

# A New Mortality Predictor in Patients of Internal Medicine Intensive Care Unit: C-Reactive Protein-to-Albumin Ratio

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## ABSTRACT

**Aims:** C-reactive protein (CRP) and albumin can be used as prognostic markers for various clinical results, the combination of these markers has even greater prognostic value. This study aimed to examine whether the C-reactive protein-to-albumin ratio (CAR) has any prognostic role in respect of mortality in intensive care unit (ICU) patients.

**Methods:** A retrospective evaluation was made of 119 patients in the ICU in respect of demographic characteristics, disease diagnosis, laboratory data, CAR, and acute physiology and chronic health evaluation II (APACHE II) scores.

**Results:** The mean APACHE II scores and the total length of stay in hospital values were significantly higher, albumin was low and the mean CRP and CAR values were high in the non-survivors group. In the multivariate analysis, CAR, and APACHE II were determined as independent determinants. The Kaplan-Meier curve and the Log-Rank test showed that total 60-day mortality was higher in the patient group with high CAR. In the ROC curve analysis applied for 60-day mortality after admission to ICU, the area under the curve values of APACHE II and CAR were calculated as 0.947 and 0.676 respectively.

**Conclusion:** Few studies are available in the literature about the CAR value in general ICU patients was evaluated in respect of mortality. It was determined that increased CAR values were associated with mortality. This can be considered an important parameter as the predictive rates of mortality are as high as those of APACHE II, and it is a low-cost and readily available parameter that can be used alone in the determination of mortality prediction.

**Key words:** Albumin, C-reactive protein, C-reactive protein-to-albumin ratio, mortality, critical care

## Introduction

Risk management in respect of prognosis stratification is of vital importance for the Intensive Care Unit (ICU) patients. Thus, the appropriate medical treatment can be initiated without any loss of time by providing rational use of limited ICU resources. Therefore, research into new biomarkers or a model that could provide information about the prognosis of ICU patients has become a focus of interest for clinicians.

Previous studies have reported that many risk factors affect mortality in ICU. These include a high APACHE II score (Acute Physiology and Chronic Health Evaluation) and complications such as respiratory failure requiring mechanical ventilation, decompensated heart failure, pneumonia, acute renal failure, sepsis, disseminated intravascular coagulation and massive hemorrhage (1, 2). It is thought that the risk factors for mortality in medical ICU are not limited to the above-

mentioned factors. C-reactive protein (CRP) and albumin are widely used as serum inflammatory markers for the prediction of mortality in critically ill patients (3). The prognostic roles of CRP and albumin can be explained by situations reflecting acute phase inflammation in critical environments and insufficient nutrition in critical patients (4-6).

To date, few studies have been conducted on the CRP-to-albumin rate (CAR). It was thought that this could be used as a predictive marker for mortality in ICU patients as seen in other diseases based on these characteristics. This study aimed to evaluate the use of this ratio as an independent predictor of mortality in internal medicine ICU patients.

## Material and Method

Approval for the study was granted by the Local Ethics Committee. A retrospective examination was made of patients in the Internal Medicine ICU

in our hospital between 2017 and 2018. Exclusion criteria were an absence of laboratory and/or clinical data, the presence of active or chronic inflammation, autoimmune diseases, rheumatological diseases, malignancy, recent blood transfusion, liver failure, or proven sepsis. Nutritional status did not use for exclusion criteria. A total of 290 patients were reviewed and exclusion criteria were applied to 171, leaving a total of 119 patients for inclusion in the study. The biochemical and hematological laboratory test results data and the clinical results of the patients were obtained from the patient records of the hospital database.

