The Relationship between Disease Severity and CRP/Albumin Levels in Cases with Covid-19 Pneumonia

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Conflict of Interest: None declared

This article has been peer reviewed.

Article Accepted on: 11th August 2021

Funding Sources: None declared

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Cite this Article: Şirikçi V, Fındikli HA, Erdoğan M. The relationship between disease severity and CRP/Albumin levels in cases with Covid-19 pneumonia. J Pioneer Med Sci. 2021; 10(2):1-5

ABSTRACT

Background: To determine disease severity in the COVID-19 pandemic, it is necessary to monitor several clinical and laboratory parameters. Non-invasive and objective inflammatory markers can be a practical and objective route in the determination of disease activity. The C-reactive protein/albumin ratio (CAR) is an inflammatory marker thought to have prognostic value for most diseases, primarily sepsis. The aim of this study was to evaluate the diagnostic performance of CAR in determining the clinical severity of COVID-19 disease.

Methods: We conducted a retrospective examination of health records of patients diagnosed with COVID-19 between 15 March and 26 May 2020. Patients with pulmonary computed tomography findings consistent with COVID-19 and confirmed by a positive result in the real-time reverse transcriptase-polymerase chain reaction test were included. The cases were separated into two groups of mild and severe according to symptom severity.

Results: Of the 105 patients, 39 (37.1%) were males with a mean age of 63.2±14.5 years. In the regression analysis, the severity of COVID-19 was associated with age (OR = 1.04; 95% CI: 1.001, 1.074; p = 0.04), heart disease (OR = 4.37; 95% CI: 1.02, 18.8; p= 0.03), CAR (OR = 1.77; 95% CI: 1.05, 2.98; p = 0.03), lymphocyte count (OR = 0.54; 95% CI: 0.32, 0.96; p = 0.02). For the diagnosis of severe disease, the highest sensitivity of CAR was 76.5%, specificity 76.1% and the greatest area under the curve (AUC) was 0.70.

Conclusion: We found a significant relationship between disease severity and CAR in COVID-19 patients. CAR is an inexpensive and practical marker for the diagnosis of severe COVID-19.

Keywords: COVID-19; Albumin; CRP; CRP to Albumin ratio

INTRODUCTION

At the end of December 2019, a new disease emerged in Wuhan, Hubei Province, China and by 31 January 2020, the disease had rapidly spread to another 19 countries with 106 infected cases. The viral agent was temporarily named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and finally named by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19) **[1, 2]**.

Common symptoms of COVID-19 infection are respiratory, fever, cough, and dyspnea. COVID-19 infection may have an asymptomatic course, cause a mild respiratory tract infection, or progress to pneumonia, acute respiratory disease syndrome (ARDS), multiple organ failure (MOF), and death **[3]**. Therefore, an examination of potential risk factors for severe COVID-19 is important to slow or halt the progression of the disease. Previous studies have shown that a higher likelihood of illness severity in elderly patients and those with underlying diseases **[4, 5]**. Further, the mechanism responsible for the severe course of the disease is thought to be an abnormal immune-inflammatory response **[6]**. In this context, some inflammatory parameters such as leukocytes (WBC), neutrophils (NEU), lymphocytes (LYM), C - reactive protein (CRP), D-dimer, serum ferritin and serum albumin have

low cost and easy accessibility. In many studies, these parameters have been associated with inflammatory conditions. However, a definitive role of these parameters in predicting the severe form of COVID-19 has not been explored **[7-9]**.
In response to infection, we often find that serum CRP levels increase while serum albumin levels fall; both can be considered important markers of the extent of acute inflammatory response **[10-12]**. Therefore, our objective was to examine the association of the CRP/albumin ratio with COVID-19 severity and to determine if it can be predictive of disease severity.

METHODS

In this retrospective study, we included COVID-19 patients who presented to the Kahramanmaraş Necip Fazil City Hospital between March 15 and March 26, 2020. Patients were diagnosed according to the WHO and the Turkish Ministry of Health diagnosis and treatment guidelines and were confirmed by a positive result in the real-time reverse transcriptase-polymerase chain reaction test (RT-PCR) from the nasal and pharyngeal swab samples **[13]**. The cases were separated into two groups of mild and severe according to the severity of symptoms.
The mild cases were defined as meeting all the following conditions: (1) epidemiology history, (2) fever or other respiratory symptoms, (3) typical CT image abnormalities of viral or atypical pneumonia, and (4) RT-PCR positivity for SARS-CoV. The severe cases were defined as those meeting at least one of the following criteria in addition to the previously stated findings: (1) shortness of breath with respiratory rate (RR) ≤30/min, (2) oxygen saturation (at rest) <93%. All the demographic, clinical, and laboratory data of the patients were obtained from the hospital medical records.
Patients were excluded if the data was incomplete, age<18 years, were pregnant, or had a diagnosis of malignancy. The criteria for discharge of a patient was no fever for at least 3 days, significant recovery in both lungs seen on chest computed tomography (CT), clinical recovery of respiratory symptoms, and at least 24 hours since a negative RT-PCR test. As this was a retrospective observational study, informed consent was not required. Approval for the study was granted by the Turkish Ministry of Health (decision no: 2020-05-27T09_31_31) and the necessary permissions were obtained.

