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Diagnostic Value of C-Reactive Protein, Albumin, and the CRP-to-Albumin Ratio for Predicting Mortality in Hospitalized Patients with COVID-19 in Brazilian hospitals

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Authors' contributions

This work was carried out in collaboration among all authors. All authors were involved from the conception of the objective of the study, capture and selection of materials for review, including those included in manual search, correction and revision of tables and Figures, from summary to conclusion. All authors read and approved the final manuscript.

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ABSTRACT

Background: In recent years, studies have been conducted to understand the immuno-inflammatory changes related to COVID-19. Different serum biomarkers have been extensively investigated as diagnostic and/or prognostic markers of various clinical outcomes.
Objective: To evaluate the diagnostic value of serum C-reactive protein (CRP) and albumin levels, and the CRP-to-albumin ratio, determined on hospital admission, for predicting mortality in patients with COVID-19.
Methods: A retrospective cohort study of patients hospitalized with COVID-19 from March to August 2020 in two reference hospitals, one public and one private, in the Central Region of Brazil. The most important laboratory data included serum C-reactive protein (CRP) and albumin concentrations determined on hospital admission. The prognostic value of each biomarker for predicting patient mortality was analyzed using the receiver operating characteristic (ROC) curve.
Results: A total of 128 patients were hospitalized with COVID-19 during the study period, of whom 70 (54.7%) were male, with a mean age of 51.4 years. The mean (standard deviation [SD]) CRP concentration in patients who died was 152.1 (108.2) mg/dL, which was higher than that in survivors (p=0.007). The mean (SD) albumin concentration was 3.0 (0.6) g/dL among patients who died, which was lower than that in survivors (p=0.004). The mean [SD] CRP-to-albumin ratio was significantly higher among patients who died than among survivors (54.8 [32.8] vs. 34.8 [43.9]; p=0.002). ROC curves showed a higher diagnostic accuracy (69%) for the CRP-to-albumin ratio than for CRP or albumin alone. Analysis of different cut-off points for this ratio showed sensitivities ranging from 71.4% to 92.9%. These results confirm previous observations that CRP, albumin and CRP-to-albumin ratio are associated with serious outcomes from COVID-19 and their measurement at hospital admission identifies patients with a worse prognosis of the disease.
Conclusions: Serum concentrations of CRP and albumin and the CRP-to-albumin ratio determined on hospital admission are accurate biomarkers with good sensitivity for predicting mortality among hospitalized patients with COVID-19.

Keywords: COVID-19; albumin; C-reactive protein; C-reactive protein-to-albumin ratio; mortality.

1. INTRODUCTION

The SARS-CoV-2 pandemic constitutes a public health crisis due to the large number of cases, leading to a considerable loss of life worldwide [1]. COVID-19 presents with a varied spectrum of clinical manifestations, depending on the patient's risk profile. Notable symptoms include cough, sore throat, runny nose, nasal congestion, anosmia, ageusia, diarrhea, abdominal pain, fever, chills, headache, and myalgia. The inflammatory process that develops in the early stages of the disease, can leads to progressive worsening of respiratory symptoms, which can progress to pneumonia with dyspnea, fatigue, and hypoxemia [2].

Comorbidities, such as hypertension, diabetes mellitus, and obesity contribute an increased risk of death in patients with COVID-19. In these cases, the case fatality rate from SARS-CoV-2 is high, owing to the cytokine storm triggered by the infection, complicating the natural inflammatory process of these comorbidities [3,4].

Because COVID-19 induces a robust immune response in individuals infected with SARS-CoV-2, numerous studies have been conducted in recent years to understand the immunoinflammatory changes that occur throughout all phases of the disease. These changes have been extensively investigated as diagnostic and/or prognostic markers for various clinical outcomes observed in patients with COVID-19 [5,6].