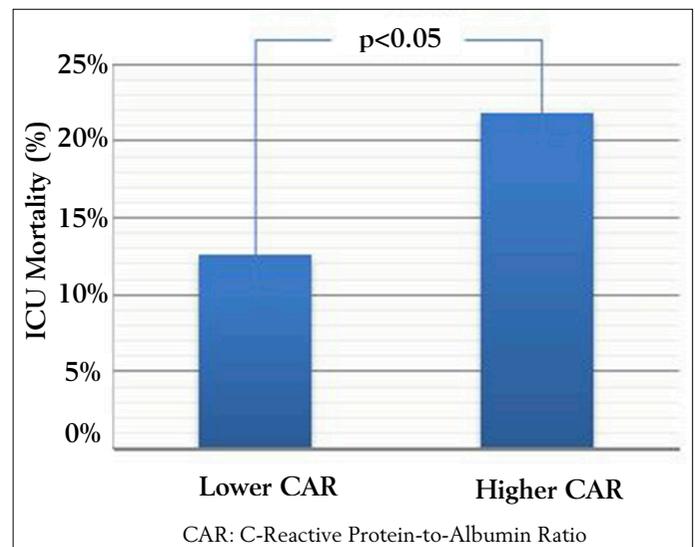
### Statistical Analysis

Statistical analyses of the data obtained in the study were made using statistical package for social sciences (SPSS) version 22.0 software. Continuous variables were stated as mean  $\pm$  standard deviation (SD), and categorical variables as number (n) and percentage (%). The patients were separated into 2 groups of survivors and non-survivors. Comparisons of continuous variables between the groups were made using the Student's t-test or the Mann-Whitney U-test according to the conformity of the data to normal distribution. The groups were compared in respect of categorical variables using the Chi-square test or Fisher's Exact test. Correlation coefficients of numerical variables that did not conform to at least one normal distribution measurement were calculated with the Pearson test and statistical significance with the Spearman test.

The two groups were categorized on the basis of the 50th percentile of CAR. A Kaplan-Meier survival curve was formed between low and high CAR patients by applying the Log-Rank test. To determine independent predictive variables of long-term total mortality, forward stepwise multivariate Cox regression analysis was applied by adding all the variables determined as  $p < 0.1$  in the univariate analysis, and the results were presented including the hazard ratio (HR) and confidence interval (CI). The cutoff values of independent significant predictors were analyzed with a Receiver Operating Characteristic (ROC) curve, and the area under the curve (AUC) was evaluated with the Hanley and McNeil method. A value of  $p < 0.05$  was accepted as statistically significant.

### Results

The study included 119 patients, comprising 68 (57.1%) males and 51 (42.9%) females with a mean age of  $59.6 \pm 16.6$  years. The survivor's group included 78 patients, and non-survivors, 41 patients. The mortality rate was determined as 34.45%. The basal demographic, clinical, and laboratory data of both groups are shown in Table 1. No significant difference was determined between the groups in respect of age, gender, and diagnosis ( $p > 0.05$ ). The APACHE II scores and mean total length of stay in hospital (TLSH) values were higher in the non-survivors group ( $p < 0.001$ ). According to the laboratory parameters, albumin (g/dL) was significantly low ( $p < 0.05$ ) and the mean CRP and CAR values were significantly high ( $p < 0.05$ ) in the non-survivors group. The Hb and WBC levels were similar in both groups ( $p > 0.05$ ). In the comparison of mortality in the hospital within 60 days of admission, the number of patients with mortality was found to be significantly greater in the group with a high CAR value (n:26, 21.8% vs. n:15, 12.6%) ( $p < 0.05$ ) (Figure 1). In the correlation

