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The C-Reactive Protein to Albumin Ratio as a predictive factor in a sample of COVID-19 patients admitted to the hospital

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Abstract

Background: To assess the c-reactive protein to albumin ratio as a predictive factor in covid-19 patients admitted to the hospital.

Methods: The Hemoglobin (Hb), white blood cells (WBCs), lymphocyte, platelet, neutrophils , D-dimer, Ferritin, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and C-reactive protein to albumin ratio (CAR) were assessed in 60 COVID-19 patients compared to 40 healthy control subjects. Colorimetric techniques were used to determine the blood levels of ALT, AST, ALP, and albumin. Ichroma^{TM} assessed serum ferritin and d-dimer, and CBC was determined using an autohematology analyzer.

Results: WBCs, neutrophils, D-dimer, Ferritin, CRP, ALT, AST, and CAR were considerably higher in COVID-19 patients compared to the control group, whereas platelet, albumin, and lymphocyte were significantly lower (P 0.0001).

Conclusion: The CAR appears to have a significant chance of improving prognosis in COVID-19 patients who are hospitalized.

Keywords COVID-19, C-reactive protein to albumin ratio, C-reactive protein.

1- Introduction

In December 2019, a pneumonia epidemic caused by a new coronavirus was discovered in the Chinese city of Wuhan. The epidemic was uncontrollable, and it quickly spread over the world, ending in a pandemic. Severe acute respiratory syndrome coronavirus 2 was the name given to the new coronavirus (SARS-CoV-2) [1]. The World Health Organization designated the virus-caused disease as coronavirus disease 2019 (COVID-19) [2]. SARS-CoV-2 is thought to enter cells via angiotensin converting enzyme 2 (ACE2) receptors, which are found in numerous organs, including the cardiovascular system (CVS), the gastrointestinal tract, and the respiratory system. Angiotensin-converting enzyme 2 reduces the impact of angiotensin II (Ang II) by converting it to Ang 1-7, which has anti-inflammatory, antioxidant, and vasodilator properties [3]. SARS-CoV-2 binding to ACE2 receptors reduces ACE2 expression in cells while increasing Ang II levels, resulting in an inflammatory response [4]. The clinical features and outcomes of COVID-19-infected hospitalized patients have been documented in several retrospective studies. C-reactive protein (CRP) and other inflammatory response laboratory indicators have been found as predictors of clinical severity and consequences [5]. CRP is an acute-phase protein that rises quickly after an inflammatory event. CRP has been linked to coronary heart disease, ischemic stroke, and hypertension in previous investigations [6]. Albumin is an anti-inflammatory and anti-hemostatic negative acute-phase reactant. Low albumin levels have been associated with an increased risk of death and morbidity in both cardiovascular disease and critical illness [7]. The CRP to albumin ratio (CAR) is a new and valuable indicator that has been related to critical illness

mortality and morbidity [8]. Increased CRP levels and reduced albumin levels in COVID-19 patients were correlated in a new finding to disease severity and fatality [9,10]. In this study, we aimed to assess the capacity of CAR to forecast the probability of progression to critical illness or death in the early stages of severe COVID-19.

2- Materials and Methods

This case control study of 100 subjects was conducted age 35 to 65 years. Between September and November 2021, 60 confirmed COVID-19 patients were admitted to Al-Amal Specialized Hospital for infectious diseases in an Najaf governorate, Iraq. Patients with COVID-19 were diagnosed based on positive quantitative RT-PCR and chest x-ray or chest computed tomography (CT) scan findings, with 40 healthy participants providing as a control group with similar ages ranges to the patients. This study excluded participants with diabetes, liver illness, chronic renal disease, pulmonary disease, pregnant women, and smokers to prevent the impact of additional comorbidities. Before participating in this study, all controls and patients provided written informed permission. The research was carried out in accordance with Iraqi and international ethical and privacy rules, as well as the declaration of helsinki of the world medical association.