In recent decades, various biochemical markers have been explored to assess the severity of different inflammatory diseases [7], including infections [8,9]. C-reactive protein (CRP), albumin, lactate dehydrogenase (LDH), and liver enzyme levels in patients with COVID-19 have already been evaluated in several studies [10]. CRP and albumin are proteins produced in the liver that are routinely measured in clinical practice. Albumin is a negative acute-phase protein, sensitive to the patient's nutritional status. The serum albumin level decreases in systemic inflammatory states due to various pathophysiological mechanisms, such as direct hepatocyte damage, resulting in reduced production, or glomerular injury, leading to increased protein clearance by the kidneys [11]. In contrast, CRP is a positive acute-phase

protein that participates in nonspecific inflammatory responses in situations of tissue damage, infection, or malignant neoplasms [12-14].

Hypoalbuminemia and elevated CRP levels have been associated with increased mortality rates in patients with various clinical conditions [15-17], including COVID-19 [18-22]. Several other studies have shown that alterations in both albumin and CRP can predict severe outcomes in patients with COVID-19 and abnormal levels have an adverse effect on prognosis [20,23].

Recently, the CRP-to-albumin ratio has been studied as an inflammatory biomarker of COVID-19. An elevated CRP-to-albumin ratio is an early biomarker to predict mortality in patients with COVID-19 [1,24,25]. The CRP-to-albumin ratio has higher sensitivity and accuracy for predicting COVID-19 severity than either CRP or albumin alone [26]. To guide healthcare professionals in managing hospitalized patients with COVID-19, inflammatory biomarkers have mainly been used to identify patients at increased risk of severe complications or death [1]. Our hypothesis is that such biomarkers are more altered upon hospital admission in those patients with a greater chance of death.

2. OBJECTIVES

To analyze the diagnostic value of serum concentrations of albumin and CRP measured at admission as well as the CRP-to-albumin ratio to predict fatal outcomes in patients with COVID-19.

3. METHODS

A retrospective cohort study was conducted on hospitalized patients with COVID-19 from March to August 2020 at two reference hospitals, one public (Hospital Universitário Júlio Müller) and one private (Hospital Santa Rosa), City of Cuiabá, Mato Grosso State, located in the Central Region of Brazil. Inclusion criteria comprised patients aged 18 years or older with SARS-CoV-2 infection confirmed using reverse transcription quantitative real-time polymerase chain reaction (RT-qPCR), rapid antigen testing, or SARS-CoV-2 IgM/IgG antibody testing. All necessary study information was obtained from patients' medical records. Demographic, clinical, and laboratory data were collected with a particular focus on identifying mortality during hospitalization. A medical history of hypertension; diabetes mellitus; chronic heart, lung, kidney, or liver diseases; cancer; and obesity were considered to have a higher risk of severe COVID-19 (comorbidities).

Serum concentrations of CRP and albumin were recorded only on the patient's admission date as baseline information and were used to analyze their value in predicting disease progression to mortality. These measurements were conducted in the laboratories of the respective hospitals, using the COBAS 6000 platform (Analyzer series, Roche Diagnostics, Indianapolis, IA, USA) or the Abbott Architect i2000 SR analyzer (Abbott Diagnostics, Abbott Park, IL, USA).

An initial descriptive analysis was conducted for all the study variables. Continuous variables were reported as means and standard deviations (SD), whereas categorical variables were reported as percentages and frequencies. The Shapiro-Wilk test was used to check for normality of the distribution of biochemical parameters and their ratios. To test the hypothesis of equal distribution of these parameters between patients who died and those who survived, the non-parametric Mann-Whitney U-test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. A nonparametric Spearman's correlation analysis was performed to justify the use of the CRP-to-albumin ratio as an additional biomarker for predicting death among the study patients.

Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of different cut-off points for serum concentrations of CRP and albumin and the CRP-to-albumin ratio measured on hospital admission for predicting fatal outcomes of COVID-19. Empirical cut-off points with higher sensitivity for diagnosing mortality were selected. The area under the ROC curve (AUC) was calculated to describe the accuracy of biomarkers in predicting death. For all analyses, a p-values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata version 12.0 (Stata Corp, College Station, TX, USA).