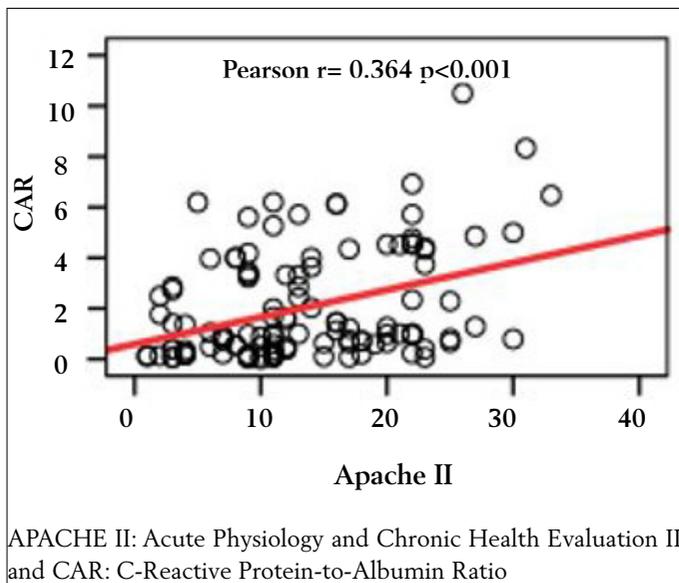


**Figure 1.** Comparisons of ICU mortality rate among patients with different CAR groups

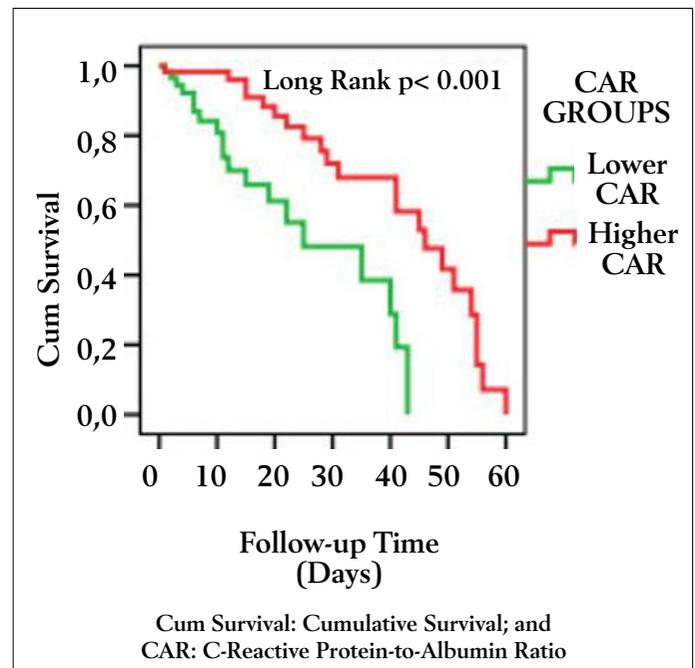
**Table 1.** Baseline Characteristics of Patients According to mortality status.

Variables Total	Survivors (n=78)	Non-Survivors (n=41)	p
Sex (male, %)	42(35.3%)	26(21.8%)	0.210
Age (years)	64(18-75)	68(18-80)	0.05
APACHE II	9(1-18)	22(10-33)	<0.001
Principal diagnosis (n, %)			0.075
Neurological disease	15(12.6%)	14(11.8%)	
Pulmonary disease	28(23.5)	13 (10.9%)	
Digestive disease	21(17.6)	4(3.4)	
Renal insufficiency	14(11.8)	10(8.4)	
TLSH(Days)	8,5(1-52)	22(1-60)	<0.001
Hemoglobin (g/dL)	12.32(2.47)	12.63(2.35)	0.657
WBC ( $\times 10^3 / \mu\text{l}$ )	11.7(4.2-26,0)	12.3(3.9-27.9)	0.586
CRP (mg/L)	2.4(0.02-31)	5.3(0.2-21)	0.048
Albumin (g/L)	3.2(1.5-5)	2.4(1.5-4.5)	<0.001
CAR	0.88(0.001-6)	1.28(0.001-11)	0.005

APACHE II score: Acute Physiology and Chronic Health Evaluation II score, WBC: White Blood Cell, CRP: C-Reactive Protein, CAR: C-Reactive Protein to Albumin Ratio, TLSH: total length of stay in the hospital, n: number



**Figure 2.** The relationship between CAR and APACHE II score.



**Figure 3.** Performance of CAR groups in predicting mortality.

**Table 2.** Univariate hazard ratios of variables for predicting ICU mortality and independent predictors of ICU mortality by multivariate cox regression analysis.

Variables	Univariate hazard ratios			Multivariate hazard ratios		
	HR	95% CI	p	HR	95% CI	p
Male	0.794	0.416-1.516	0.484			
Age (years)	0.968	0.976-1.022	0.938			
CAR	3.384	1.635-7.04	<0.001	3.444	1.052-11.273	0.041
APACHE II	1.069	1.023-1.116	0.003	1.110	1.049-1.176	<0.001
Hemoglobin (g/dL)	1.015	0.888-1.159	0.829			
WBC ( $\times 10^3 /\mu\text{l}$ )	0.984	0.925-1.047	0.614			
CRP (mg/L)	0.916	0.856-0.981	0.012			
Albumin (g/L)	0.687	0.477-0.990	0.044			
Principal diagnosis						
Pulmonary disease	1	-	-			
Neurological disease	0.683	0.305-1.530	0.355			
Digestive disease	0.543	0.175-1.678	0.289			
Renal insufficiency	0.784	0.334-1.838	0.575			

APACHE II score: Acute Physiology and Chronic Health Evaluation II score, WBC: White Blood Cell, CRP: C-Reactive Protein, CAR: C-Reactive Protein-to-Albumin Ratio

