other hand, the systemic inflammation due to viral infections, including COVID-19 infection, can lead to decrease of albumin levels in the body. In a recent published study, it has been found that lower levels of serum albumin were significantly associated with poorer outcome and a longer stay in the hospital in patients with COVID-19 (14). However, albumin levels would be decreased secondary to malnutrition during prolonged hospitalization. For that reason, it might not be a specific indicator for infections and inflammation.

The CAR is a newly defined inflammatory marker that includes both CRP and albumin levels. The prognostic value of CAR has been documented in previous clinical studies, including patients with cancer (Hazard ratio (HR): 2.47, 95% CI: 1.47–4.14), acute coronary syndrome HR: 1.033, 95% CI: 1.007–1.061), and stroke (5–7,15). Previously, Ranzani OT, et al. examined the patients with severe sepsis (*n* = 229) and septic shock (*n* = 111) at the time their admission to the intensive care unit and after their discharge (after 90 d of follow-up), and they found that the predictive value of CAR was much higher than that of CRP alone (CRP; OR: 2.34, 95% CI: 1.14–4.83 and CAR; OR: 2.18, 95% CI: 1.10–4.67) (16). Moreover, in a retrospectively screened 875 cases, Park JE, et al. conducted a study to determine the effect of CAR on 28 d mortality in intensive care patients. In their analysis, the

CAR ratio was found to be associated with 28 d mortality (OR: 1.01, 95% CI: 1.00–1.02) (17). However, to the best of our knowledge, the prognostic importance of the CAR has not been investigated in patients COVID-19 patients. In our study, we classified the patients from low to high (T1, T2, T3) according to the CAR values at the time of hospital admission. We noted that when patients in the T1 group was accepted as the reference group, the in-hospital mortality rate in the T3 group was 8.2 (95% CI: 4.2–48.1) times higher.

We considered that our study results would be clinically important regarding the follow-up and treatment plans for COVID-19 cases. Particularly, in patients who need invasive mechanical ventilation due to COVID-19, the mortality rate might reach up to 100% in some studies (18,19). This creates an even faster treatment requirement than the classic acute respiratory distress syndrome (ARDS) chart. It has been supported by many studies that antiviral therapy is effective in the early period (20). Starting an effective treatment with an agent, such as favipiravir or remdesivir or biologic agents (such as IL-6 blockers) in the first 7 d, might be useful for COVID-19 patients with higher admission CAR values or those demonstrating an increased CAR values during the in-hospital stay (21–23). This treatment approach might be a crucial and effective in the rapid recovery of symptoms as well as reducing mortality among these patients.

Study Limitations

The present research had the following limitations. Firstly, the design of the study was based on the retrospective findings, which might include selection bias. However, we enrolled all consecutive COVID-19 cases in this analysis. Secondly, another important limiting factor related to CAR ratio is that it independently responds to the inflammatory response. For that reason, this value would increase in chronic diseases triggered by concomitant additional infections and malignancy. Thirdly, the present research was conducted in one geographical area; thus, this might restrict the generalizability of our results to other geographical areas. Fourthly, we acknowledged that there might be a possible presence of residual confounding from unmeasured variables, which might affect the outcome of the study. Finally, further multi-center, prospective studies are necessary to elucidate the exact relation between CAR values and in-hospital mortality in COVID-19 patients.

Conclusion

Based on our study results, we found that the CAR value was a significant predictor of in-hospital death in COVID-19 patients. Hence, the CAR ratio, which is a fast, inexpensive, repeatable inflammatory biomarker, might be used

for early treatment plans to decrease in-hospital mortality among these patients.

Conflict of Interest

None to declare.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2021.02.006.

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