4. RESULTS

A total of 128 hospitalized patients with COVID-19 who met the inclusion criteria were included in the study. Among them, 84 (65.6%) were admitted to the private hospital and 44 (34.4%) were admitted to the public hospital. Of the total, 70 were male (54.7%), with a mean (SD) age of

51.4 (18.0) years, and the majority (49.5%) had a brown skin color. Older adults (≥65 years) accounted for 34.4% of the cases. Sixty-two (49.6%) patients were married and 118 (92.9%) declared their residence in the urban area of Cuiabá, Mato Grosso, Brazil (Table 1).

COVID-19 was confirmed by RT-PCR in 73 (57.0%) patients, by rapid antigen testing in 1 (0.8%) patient, by rapid antibody testing (IgM/IgG) in 33 (25.8%) patients, and by a combination of clinically and image-compatible data in 21 patients (16.4%). Of the patients, 69.5% had one or more comorbidities. Hypertension (44.5%), diabetes mellitus (25.0%), and obesity (24.2%) were the most common comorbidities. The need for ICU admission and ventilatory support was documented in 96.7% and 77.7% of the cases, respectively. Of the patients 98 (76.5%) were discharged from the hospital, 28 (21.9%) died, and 2 (1.6%) had no information available on the outcome due to transfer to another healthcare institution (Table 1).

Table 1. Demographic and clinical characteristics of patients with COVID-19 hospitalized in two hospitals in Central Brazil, March to August 2020

Characteristic		n	%
Hospital category	Private	84	65.6
	Public	44	34.4
Age (years) (n=125)	18–49	55	44.0
	50–64	27	21.6
	65–79	32	25.6
	≥ 80	11	8.8
Sex	Male	70	54.7
	Female	58	45.3
Place of residence	Cuiaba Metropolitan Area	118	92.9
(n=127)	Mato Grosso State interior	9	27.1
Marital status (n=125)	Married	62	49.6
	Single	31	24.8
	Widower	15	12.0
	Common-law marriage	11	8.8
	Divorced	6	4.8
Skin color (n=101)	Black	5	5.0
	Yellow	8	7.9
	White	38	37.6
	Brown	50	49.5
COVID-19 confirmation	RT-qPCR	73	57.0
	Rapid IgM/IgG test	33	25.8
	Clinical features/image suggestive	21	16.4
	Rapid antigen test	1	0.8
Comorbidity reported	Yes	89	69.5
	No	39	30.5
Comorbidities*	Hypertension	57	44.5
	Diabetes mellitus	32	25.0
	Obesity	30	24.2
	Chronic heart disease	13	10.2
	Chronic lung disease	9	7.0
	Chronic liver disease	7	5.5
	Chronic renal disease	7	5.5
	Cancer	3	2.3
	HIV under treatment	2	1.6
Need for intensive	Yes	119	96.7
therapy (n=123)	No	4	3.3
Need for ventilatory	Yes	94	77.7
support (n=121)	No	27	22.3
Outcome	Discharge	98	76.5
	Death	28	21.9
	Transfer to another hospital	2	1.6

** Patients could have more than one comorbidity. The number of observations (n) varied due to missing data in some patients. RT-qPCR, reverse transcription quantitative real-time polymerase chain reaction*

The distribution of known risk factors for COVID-19 severity according to the outcome (death or survival) is shown in Table 2. Male sex and comorbidities such as systemic arterial hypertension, diabetes mellitus, obesity, chronic liver disease, heart disease, chronic kidney disease, and lung disease were not associated with fatal outcomes in the studied patients. Age over 70 years was associated with mortality among the analyzed patients (p<0.001). The mean (SD) serum concentration of CRP in patients who died was 152.1 (108.2) mg/dL, which was significantly higher than that of patients who survived (p=0.007). Conversely, the mean (SD) albumin concentration in patients who died was 3.0 (0.6) g/dL, which was significantly lower than that of patients who survived (p=0.004). Given the observed inverse and significant correlation between serum levels of CRP and albumin (Fig. 1), an analysis of the association between the CRP-to-albumin ratio and mortality was conducted. Patients who died had a significantly higher mean [SD] CRP-to-albumin ratio than patients who survived (54.8 [32.8] vs. 34.8 [43.9]; p=0.002).