Statistical Analysis: Statistical analyses of the data obtained in the study were conducted using SPSS v 22.0 software (Statistical Package for Social Sciences). Continuous variables were tested for normal distribution. Normally distributed variables are expressed as mean ± SD, whereas non-normally distributed variables are reported as median and interquartile ranges (IQR). Categorical variables are reported as counts with proportions. Continuous variables between the groups were compared using the Student's t-test or the Mann-Whitney U-test according to the conformity of the data to normal distribution. Categorical variables were compared across the two groups using the Chi-square test or Fisher's Exact test. Receiver operating characteristic (ROC) curve analysis was used to determine the sensitivity and specificity of the predictive values of parameters. The optimal cut-off value of CRP/albumin was derived from the Youden index. Backward stepwise logistic regression was performed to examine the potential relationship of each variable with disease severity. The following variables were included in the model: sex, age, comorbidity, CRP/albumin, sodium, hemoglobin, lymphocyte, and neutrophil included in the model.

RESULTS

Of the 105 patients, 34 had severe disease (9 males with mean (SD) age 68.8 (8.4) years) and 71 had the mild disease (30 males with mean (SD) age 60.5 (16.1) years). The groups had similar gender ($p>0.05$) distribution while the mean age was greater in the severe disease group ($p<0.05$). As expected, length of stay in hospital was significantly longer in the severe group at median 9 days (IQR=7) compared to the mild group at median 6 days (IQR=4) ($p<0.05$). Heart diseases were more common in the severe disease group ($p<0.05$), while other diseases had a similar distribution ($p>0.05$). The WBC, platelets, serum glucose, urea, creatinine, and potassium values were similar in both groups ($p>0.05$) while serum sodium, neutrophil counts, CRP, and CRP/albumin ratio were statistically significantly higher in the severe patient group ($p<0.05$). On the other hand, the albumin and lymphocyte values were significantly lower in the severe group than in the mild group ($p<0.05$). The demographic and laboratory characteristics of the patients are shown in Table 1.
In the ROC curve analysis, CRP/albumin ratio of ≥1.00 with 76.5% sensitivity and 76.1% specificity (AUC: 0.70, 95% CI: 0.58-0.81) was

Table 1: Demographic and clinical characteristics in patients with COVID-19

	All patients	**Severe type**	**Common type**	**P-value**
	(n=105)	**(n=34)**	**(n=71)**	
Age (years)	63,2± 14,5	68,8 ± 8,4	60,5 ± 16,1	0.006
Gender n (%)				
Male	39 (37,1)	9 (26,5)	30 (42,3)	0,117
Female	66 (62,9)	25 (73,5)	41 (57,7)	
Length of hospital stay	6 (5 - 9)	9 (5 - 12)	6 (4 - 8)	0.010
Comorbidity n (%)				
Diabetes	21 (20)	8 (23,5)	13 (18,3)	0.532
Hypertension	27 (25,7)	11 (32,4)	16 (22,5)	0.280
Heart disease	11 (10,5)	7 (20,6)	4 (5,6)	0.036
Renal dysfunction	7 (6,7)	3 (8,8)	4 (5,6)	0.679
Pulmonary disease	15 (14,3)	8 (23,5)	7 (9,9)	0.077
Others	9 (8,6)	3 (8,8)	6 (8,5)	0.949
Glucose, md/dL	120 (104-157)	114 (96-154)	123 (106-160)	0.179
Urea, mg/dL	33,8 (25,0-51,5)	36,2 (29,1-48)	33,7 (23,4-57,3)	0.459
Cr, mg/Dl	1,1 (0,95-1,4)	1,1 (1-1,6)	1,1 (0,9-1,3)	0.236
Na, mmol/L	136 ± 4,36	138 ± 5,0	136 ± 4,0	0.038
K, mmol/L	4,3 ± 0,63	4,2 ± 0,8	4,4 ± 0,6	0.165
Crp, mg/L	29 (17,0 –45,5)	39 (26,2–58,7)	27 (16 - 37)	0.005
Albumin, g/L	34 (30–37,9)	31 (29,4– 35,6)	35,2 (30,6– 38,9)	0.020
Crp/Albumin	0,87 (0,47 - 1,43)	1,29 (1,00–1,65)	0,80 (0,43–0,96)	0.001
Wbc, × 10^9/L	7,2 (5,1 - 9,4)	8,0 (5,9 - 10,9)	6,9 (4,9 - 9,1)	0.099
Hgb, g/dL	12,1 (11,2 - 12,8)	11,1 (10,2 - 12,8)	12,4 (11,6 - 13,0)	0.040
Plt, × 10^9/L	238 (198 - 311)	226 (165 - 312)	240 (206 - 310)	0.154
Lym, × 10^9/L	1,71(1,0–2,56)	1,38(0,81–2,0)	1,98(1,1–2,74)	0.014
Neu, × 10^9/L	6,8 ± 1,56	7,26 ± 1,36	6,58 ± 1,61	0.036

Abbreviations: Cr, Creatinine; Na, Sodium; K, Potassium; Crp, C-Reactive Protein; Wbc, White Blood Cell; Hb, Hemoglobin; Plt, Platelet count; Lym, Lymphocyte; Neu, Neutrophil.

