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Comparison of C-reactive protein and C-reactive protein-to-albumin ratio in predicting mortality among geriatric coronavirus disease 2019 patients

Rohat Ak[1]*, Fatih Doğanay[2], Erdal Yilmaz[1]

SUMMARY

OBJECTIVE: The aim of this study was to evaluate and compare C-reactive protein and C-reactive protein-to-albumin ratio performances in predicting mortality of geriatric patients who visited the emergency department.

METHODS: The data of patients with COVID-19 and aged 65 years and above, who visited emergency department during the study period, were retrospectively analyzed. The data were obtained from an electronic-based hospital information system. The area under the receiver operating characteristic curve and the area under the curve were used to assess each cutoff value discriminatory for predicting mortality.

RESULTS: The mean age of the population included in this study was 76 (71–82) years, while 52.7% were males. The sensitivity, specificity, and area under the curve values for C-reactive protein in terms of mortality were calculated as 71.01, 52.34, and 0.635%, respectively, while the sensitivity, specificity, and area under the curve values for C-reactive protein-to-albumin ratio were calculated as 75.74, 47.66, and 0.645%, respectively ($p<0.001$). In the pairwise comparison for the receiver operating characteristic curves of C-reactive protein and C-reactive protein-to-albumin ratio, no statistically significant difference was found.

CONCLUSIONS: Geriatric patients are the "most vulnerable" patient group against the COVID-19. In this study, both C-reactive protein and C-reactive protein-to-albumin ratio were found to be successful in predicting mortality for geriatric COVID-19 patients.

KEYWORDS: Albumins. COVID-19. C-reactive protein. Geriatrics. Mortality.

INTRODUCTION

It has been more than a year and a half since the first case was emerged in Wuhan (China), in December 2019[1]. The novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused an epidemic described as coronavirus disease 2019 (COVID-19)[2]. The spectrum of COVID-19 ranges from possibly asymptomatic patients to acute respiratory distress syndrome, which leads to severe progressive pneumonia and death[3,4].

There is obvious evidence that geriatric patients have a higher risk of mortality from COVID-19[5]. Elderly individuals are more susceptible to the outcomes of SARS-CoV-2 infection than younger people due to weaker immune systems, comorbidities, and the presence of underlying conditions[6,7]. Therefore, early identification of patients who will require critical care is vital for the geriatric patient population.

It has been understood that the C-reactive protein (CRP) level is associated with inflammation, and its concentration in the blood is not influenced by age, gender, or physical condition[8]. The CRP is a well-known index of serious pulmonary infections, and it has been reported to be positively correlated with severity in COVID-19 disease[9]. Albumin is an important component of serum proteins and is an indicator of systemic inflammation[10]. Low albumin is shown to have the poor nutritional status and liver and kidney dysfunction. It is further accepted as an independent indicator of poor survival in critically ill patients[11]. Low albumin levels in COVID-19 patients were found to be associated with a poor prognosis[12]. In a recent study, the ratio of these two inflammatory markers to each other was reported to be associated with mortality in CRP-to-albumin ratio (CAR) and COVID-19 patients[13].

The aim of this study was to examine the relationship between CAR and mortality at the time of admission in patients with COVID-19 who visited the emergency department (ED).

METHODS

This single-center, retrospective, and observational study was carried out in the ED of a tertiary care teaching hospital between

[1]Kartal Dr. Lütfi Kırdar City Hospital, Department of Emergency Medicine – Istanbul, Turkey.
[2]Edremit Public Hospital, Department of Emergency Medicine – Balıkesir, Turkey.
*Corresponding author: rohatakmd@gmail.com
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February 1, 2021, and April 1, 2021. The institutional review board approved the analysis and issued a waiver of consent (Ethics Committee ruling number: 2021/514/200/28, dated: April 28, 2021). During the two-month period assigned for this study, CRP and albumin tests were requested at the time of admission to the ED, and the patients who were aged 65 years and above and hospitalized were included in this study. The diagnosis of COVID-19 was determined according to the World Health Organization (WHO) guidelines. This study included only patients who had positive results in the reverse transcriptase polymerase chain reaction (RT-PCR) test of nasal and pharyngeal swab samples[14]. Patients with negative RT-PCR test results, patients with deficient CRP and/or albumin values, patients transferred from another hospital, patients who died or were discharged from the ED, and patients aged below 65 years were excluded from this study.

The following data were collected from each patient scanning the hospital-based electronic data recording system: age, gender, PCR test results, comorbidities [chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), hypertension (HT), diabetes mellitus (DM), congestive heart failure (CHF), atrial fibrillation (AF), chronic neurological disease (CND), and chronic renal failure (CRF)], and laboratory results [complete blood count (CBC), CRP, and albumin levels]. If an eligible patient was admitted more than once during the study period, only the most initial visit was included in the analysis. The most abnormal values were registered in patients who had more than one laboratory test in the ED. CAR (mg/g) values were calculated by dividing the CRP (mg/L) value by the albumin (g/L) value. The study data were registered into an Excel database (Microsoft Inc., Richmond, WA, USA) and analyzed by the first researcher. After data analysis, other researchers performed quality improvement feedback. The primary study outcome was the patient's mortality, and the survival follow-up was assessed 28 days after admission.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 26.0 and MedCalc Statistical Software version 19.0.6. The Mann-Whitney U test was used for continuous data analysis, and the chi-square test was used for categorical data analysis. The continuous data were reported as median and interquartile range (IQR). The categorical data were presented as frequency and percentage (Tables 1 and 2). A $p<0.05$ was considered statistically significant.