Table 2. Analysis of the association between risk factors or biomarkers mortality in hospitalized patients with COVID-19

Risk factor/biomarker	Death n (%)	Survivor n (%)	P*
Age > 70 years (n=30)	16 (53.3)	14 (46.7)	<0.001
Male sex (n=68)	16 (23.5)	52 (76.5)	0.702
Obesity (BMI ≥30 kg/m^2) (n=30)	4 (13.3)	26 (86.7)	0.268
Arterial hypertension (n=55)	15 (27.3)	40 (72.7)	0.370
Diabetes mellitus (n=32)	12 (37.5)	20 (62.5)	0.101
Chronic kidney disease (n=6)	3 (50.0)	3 (50.0)	0.221
Chronic heart disease (n=13)	3 (23.1)	10 (76.9)	0.639
Chronic lung disease (n=13)	2 (22.2)	7 (77.8)	0.792
Chronic liver disease (n=13)	0 (0.0)	7 (100.0)	..
	Mean (SD)	**Mean (SD)**	
CRP (mg/dL)	152.1 (108.2)	105.6 (118.9)	0.007
Albumin (g/dL)	3.0 (0.6)	3.5 (0.7)	0.004
CRP-to-albumin ratio (×1000)	54.8 (32.8)	34.8 (43.9)	0.002

** Mann-Whitney U test. Abbreviations: BMI, body mass index; CRP, C-reactive protein; SD, standard deviation*

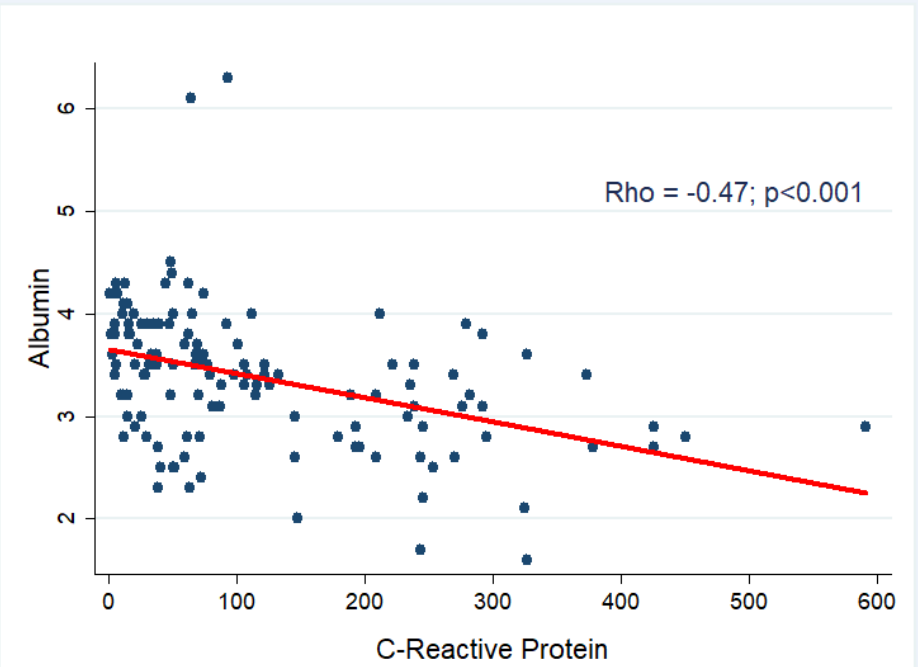

Fig. 1. Correlation between serum concentrations of C-reactive protein and of albumin measured on admission in hospitalized patients with COVID-19 (ρ=−0.47; p<0.001; Spearman correlation).

