Research Article (Araştırma Makalesi)

Clinical Significance of CRP/Albumin Value on Hospitalization and Length of Hospital Stay of Patients with Coronavirus-19: A Prospective Study

CRP/Albumin Değerinin Koronavirüs-19 Hastalarının Hastanede Yatış Süresi ve Hastanede Kalış Süresi Üzerindeki Klinik Önemi: Prospektif Çalışma Çalışma

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Özet

Amaç: İlk tanısı acil servis te yapılan Koronavirüs 2019 (COVID-19) hastalarda C- reaktif protein/albümin oranının (CAR) tanısal ve prognostik önemini araştırması.

Gereç ve Yöntemler: Burada sunduğumuz çalışma, tek merkezli, ileriye dönük gözlemsel bir çalışmadır. Çalışmaya toplam 745 katılımcı (385 hasta, 360 kişi) dâhil edildi. CAR, C-reaktif protein (CRP; mg/L) değerinin albümin değerine (gr) bölünmesiyle hesaplandı. Veriler MedCalc İstatistik Yazılımı v12.7.0.0 (Oostende, Belçika) ve Student t testi, ki kare testi ve Pearson korelasyon katsayısı kullanılarak analiz edildi. p<0.05 değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Toplam 355 hasta yatarak tedavi edildi ve bunların 30'u ayaktan takip edildi. Hastanede yatan hastaların ve ayaktan hastaların ortalama CAR değerleri sırasıyla 0.34±0.89 ve 0.39±0.72 idi (%95 güven aralığı [GA]: -0.31 ila 0.40; p = 0.796). 309 hasta koğuşlarda, 46 hasta ise yoğun bakım ünitelerinde tedavi edilirken; ortalama CAR değerleri sırasıyla 0.33±0.92 ve 0.44±0.74 idi (%95 GA: -0.17 ila 0.39; p=0.449). CAR değeri arttıkça hastanede kalış süresi de arttı (p< 0,0001). COVID-19 teşhisi için en iyi kesme noktasında CAR'ın %82.66 özgüllük, %69.72 duyarlılık, 4.02 pozitif olasılık ve 0.37 negatif olasılığa sahip olduğu gösterildi.

Sonuç: Çalışmadaki COVID-19 hastalarının hastanede kalış süresi, ilk acil servise başvuru anında tespit edilen CAR değerleri ile yakından ilişkiliydi.

Anahtar kelimeler: C-reaktif protein-albümin oranı, İlk başvuru, Hastanede kalış süresi, Koronavirüs hastalığı

Abstract

Objective: To investigate the diagnostic and prognostic significance of the C-reactive protein-to-albumin ratio (CAR) in coronavirus disease 2019 (COVID-19) patients admitted for the first time to a hospital emergency department (ED).

Materials and methods: The study we report herein was a single-center, prospective observational study. A total of 745 participants (385 patients, 360 individuals) were included in the study. The CAR was calculated by dividing the C-reactive protein (CRP; mg/L) value by the albumin value (gr). The data were analyzed using MedCalc Statistical Software v12.7.0.0 (Ostend, Belgium) and Student's t-test, chi square test, and Pearson's correlation coefficient. A p-value of <0.05was considered statistically significant.

Results: A total of 355 patients were hospitalized, and 30 of them were followed as outpatients. The mean CAR values of the hospitalized patients and the outpatients were 0.34±0.89 and 0.39±0.72 respectively (95% confidence interval [CI]: -0.31 to 0.40; p=0.796). A 309 patients were hospitalized in wards and 46, in intensive care units; their mean CAR values were 0.33±0.92 and 0.44±0.74, respectively (95% CI: -0.17 to 0.39; p=0.449). As the CAR value increased, the length of hospital stay also increased (p<0.0001). At the best cut-off point for COVID-19 diagnosis, CAR was shown to have 82.66% specificity, 69.72% sensitivity, 4.02 positive likelihood, and 0.37 negative likelihood.

Conclusion: The length of stay in the hospital of the COVID-19 patients in the study was closely related to their CAR values obtained at the time of their first ED admission.