Venous blood samples were collected from patients and control groups. Two tubes of blood samples were used. Allow 3 ml to clot for 10-15 minutes at room temperature before centrifugation at 3000 Xg for 10 minutes to obtain serum. The serum samples were then divided into tubes and refrigerated at -20°C until they were ready to be analyzed. The rest of the blood (2 ml) was used to calculate the complete blood count. Using

Biolabo® kits from Maizy, France, the levels of serum ALT, AST, ALP, and albumin were measured spectrophotometrically. Fluorescence immunoassay was used to determine serum ferritin, C-reactive protein, and D-dimer levels were measured by (ichroma^{TM}). An autohematology analyzer was used to determine the whole blood count (linear, Spain).

3- Statistical Analysis

The data was analyzed with SPSS-26 (statistical program for social science-version 26) and Graphpad Prism (Version 9.3.1) for graphical representation. To investigate the relationship between the two groups and compare to the remaining groupings. The variable was denoted by "mean ± SD," and the t-test was performed to determine the difference between the groups for each and every variable. Pearson's correlation coefficient was used to determine the correlation of parameters, using a $p \leq 0.05$ significance level.

4- Results

The present study was performed based on 100 adults of Iraqi populations. It was included 60 patients with COVID -19 , (46 survivors and 14 nonsurvivors), (38 males and 22 females), their ages min.-max. (35-65) years, are compared with 40 apparently healthy adults who were recruited as control group (25 males and 15 females) , their ages min.-max. (34-63) years. When the impacts of laboratory parameters on the COVID-19 prognosis were analyzed, a significant difference was found between the groups (patients and healthy controls) for WBCs, neutrophils, lymphocytes, CRP, albumin, platelets, and CAR, while no significant difference was found between the groups for age and hemoglobin (Table 1).

Table 1. Comparison of the demographical and laboratory data of patients with COVID-19 and control groups.

Variables	Groups			P-Value
	Subjects	Patients with COVID19 Mean±SD (n=60)	Healthy control Mean±SD (n=40)	
Age (year)	Total Male Female	47.81±8.53 48.55±8.824 46.54±8.04	46.87±5.05 46.68±5.64 47.2±4.04	0.490 0.308 0.746
Gender, n(%)	Total Male Female	60 38(63.33) 22(36.66)	40 25(62.5) 15(37.5)	----
Hb (g/dL)	Total Male Female	13.34±0.61 13.33±0.67 13.36±0.50	13.6175±0.32 13.556±0.28 13.72±0.37	0.005 0.077 0.019
WBCs $\times10^9$/L	Total Male Female	11.19±1.90 11.24±2.02 11.09±1.73	8.09±1.07 8.12±1.11 8.04±1.04	0.000 0.000 0.000
Neutrophil $\times10^9$/L	Total Male Female	7.69±1.82 7.66±1.86 7.74±1.80	4.02±0.70 4.072±0.76 3.94±0.60	0.000 0.000 0.000
Lymphocyte $\times10^9$/L	Total Male Female	1.89±0.80 1.76±0.83 2.10±0.71	4.11±0.77 4.12±0.79 4.14±0.75	0.000 0.000 0.000
Platelet $\times10^9$/L	Total Male Female	195.5±24.16 192.65±26.94 200.41±17.94	355.17±16.48 353.32±5.03 358.26±26.41	0.000 0.000 0.000
D-Dimer (mg/L)	Total Male Female	2.68±1.36 2.87±1.43 2.36±1.18	0.19±0.04 0.18±0.042 0.21±0.03	0.000 0.000 0.000
Ferritin (ng/ml)	Total Male Female	615.96±45.85 622.05±47.33 605.45±42.15	96.65±9.61 96.12±9.266 97.53±10.43	0.000 0.000 0.000
CRP (mg/L)	Total Male Female	41.21±18.04 42.89±19.80 38.32±14.51	3.9025±0.98 3.78±1.07 4.10±0.80	0.000 0.000 0.000
ALT (U/L)	Total Male	37.35±11.77 38.32±12.49	18.05±2.89 18.32±3.02 18.13±2.77	0.000 0.000 0.000