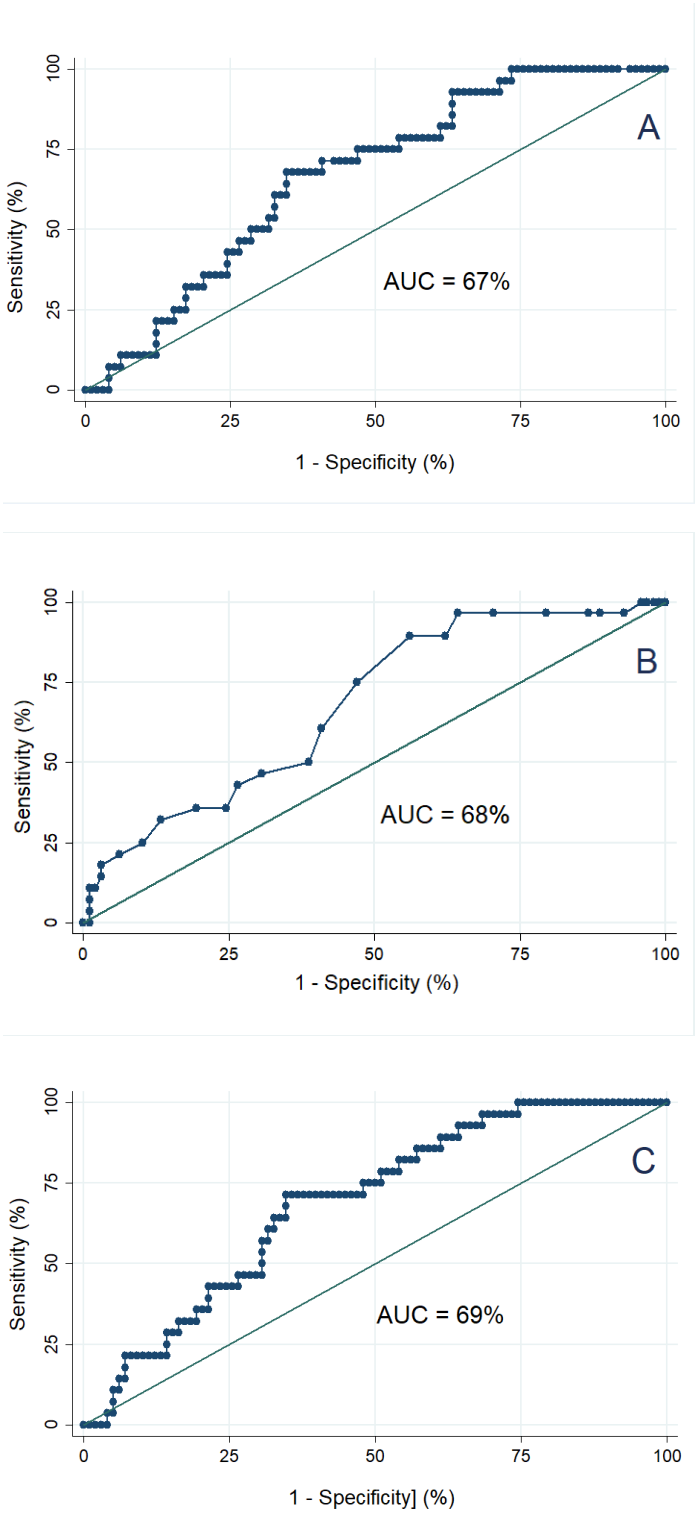

Fig. 2. Receiver operating characteristic (ROC) curves of the accuracy of serum concentrations of C-reactive protein (CRP) (A), albumin (B), and the CRP-to-albumin ratio (C) determined on admission for predicting the mortality of hospitalized patients with COVID-19. Abbreviations: AUC, area under the curve; CRP, C-reactive protein; ROC, receiver operating characteristic

ROC curves constructed from serum concentrations of CRP and albumin, and the CRP-to-albumin ratio measured on hospital admission in patients with COVID-19, demonstrated satisfactory accuracy in predicting mortality. The highest accuracy (69%) was recorded for the CRP-to-albumin ratio. The cutoff points of 3 g/dL for albumin, 40 mg/dL for CRP, and 10 for the CRP-to-albumin ratio showed sensitivities of 64.3%, 82.1%, and 92.9%, respectively (Fig. 2).