Keywords: Coronavirus disease, C reactive protein to albumin ratio, First admission, Length of stay in the hospital

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INTRODUCTION

CRP is an inflammatory peptide, increasing quickly early stage of the occurrence of infectious diseases and inflammation. The albumin is known as a negative acute inflammatory marker of inflammation and infectious diseases, which opposite correlation with inflammation severity. Nowadays a new inflammatory marker was introduced which is calculated by dividing CRP to albumin, and was claimed to be a predictor parameter of inflammation severity, adverse events, and mortality. A number of previous studies have speculated that an increased CAR value is a powerful predictor of a worst clinic conditions, especially in cancer patients, cardiovascular disease, and other medical illnesses which, has been reported that CAR is more sensitive and specific tool for measuring the systemic inflammation (1-5).

The COVID-19 related pandemic goes on to be a challenge on the health care systems of countries across the world, and the number of affected patients and death rates continue to rise day by day. In many cases, the COVID-19 disease is mild, but in some cases, the clinical picture is moderate or severe, and it can quickly result in acute respiratory failure, sepsis-septic shock, multiple organ failure, disseminated intravascular coagulopathy and ultimately death. Older people are frail and more vulnerable to pneumonia, respiratory dysfunction or various complications related to severe COVID-19 (6,7).

One of the main difficulties for ED physicians is how to quickly identify COVID-19 patients at high risk for worse outcomes and triage for hospitalization (8). Hence, identifying diagnostic and prognostic biomarkers and initiating an appropriate treatment regimen by making an early diagnosis of the cases that are likely to progress to severe or life-threatening forms are vitally important in terms of saving lives and reducing treatment costs. Thus, in the current study, we comprehensively investigated whether there are relationships between severity of illnesses, hospitalization, hospital stay, and CAR values in patients with first admission to the ED and first diagnosed with COVID-19 therein.

MATERIALS AND METHODS

This study is a prospective single center, observational scientific work which carried out over a 3-month period (April 1–June 30, 2020) in pandemic hospital ED of a tertiary care in southeast Turkey that is a referral center. This work was approved by the ethics committee of Turkish Ministry of Health care and Adiyaman University ethical committee (Approval No. 2020/6-42). From all the study participants written informed consent was obtained.

A total of 745 participants (385 patients, 360 control individuals) were collected in the study. The participants were selected among the patients who admitted to our hospital ED for the first time and diagnosed with COVID-19 on the basis of the World Health Organization and the Turkey Ministry of Health COVID-19 Commission Interim Guidance were accepted in the study scope. The control group was composed of the individuals who have non-infectious and non-inflammatory disease and visiting emergency department in the same study period days. The participants who had diseases with high CRP levels such as malignancies rheumatic diseases, other concomitant infections, applied for trauma, were referred to our hospital from another hospital for COVID-19 treatment, had missing data in their medical records and patient charts, were returning to the ED on the same day, refused diagnosis and treatment, and did not want to join the study were excluded from the study scope (**Figure 1**).

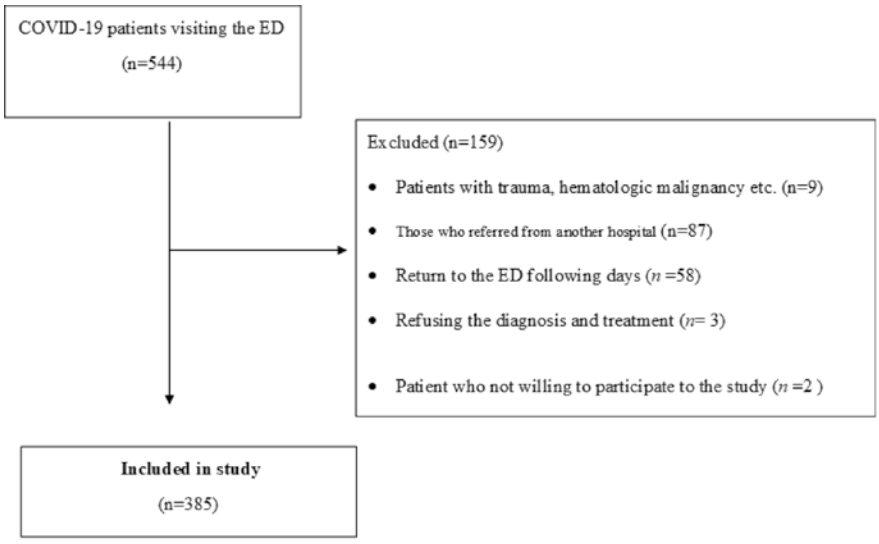

Figure 1. Patient flow diagram (n: number of patients, ED: emergency department)