	Female	36.22±10.59		
ALT (U/L)	Total	37.35±11.77	18.05±2.89	0.000
	Male	38.32±12.49	18.32±3.02	0.000
	Female	36.22±10.59	18.13±2.77	0.000
AST (U/L)	Total	49.13±10.77	18.5±2.87	0.000
	Male	50.34±11.32	18.88±2.87	0.000
	Female	47.04±9.64	17.86±2.85	0.000
Albumin (mg/L)	Total	2.64±0.75	3.79±0.28	0.000
	Male	2.63±0.78	3.81±0.26	0.000
	Female	2.67±0.71	3.75±0.32	0.000
CAR	Total	18.70±14.31	1.03±0.27	0.000
	Male	19.87±15.22	0.99±0.28	0.000
	Female	16.68±12.63	1.09±0.22	0.000

Hb, Hemoglobin; WBCs, white blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CAR, C-reactive protein to albumin ratio.

When the patients were divided into two groups as survivors (27 males and 19 females) and nonsurvivors (11 males and 3 females) the age and terms of laboratory findings, WBCs, neutrophils , D-dimer, Ferritin, CRP, ALT, AST, and CAR were significantly higher in the nonsurvivor group than the survivor group ($P \leq .0001$). In contrast, the lymphocyte, Platelet, and albumin levels were significantly lower in nonsurvivors compared with the survivors ($P \leq .0001$). However, no significant differences were observed in hemoglobin (Table 2).

Table 2. Characteristics of survivor and nonsurvivor patient with the diagnosis of COVID-19.

Variables	Patients with COVID-19 (Survivors) (n=46)	Patients with COVID-19 (Nonsurvivors) (n=14)	p- value
Age (year)	44.21±5.90	59.64±3.60	0.000

Hb (g/dL)	13.35±0.63	13.34±0.56	0.977
WBCs $\times 10^9$/L	10.42±1.37	13.7±1.05	0.000
Neutrophil $\times 10^9$/L	6.91±1.12	10.27±1.28	0.000
Lymphocyte $\times 10^9$/L	2.17±0.65	0.94±0.45	0.000
Platelet $\times 10^9$/L	207.78±9.43	155.14±7.41	0.000
D-Dimer (mg/L)	1.98±0.40	5.01±0.53	0.000
Ferritin (ng/ml)	594.26±26.13	687.28±5.79	0.0000
CRP (mg/L)	31.69±5.24	72.5±2.92	0.000
ALT (U/L)	31.41±4.89	56.85±3.37	0.000
AST (U/L)	43.80±4.75	66.64±4.32	0.000
Albumin (mg/L)	2.91±0.62	1.77±0.37	0.000
CAR	11.4±3.02	42.70±9.36	0.000

Hb, Hemoglobin; WBCs, white blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CAR, C-reactive protein to albumin ratio.

Level of D-dimer have been a significant positive correlation with CAR (r=0.905, p=0.0001). While, it has a significant negative correlated between lymphocyte and CAR (r=0.736, p=0.0001) in patients with COVID-2019 group as shown in Figures 1 and 2 respectively.