5. DISCUSSION

In this study, the serum CRP concentration was significantly increased on admission in hospitalized patients with COVID-19, whereas the serum albumin concentration was decreased. A moderate and significant inverse correlation was found between the serum CRP and albumin concentrations, and patients with severe COVID-19 who died had significantly higher CRP-to-albumin ratios on admission than those who survived. As it is difficult to accurately predict the clinical characteristics that indicate a fatal prognosis of COVID-19 [25], these findings may contribute to better clinical management of hospitalized patients with COVID-19.

Notably, the demographic, clinical, and comorbidity profile of the patients analyzed in this study was similar to that observed in other studies on hospitalized patients with COVID-19 [2,27,28]. International and Brazilian studies have shown that the presence of comorbidities such as hypertension, diabetes mellitus, and obesity increases the risk of death among patients with COVID-19 [1,2]. In this study, the most common comorbidity was hypertension, followed by diabetes mellitus, obesity, and cardiovascular disease. These four comorbidities have also been the most prominent in other studies of hospitalized patients with COVID-19 [4,29,30]. Such comorbidities are associated with an increased risk of death in COVID-19, especially in patients requiring ventilatory support or intensive care [31]. As the COVID-19 mortality rate ranges from 2.0% to 10.0% in the general population [5,32,33], it is likely that the high prevalence of comorbidities explain the higher lethality case fatality rate (21.8%) observed in this study.

Inflammation is a sign of disease severity and poor prognosis in patients with COVID-19. A systematic review with a meta-analysis of 23 studies found that patients with severe disease had higher levels of procalcitonin, CRP, D-dimer, and LDH and lower serum levels of albumin than patients with non-severe disease. CRP is a positive acute-phase marker with clinical applicability in reflecting host inflammatory responses. Serum albumin, in addition to demonstrating nutritional status, is considered a negative acute-phase reactant, and the serum concentration usually decreases during inflammation [15]. A decreased serum albumin concentration is a common finding in patients withCOVID-19, and hypoalbuminemia is associated with increased mortality [1,18,34].

For several years, both CRP and albumin have been used as biomarkers to predict mortality in patients with infectious diseases and sepsis [13,14]. During the progression of COVID-19, an increase in CRP levels has been reported to be associated with severe disease and increased mortality [28]. Catabolic activation occurs during the inflammatory process, resulting in the loss of muscle mass [18]. The resulting reduction in proteins, especially albumin, leads to an increase in the CRP-to-albumin ratio. Therefore, the CRP-to-albumin ratio has been used as a biomarker in various clinical conditions associated with inflammation [19,35,36].

Several studies have shown an association between the CRP-to-albumin ratio and the prognosis of patients with systemic inflammation from various types of neoplasms [35], and severe infections [36], and the CRP-to-albumin ratio is generally also increased in severe COVID-19[25]. In a recent systematic review, an association was found between the CRP-to-albumin ratio and severity and mortality of patients with COVID-19 [37].

A possible explanation for the elevated CRP-to-albumin ratio in patients with systemic inflammation could be a reduction in protein synthesis induced by liver damage. However, in this study baseline liver disease as a comorbidity was not associated with an increased risk. Similarly, Güney et al. [24] confirmed that the CRP-to-albumin ratio is an independent predictor of in-hospital mortality in hospitalized patients with COVID-19 with comorbidities.

This study has some limitations. The selection of patients from only two hospitals and the short analysis period may have introduced selection bias. In addition, this was a retrospective analysis of medical records, and the quality of the collected information is questionable, mainly because of the omission of relevant information on disease progress. Larger prospective cohort

studies with subgroup analysis by risk subgroups is essential to validate the findings of this study. Despite the lack of novelty in identifying the severity prediction values of the biomarkers studied here, the results confirmed the results of previous studies [9,38,39].

6. CONCLUSIONS

Analysis of serum concentrations of CRP and albumin, and the CRP-to-albumin ratio, at the time of hospital admission of patients with COVID-19 is a simple and valid strategy for predicting mortality. These biomarkers obtained early during hospitalization have the potential to alert healthcare professionals about the need for appropriate intensified clinical care to improve the prognosis of hospitalized patients with COVID-19.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was approved by the Ethics and Research Committee of Hospital Universitário Júlio Muller (HUJM) on September 1, 2020 (approval number 4,252,218).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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