Data were collected for the study by emergency medicine residents and attending physicians. The diagnoses were confirmed via patient history, physical examination, computerized tomography, and nasal and pharyngeal swab samples assay with real-time reverse transcriptase polymerase chain reaction of coronavirus.

Blood samples were obtained from all the participants to analyze their serum albumin and CRP levels at the time of their initial first acceptance to the ED COVID-19 facility. Taking into account each participant's blood value measured upon his/her admission to the hospital ED, the CAR value was calculated by dividing the CRP (mg/L) value by the albumin (gr) value. The CRP assay was measured using the nephelometric technique (normal range: 0-0.8 mg/dL). The serum albumin analyzed by automatic photometry commercial kits (Abbott C8000i; Abbott Park, Illinois), (normal range: 3.5-5 gr/dL).

Statistical Analysis

This study's results were analyzed using MedCalc Statistical Software v12.7.0.0 (Ostend, Belgium). Continuous data with a normal distribution were shown as mean and standard deviation (SD) while categorical data were shown as frequency and percentage. To compare the means and to analyze the differences between study groups Student's t-test was performed. To analyze categorical data chi-square test were used. The relationship between length of hospital stays and CAR was tested using Pearson's correlation coefficient. To evaluate the diagnostic performances of the albumin, CRP, and CAR continuous variables, the receiver operating characteristic (ROC) was performed, and the positive and negative likelihood values at the best cut-off point for each variable were calculated. Each independent variable was presented using a 95% confidence interval (CI), and a P value of <0.05 was considered statistically significant.

RESULTS

The study population was composed of 385 patients (210 men, 175 women) and a control group consisting of 360 controls (178 men, 182 women). The median ages of the patients and controls were 51.28 and 46.92 years, respectively, which were statistically significant (p=0.003). There were no statistically significant differences between the groups according to gender and co-morbidities, but there were statistically significant differences according to age (p=0.003), immune and allergic condition (p=0.003), and other diseases (p=0.0001) (**Table 1**).

Table 1. Characteristics of the patient and control groups

	Total	Patients n=385	Controls n=360	p*
Age. years (SD)		51.28 (19.26)	46.92 (19.92)	0.003**
Gender (%)				
Female	357 (47.9)	175 (45.5)	182 (50.6)	0.16
Male	388 (52.1)	210 (54.1)	178 (45.9)	
Comorbidity n (%)				
Diabetes Mellitus	89 (12.2)	48 (13.1)	41(11.4)	0.50
Hypertension	141 (19.3)	66 (17.8)	75 (20.8)	0.31
Coronary artery disease	144 (19.8)	70 (19.6)	74 (20.6)	0.59
Congestive heart failure	22 (3.0)	13 (3.5)	9 (2.5)	0.42
Chronic obstructive pulmonary disease	58 (7.9)	35 (9.5)	23 (6.4)	0.13
Cancer	7 (1.0)	3 (0.8)	4 (1.1)	0.77
Hyperlipidemia	32 (4.4)	20 (5.4)	12 (3.3)	0.18
Chronic renal failure	11 (1.5)	5 (1.3)	6 (1.7)	0.72
Stroke	14 (1.9)	3 (0.8)	11 (3.1)	0.03
Neurodegenerative and Neurological Disorders	27 (3.7)	7 (1.9)	20 (5.6)	0.01
Thyroid diseases	18 (2.5)	6 (1.6)	12 (3.3)	0.13
Immune and Allergic Condition	54 (7.4)	17 (4.6)	37 (10.3)	0.003
Psychiatric Disorder	23 (6.4)	23 (6.4)	0	>0.05
Gastrointestinal Tract Disease	68 (18.9)	68 (18.9)	0	>0.05
Other	200 (27.4)	128 (34.7)	72 (20.0)	0.0001