Receiver operating characteristic (ROC) analysis was performed using the DeLong method to evaluate the prognostic performance of CRP and CAR[15]. The area under the curve (AUC) was calculated to evaluate the prognostic performance of the CRP and CAR parameters. The Youden's J index (YJI) analysis was used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the threshold value at the highest AUC[16].

RESULTS

This study was conducted using data from a total of 404 patients, of which 191 were women and 213 were men. There were 235 patients in the survivor group and 169 patients in the nonsurvivor group. The median age of the population included in this study was 76 (71–82) years, with a minimum age of 65 and a maximum age of 102. The median age was 75 (70–81) years for the survivor group and 78 (72–84) years for the nonsurvivor group.

When the impacts of the chronic diseases on the COVID-19 prognosis were examined, a significant difference was found between the groups for DM, CHF, and CRF, while no significant difference was found between the groups for COPD, HT, CAD, AF, and CND (Table 1). When the impacts of laboratory parameters on the COVID-19 prognosis were analyzed, a significant difference was found between the groups for white blood cells (WBCs), neutrophils, lymphocytes, CRP, albumin, and CAR, while no significant difference was found between the groups for hemoglobin and platelets.

The predictive values of the CRP and the CAR in terms of in-hospital mortality were analyzed by ROC analysis. The sensitivity, specificity, PPV, NPV, AUC, and YJI values of the CRP were calculated as 71.01, 52.34, 51.7, 71.5, 0.635, and 0.23%, respectively ($p<0.001$), in terms of in-hospital mortality (Figure 1 and Table 2). The sensitivity, specificity, PPV, NPV, AUC, and YJI values of the CAR were calculated as 75.74, 47.66, 51.0, 73.2, 0.645, and 0.23%, respectively, in terms of in-hospital mortality.

When the ROC curves of the CRP and the CAR were compared, the difference between AUCs was calculated as 0.0104, and the p-value was 0.056. No statistically significant difference was found in the pairwise comparison of the ROC curves.

DISCUSSION

In this study, geriatric COVID-19 patients who were admitted to the ED were examined in two groups as survivor and nonsurvivor. It was concluded that the mortality group had significantly higher CAR and CRP values at the time of admission. However, no significant difference was found between CRP and CAR.

Depending on the increase in human life span, changes occur in many physiological systems of geriatric individuals. The immune system may be suppressed due to aging. This can further be defined by the reduction in T cells and T-cell receptors produced in the thymus. These changes increase the risk of infections and cause an increase in mortality rates of elderly individuals[17]. This weak situation that appears with aging has additionally shown its impact on the COVID-19 epidemic period. For instance, Italy had an overall mortality rate of 12.6% due to the epidemic. Furthermore, the mortality rate was found to increase significantly with age: it increased to <1% in patients below 50 years of age, 2.6% in the fifth decade, 9.8% in the sixth decade, 24.2% in the seventh decade, and 29.0% in the eighth decade[5].

The COVID-19 epidemic had a significant impact on geriatric individuals, and advanced age was reported to be an independent risk factor for the disease[18]. Therefore, early risk prediction tools in ED admissions of geriatric patients have been an important research topic in the literature. The inflammatory reaction plays a significant role in the pathophysiology of

Table 1. Demographic and comorbidity data of the study population.