Table 2: Backward stepwise logistic regression analysis of variables associated with the severity of COVID-19

		95% C.I.		
Variable(s)	OR	Lower	Upper	P-value
Age	1.037	1.001	1.073	0.041
Heart disease	4.372	1.018	18.76	0.031
Crp/Albumin	1.773	1.053	2.985	0.031
Lymphocyte, × 10^9/L	0.541	0.319	0.918	0.023
Constant	0.058	----	----	0.024

Abbreviations: OR, odds ratio; CI, confidence interval. The backward selection model started with all candidate variables (sex, age, comorbidity, Crp/Albumin, Sodium, Hemoglobin, Lymphocyte, Neutrophil) in the model. At each step, the variable that is the least significant was removed. This process continued until no non-significant variables remain.)

seen to have the high capability in the diagnosis of disease severity (Figure 1). To determine the clinical and laboratory predictors of disease severity, backward stepwise logistic regression analysis was applied. A relationship with the severity of COVID-19 was determined with age (unadjusted OR = 1.04; 95% CI: 1.00, 1.07; p = 0.04), heart disease (unadjusted OR = 4.37; 95% CI: 1.02, 18.8; p= 0.03), CAR (unadjusted OR = 1.77; 95% CI: 1.05, 2.98; p = 0.03), lymphocyte count (unadjusted OR = 0.54; 95% CI: 0.32, 0.96; p = 0.02) Table 2.

DISCUSSION

In this study examining the relationship between the CRP/albumin ratio and COVID-19 disease severity, we found that patients with severe COVID-19 had higher CRP/albumin ratio than those with mild COVID-19. Further, we found that CRP/albumin ratio had a higher predictive potential for severe COVID-19 than CRP, lymphocytes, or neutrophils alone. To the best of our knowledge, this is the first study to have shown a correlation between CRP/albumin ratio and the severity of COVID-19.

Inflammation markers are a non-invasive, objective means of measuring inflammation and often disease activity/severity. Routine laboratory examinations have revealed a series of abnormalities in COVID-19 patients. In a meta-analysis of 19 observational studies encompassing approximately 3000 confirmed diagnosed COVID-19 cases, the laboratory characteristics most commonly associated with COVID-19 infection were low serum albumin (76% prevalence), high CRP (58%), high LDH (57%), and lymphopenia (43%) **[14]**. Lymphopenia, neutrophilia, high serum ALT and AST levels, and high LDH, CRP, and ferritin levels have been associated with greater disease severity in COVID-19 patients **[7, 8, 15, 16]**.

CRP is an acute-phase reactant synthesized from the liver in response to inflammation **[17]**. Studies have found that CRP levels may be used to determine the COVID-19 disease severity **[18-19]**. Consistent with these findings, we found that serum the CRP levels were significantly higher in the severe disease group. In contrast, albumin is a negative acute-phase reactant known to be affected by several factors such as nephrotic syndrome, cirrhosis of the liver, advanced heart failure, and inflammation **[20]**. Further, hypoalbuminemia has been associated with prolonged length of stay in hospital and complications **[11, 12, 21]**.

Studies have also found an inverse relationship between serum albumin levels and disease severity, findings consistent with our results **[15, 16, 22]**. Prior studies have shown that simultaneous consideration of serum levels of CRP and albumin may be a better predictor of the extent of inflammation and prognosis **[23-26]**. Using the CRP/albumin ratio in the ROC curve analysis, we show it to be a strong predictor of the severity of COVID-19 illness.

Our study has some potential limitations, primarily that it was a retrospective study and conducted at a single center. Another limitation was that the nutritional status of the patients was not evaluated and thus it is difficult to know if serum albumin levels were affected by chronic poor nutrition, inflammatory state, or both.

CONCLUSION

In conclusion, albumin and CRP were combined as a single index in this study as an inflammation-based prognostic score. A significant relationship was determined between the CRP/albumin ratio and disease activity and CRP/albumin ratio showed high specificity and positive predictive value in the prediction of severe COVID-19 cases. CRP/albumin ratio is a simple, easily calculated parameter, which can be used to determine severe clinical activity.

Figure 1. The receiver operating characteristic curve for CRP/albumin ratio in diagnosis of the severity of COVID-19

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