*Chi-square test, ** Student t test

The patients' and controls' mean albumin levels and the mean total albumin level were 3.78±0.66, 4.34±1.90, and 4.05±1.43, respectively, which were all statistically significant (95% CI: 0.36–0.76; p<0.0001). The patients' and controls' mean CRP levels and the mean total CRP level were 3.67±5.02, 0.95±2.06, and 2.33±4.09, respectively, which were also all statistically significant (95% CI: -3.28 to -2.16; p<0.0001). The mean total CAR value was 0.68±1.31, and the patients' and controls' mean CAR values were 1.11±1.64 and 0.25±0.61, respectively. There was a statistically significant difference between the patients and the controls in terms of mean CAR value (95% CI: -1.04 to -0.68; p < 0.0001) (**Table 2**).

Of all the patients, 355 were hospitalized for COVID 19 pneumonia, and 30 were treated as outpatients. The inpatients and outpatients' mean CAR values were 0.34±0.89 and 0.39±0.72, respectively. There was no statistical difference between the inpatients and outpatients in terms of the mean CAR value (95% CI: -0.31 to 0.40; p=0.796). The mean CAR values of the patients who were admitted to a hospital room (n=309) and of the patients who were admitted to the intensive care unit (ICU) (n=46) were 0.33±0.92 and 0.44±0.74, respectively. There was no statistically significant difference between the patients admitted to the wards and those admitted to the ICU in terms of the mean CAR value (95% CI: -0.17 to 0.39; p=0.449) (**Table 3**). As the CAR value increased, the length of stay in hospital also increased, but they had a weak correlation (r: 0.3000; 95% CI: 0.18–0.41; p<0.0001) (**Figure 2**).

The best cut-off points (optimal cut-off) for distinguishing the two groups were 4.09, 0.32, and 0.09 for the albumin level, CRP level, and CAR value, respectively. At the best cut-off point for COVID-19 diagnosis, albumin had 55.6% specificity, 60.69% sensitivity, a 2.5 positive likelihood value, and a 0.53 negative likelihood value; CRP had 88.2% specificity, 64.4% sensitivity, a 5.5 positive likelihood value, and a 0.40 negative likelihood value; and CAR had 82.7% specificity, 69.7% sensitivity, a 4.02 positive likelihood value, and a 0.37 negative likelihood value (**Table 4, Figure 3**).

DISCUSSION

The study findings showed that the COVID-19 patients' mean CAR value was higher than the controls', and as CAR value increased, length of hospital stay also increased. Additionally, CAR had 82.7% specificity and 69.7% sensitivity for COVID-19 diagnosis. COVID-19 pandemic outbreaks rapidly across the globe, and infected large numbers of individual. Although there have been many publications on it, many of these are conflicting, and various clinical aspects of the disease remain unclear needing to explanation. The findings of this study will enable the early recognition of high-risk patients requiring timely initiation of more appropriate management protocols and specific treatments, which can save lives and lessen the cost of medical treatment (9,10).

Table 2. Patients, controls and total mean albumin levels

	Patients	Controls	Total	95% CI	p value*
Albumin . mean ±SD (gram/dL)	3.78±0.66	4.34±1.90	4.05 ±1.43	0.36 to 0.76	< 0.0001
CRP. mean±SD	3.67 ±5.02	0.95 ±2.06	2.33±4.09	-3.28 to -2.16	< 0.0001
CRP to Albumin ratio±SD	1.11± 1.64	0.25± 0.61	0.68±1.31	-1.04 to -0.68	< 0.0001

*Student T test,

Abbreviations: SD; standard deviation, CRP: C-Reactive Protein

Table 3. Participants CAR values

	CAR value±SD	95% CI	p value
Patients	1.11± 1.64	-1.04 to -0.68	< 0.0001
Controls	0.25± 0.61		
Inpatients	0.34± 0.89	-0.31 to 0.40	0.796
Outpatients	0.39± 0.72		
Hospital room	0.33± 0.92	-0.17 to 0.39	0.449
Intensive care unit	0.44±0.74		
Total	0.68±1.31		