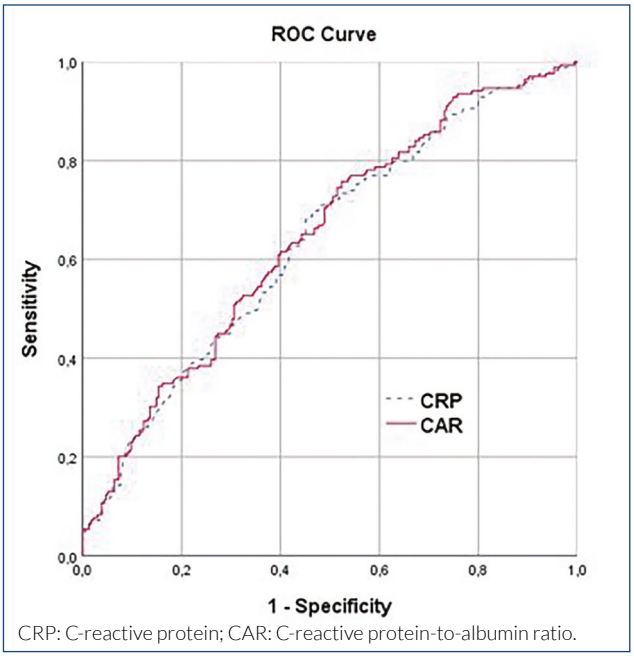
	Category	Survivor (n=235)		Nonsurvivor (n=169)		Total	Significance
		n	%	n	%	n	p-value
Gender	Female	124	64.9	67	35.1	191	0.009
	Male	111	52.1	102	47.9	213	
COPD	No	212	58.2	152	41.8	364	0.928
	Yes	23	57.5	17	42.5	40	
DM	No	152	54.3	128	45.7	280	0.017
	Yes	83	66.9	41	33.1	124	
HT	No	129	54.7	107	45.3	236	0.090
	Yes	106	63.1	62	36.9	168	
CHF	No	216	60.2	143	39.8	359	0.021
	Yes	19	42.2	26	57.8	45	
CAD	No	198	56.9	150	43.1	348	0.196
	Yes	37	66.1	19	33.9	56	
AF	No	229	58	166	42	395	0.740*
	Yes	6	66.7	3	33.3	9	
CRF	No	224	60.2	148	39.8	372	0.004
	Yes	11	34.4	21	65.6	32	
CND	No	230	58.1	166	41.9	396	>0.999*
	Yes	5	62.5	3	37.5	8	
		Survivor		Nonsurvivor		Total	
		Median	IQR	Median	IQR	Median	IQR
Age		75	70–81	78	72–84	76	71–82	0.002

COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HT: hypertension; CHF: congestive heart failure; CAD: coronary artery disease; AF: atrial fibrillation; CRF: chronic renal failure; CND: chronic neurological disease. *Fisher's exact test.

Table 2. Predictive performance of C-reactive protein and C-reactive protein-to-albumin ratio in terms of severity in COVID-19 patients.

	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	AUC (95%CI)	YJI (95%CI)	Criterion of YJI	p-value*
CAR	75.74 (68.6–82.0)	47.66 (41.1–54.3)	51.0 (47.3–54.7)	73.2 (67.0–78.6)	0.645 (0.596–0.692)	0.23 (0.14–0.31)	>1.54	<0.001
CRP (mg/L)	71.01 (63.5–77.7)	52.34 (45.7–58.9)	51.7 (47.6–55.8)	71.5 (65.8–76.6)	0.635 (0.586–0.682)	0.23 (0.14–0.32)	>62.3	<0.001

CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; YJI: Youden's J index; CAR: C-reactive protein-to-albumin ratio; CRP: C-reactive protein. *In the pairwise comparison of the Receiver operating characteristic curves of C-reactive protein and C-reactive protein-to-albumin ratio, p=0.056.



CRP: C-reactive protein; CAR: C-reactive protein-to-albumin ratio.

Figure 1. Receiver operating characteristic curves of C-reactive protein and C-reactive protein-to-albumin ratio for mortality prediction in COVID-19 patients.

COVID-19[19]. Therefore, inflammatory markers such as CRP have been studied as prognostic indicators of COVID-19[20]. It has been shown that albumin, which is expected to decrease in inflammatory conditions, also decreases in severe COVID-19 patients[21]. El-Shabrawy et al. examined the importance of biomarkers in predicting the prognosis of COVID-19 in their study. In this study, a total of 116 patients were studied in two groups as severe and nonsevere, and it was concluded that a high CAR value could be used as an independent marker during the prediction of 30-day mortality in COVID-19 patients[13]. In the light of this information, the results of our study were found to be in line with the literature.

In this study, the relationship between patients' comorbidities and their mortality was also examined. A significant correlation was found among DM, CHF, CRF, and mortality. These outcomes are not unexpected. One of the most common comorbidities in geriatric individuals with COVID-19 infection is DM[22]. In a meta-analysis, the prevalence of diabetes in hospitalized patients was 9.7%. In a large-scale worldwide observational study including 169 hospitals and approximately 9000 patients from three continents, CHF was found to be an independent predictor of in-hospital mortality[23]. The mortality rate associated with pneumonia in patients with CRF appears to be 14–16 times higher than that in the general population[24]. In a meta-analysis including 1389 COVID-19 patients, a significant association was found between the CRF and severe COVID-19[25].

As with any retrospective study, this study has some limitations. First, our sample size was small, thus limiting the potential of our analysis. In addition, we conducted the study at a single institution; therefore, the findings may not be representative of the general population of COVID-19 patients aged ≥65 years. Conclusively, the study focused on patient mortality. Accordingly, we cannot predict other related outcomes for the geriatric population, such as patients' persistent oxygen demand or requirement for transfer to a care center.

CONCLUSIONS

Geriatric patients are the patient group with the highest risk of poor outcome for COVID-19. This study demonstrated that the CRP and CAR geriatric patient population had good predictive performance in predicting mortality.

AUTHOR CONTRIBUTIONS

EY: Conceptualization, Data curation, Supervision. **FD:** Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. **RA:** Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing.

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