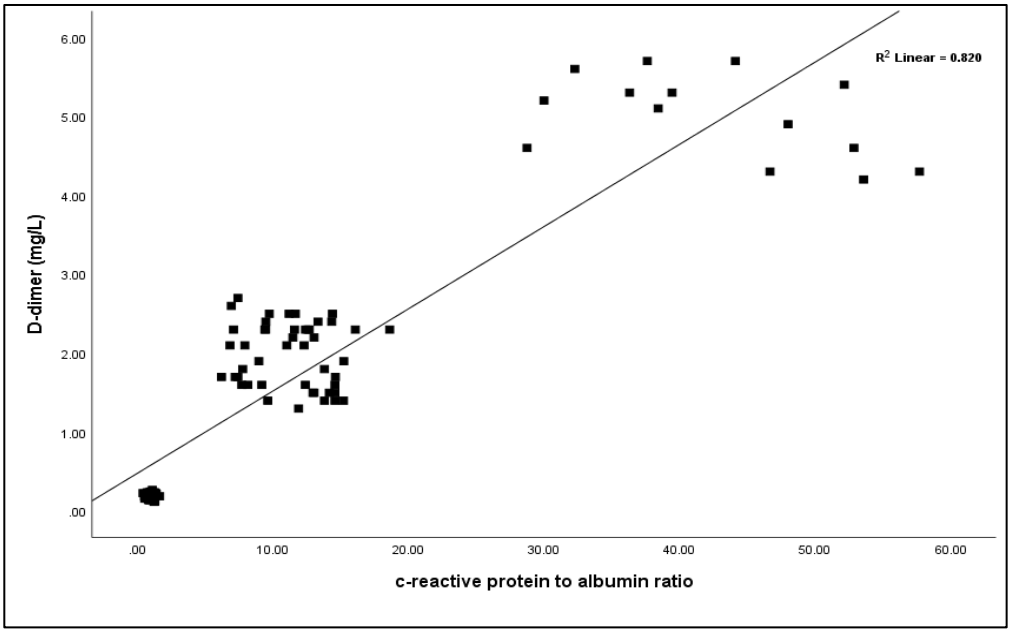

Figure 1. Correlation between C-reactive protein to albumin ratio and D-dimer level in patients with COVID-19.

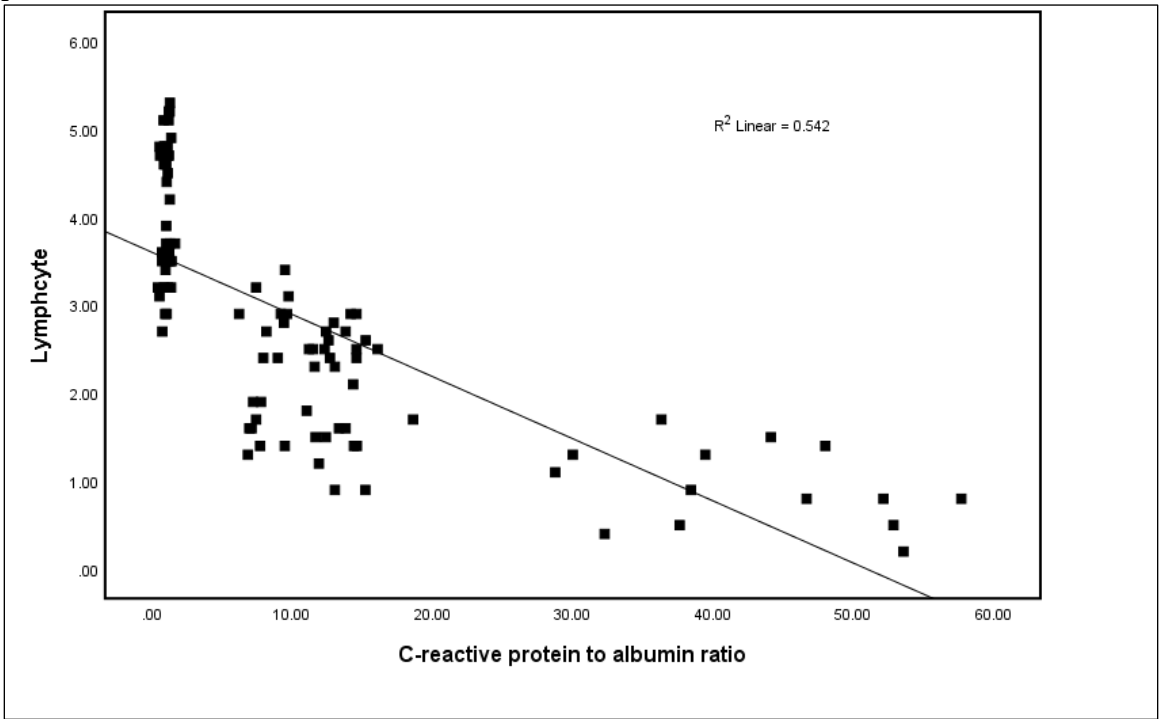

Figure 2. Correlation between C-reactive protein to albumin ratio and lymphocyte level in patients with COVID-19.