Abbreviations: CAR; C-reactive protein to albumin ratio, SD; standard deviation

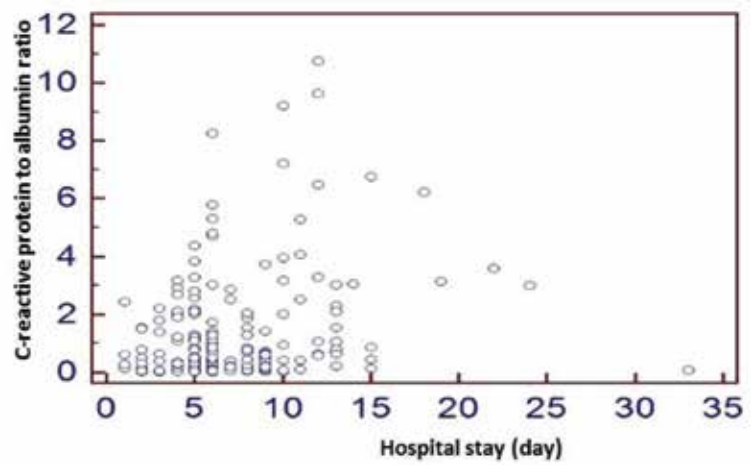

Figure 2. Relationships between CAR and hospital stay (day)

Table 4. Areas under curve (AUC) of Albumin, CRP and CAR

Test result Variables	AUC	Std. Error	p value	Asymptotic 95% Confidence Interval	
				Lower bound	Upper Bound
Albumin	0.722	0.0186	<0.0001	0.688	0.754
CRP	0.789	0.0171	<0.0001	0.756	0.823
CAR	0.805	0.0165	<0.0001	0.773	0.838

Abbreviations: AUC; Areas under curve, CRP: C-reactive protein, CAR: C-reactive protein to albumin ratio, Std.; standardized

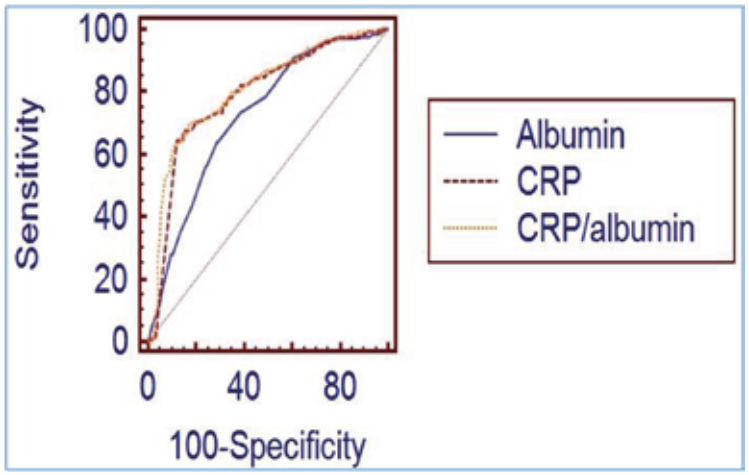

Figure 3. ROC curve graph for CRP and CRP to Albumin ratio

Serum albumin has been known as a non-specific biomarker of diseases which is inversely correlated severity and poor outcome, in the literatures. It is mainly produced in the liver, and can be negatively affected by many acute and chronic diseases due to the magnitude of the inflammatory response rather than nutritional intake. Some authors have reported that early identification of the serum albumin and CRP levels during hospitalization may help in the risk grading of patients, in which hypoalbuminemia is associated with the development of a poor prognosis and potential life-threatening adverse effects such as pneumonia, septic shock, acute cardiac insufficiency, acute respiratory insufficiency, and acute renal failure. It has also declared by some authors that many older patients have coexisting poor conditions and outcomes (1,11-17). In our study, the patients' mean albumin level was 3.78 ± 0.66, significantly lower than the controls' (4.34 ± 1.90), which is compatible with the data in the literature (**Table 2**).

CRP is commonly used in clinical situations and mediated by pro-inflammatory cytokines, especially IL-6 (9,10,18). The presence of a systemic inflammatory status, which is produced and secreted by the hepatocytes to the systemic blood circulation, promotes the host's defense system. CRP is also a well-known inflammatory mediator of severe pneumonia and has been speculated to be directly correlated with disease severity of COVID-19 patients (7,11). It has been reported that serum CRP allows good discrimination among intense resistant, non-intense, and mild COVID-19 infections. Accordingly, in many studies, CRP was found to be close correlation with morbidity and mortality with COVID-19 patients. Similarly, our data suggested that the COVID-19 patients' mean serum CRP level was higher than the controls', which is concordant with previous publications (19-21). Additionally, a meta-analysis declared that, while the serum CRP levels of severe COVID-19 infected patients increase the serum albumin levels decreased which this finding correlated our study results (11).

Combining albumin and CRP in an index for various disease conditions has previously been explored. Recently, CAR has been outlined as a new useful indicator of disease intensity in cancer and hypertension sepsis, major cardiovascular events, and several other medical conditions. In some recent studies, CAR was demonstrated to be an independent early predictor of disease prognosis in hospitalized COVID-19 patients (4,10,22). Karakoyun et al. reported that CAR is a helpful marker for early determination of disease severity in hospitalized COVID-19 patients with higher length of hospital stays and mortality rates (4,10). Wang et al. argued that a high CAR value may be an early warning sign of COVID-19 severity (20). Xue et al. speculated that CAR is a novel systemic inflammatory marker for COVID-19 severity (23). Our findings suggest that there is a significant difference between the patients' and controls' mean CAR values with the patients' values higher than the controls', and that while the CAR value increased, the length of hospital stay also increased, similar to the above authors' findings (**Table 3**). We also found, after performing ROC curve analysis for COVID-19 diagnosis, that CAR had higher sensitivity but lower specificity (69.7% and 82.7%, respectively) than the CRP and albumin levels separately (**Table 4, Figure 3**).

The determination of potential predictive biomarkers may help physicians in the based-on evidence diagnosis and treatment of COVID-19, especially in critical medical facilities, such as the ED and ICU, which may affect the management and prognosis of such patients. CAR is a cost-effective, and easy-to-calculate marker for indicating whether a COVID-19 patient with a high morbidity risk admitted to the ED or another critical care facility needs to be hospitalized or can be discharged without a need for further examinations (2,21).

Our findings also suggest that there are no differences in the CAR values of outpatients, inpatients, and ICU admissions from the ED, but as these values increase, the length of hospital stay also increases, which, this may warn clinicians of poor clinical outcomes and possible impending COVID-19 complications, as mentioned above (**Figure 2**). We think that the absence of a statistically significant difference in CAR values in outpatients and inpatients is due to the fact that clinicians who made the initial hospitalization decision kept the hospitalization indications wide and flexible. Earlier identification of the potentially risky patients via the CAR value and maintaining efficient treatment might be crucial for rapid recovery from COVID-19 and might be cost-effective in the early grades of the disease.

Our work has some limitations. First, sample size was limited. Second, as the research was proceeded in a one center COVID-19 referral institution, its results are not generalizable, and it is not a parameter that guides treatment options or determines hospitalization or discharge. Third, because the study was conducted in the ED, the patients' final outcomes were not followed up, and it is not known whether the patients were redistributed to other facilities, such as wards or ICUs.

In conclusion, CAR is a considerably efficient tool for predicting the length of stay in hospital of patients in first ever admission to a COVID-19 unit. A high CAR value might be an early sign of the need to initiate a more effective treatment strategy, but it was found not to have a direct correlation to the prediction of outpatient follow-up, hospitalization, or ICU admission from the ED. There is a need for comprehensive, prospective studies with large patient number to confirm results of study.

Conflict of Interests: None

Funding Statement: No financial funding was needed to conduct this study.

Ethical statements: The study was approved by the ethics committee of Turkish Ministry of Health care and Adiyaman University ethical committee (Approval No. 2020/6-42). All the participants read and signature their informed consent to the collection of their clinical and laboratory test results.

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