As it was shown in Figure 3, C-reactive protein to albumin ratio significantly increase in the nonsurvivor group in comparison with survivor group (42.70±9.36 vs 11.4±3.02, p<0.0001).

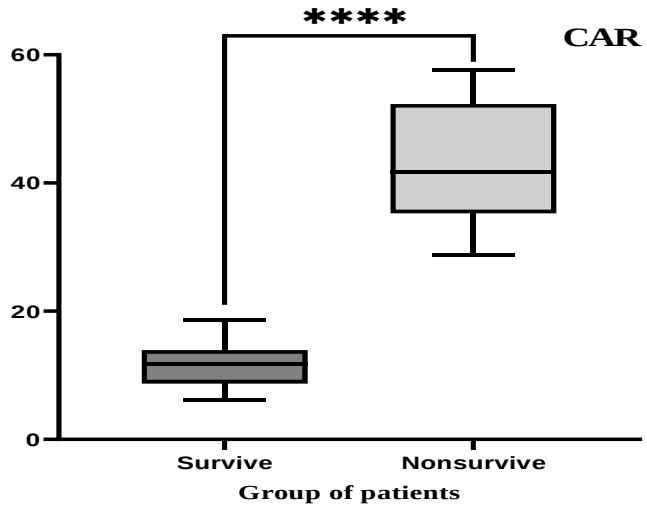

Figure 3**:** Comparison between survives and nonsurvives patients of C-reactive protein to albumin ratio (CAR), **** p<0.0001.

5- Discussion

This study has shown that the CAR was higher in nonsurvivor patients with COVID-19 than in survivors. Furthermore, in those individuals, the CAR was an independent predictor of death. Advanced age was reported to be an independent risk factor for the disease as a result of the COVID-19 outbreak [11]. The pathophysiology of COVID-19 is complicated by the inflammatory response. As a result, inflammatory markers like CRP have been investigated as COVID-19 prognostic indicators [12]. Albumin, which is predicted to decrease in inflammatory circumstances, has been found to decrease in severe COVID-19 patients [13].

C-reactive protein (CRP) induction is a component of the acute phase response, which involves increasing the synthesis of certain plasma proteins while decreasing the synthesis of others, including albumin [14]. Inflammatory indicators, such as CRP, were shown to be higher in individuals who required invasive breathing. In patients with COVID-19, hypoalbuminemia [15] and increased CRP have been linked to severe illness and mortality. In critically sick patients, the CRP to albumin ratio has been demonstrated to be more accurate than CRP alone in predicting 28-day death [16]. The CAR has recently been reported as a valuable tool for predicting prognosis in patients with a variety of conditions, including cancer, severe sepsis, and cardiovascular disease [17]. It has been confirmed to be a more definitive indicator than CRP and albumin levels alone. Huang et al. [18] In patients with severe illness, a higher CAR on admission to the intensive care unit constituted an independent risk factor for 30-day death. The CAR was found to be an independent predictor of illness severity in COVID-19 patients who were hospitalized in a recent research [19]. Furthermore, Saylik et al [20]confirmed that the CAR was a reliable predictor of in-hospital death in COVID-19 patients.

In addition, as a biomarker of disease progression in patients with severe COVID-19, the CRP/Alb ratio has the following advantages. First, some inflammatory markers (such as ferritin, TNF-α, and IL-6) that were confirmed to be elevated during cytokine storm in patients with severe COVID-19 may not be available in most grassroots hospitals or laboratories in developing countries and are mainly used for research purposes. However, the detection techniques for CRP and Alb are reliable, simple, and

cheap; they are usually part of the admission examination in general hospitals, especially in the ICU, and are easy to obtain. Second, previous studies have reported that CRP levels in patients with severe COVID-19 increased significantly in the early stages before lung lesions were found on computed tomography [21,22].

6- Conclusion

This study showed that nonsurvivor COVID-19 patients had a greater CAR than survivors. In COVID-19 patients, the C-reactive protein to albumin ratio may be an independent predictor of fatality; CAR was also better at predicting in-hospital mortality than CRP and albumin independently.

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