**Table 3.** Performance of variables in predicting mortality.

Variables	AUC ROC	value	Cutoff value	Sensitivity (%)	Specificity (%)
APACHE II score	0.947 $\pm$ 0.022	<0.001	$\geq 14.5$	85.4	83.3
CAR	0.656 $\pm$ 0.052	0.005	$\geq 0.97$	65.9	54.8

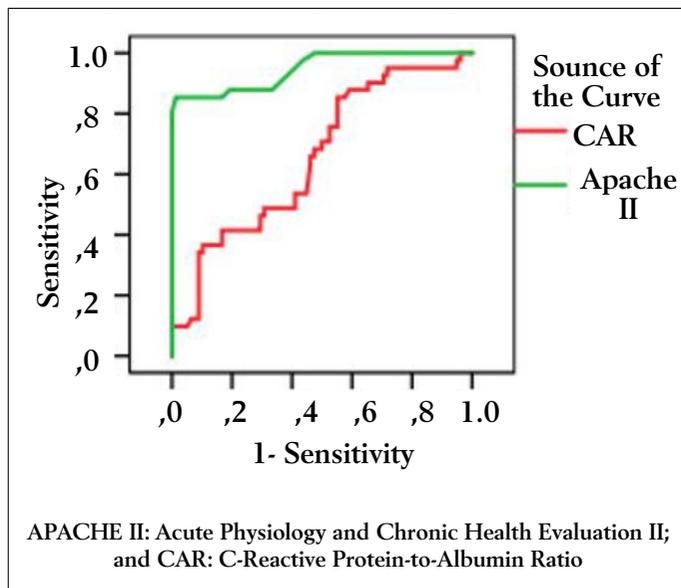
AUC ROC: area under the receiver operating characteristic curve; APACHE II: Acute Physiology and Chronic Health Evaluation II; and CAR: C-Reactive Protein-to-Albumin Ratio

analysis, a significant positive linear relationship was determined between CAR levels and APACHE II scores (Pearson  $r=0.839$ ,  $p<0.001$ ) (Figure 2).

The results of the univariate-multivariate Cox regression analysis applied to show predictive factors in respect of mortality are shown in Table 2. In the multivariate analysis, CAR (HR: 0.293 CI:

0.134-0.639  $p=0.002$ ), and APACHE II (HR: 1.074; CI: 1.027-1.123;  $p=0.002$ ) were determined as significant independent determinants after correction of the other variables.

The Kaplan-Meier curve and the Log-Rank test showed that total 60-day mortality was higher in the patient group with high CAR ( $p=0.018$ ) (Figure 3).



**Figure 4.** ROC curve with Area Under the Curve for APACHE II score, and CAR predicting ICU mortality for 60 days

In the ROC curve analysis applied for 60-day mortality after admission to ICU, the AUC values of APACHE II and CAR were calculated as 0.947 and 0.676 respectively. The cutoff values were determined as  $\geq 14.5$  for APACHE II and  $\geq 1.24$  for CAR (Table 3, Figure 4).

## Discussion

In this study, it was investigated whether the C-reactive-protein to albumin ratio has a prognostic role in respect of mortality in patients in intensive care units. The results of the study showed that the in-hospital mortality rates were higher in the patients with high CAR levels. The CAR level of ICU patients on admission was determined to be an independent predictor in respect of 60-day mortality.

Just as CRP and /or albumin levels may be prognostic markers for results in various clinical environments, the combination of these markers could have even greater prognostic value than both inflammation and nutritional status (7, 8). In previous studies, CAR has been accepted as a noteworthy prognostic marker reflecting the inflammation status under several conditions for the determination of the mortality risk (9-10). From a scan of the relevant literature, it can be seen that Jaehun Oh et al found CAR to be a predictor of in-hospital mortality in elderly adults presenting at the Emergency Department, Otavio T Ranzani et al. reported that it was a marker for 90-day mortality in septic patients, and Kim MH et al found CAR to be an independent predictor of mortality in patients with sepsis or septic shock (11-

13). Additionally, Tak Kyu Oh et al. found in two separate studies that intensive care patients' CAR value measured after intake is an independent risk factor for 30-day mortality. Tak Kyu Oh et al. also found that in one of these studies, the value of CAR is predictive for 1-year mortality (14, 15). In the univariate analysis of the current study, prognostic scores based on inflammation were shown to be statistically significant for mortality. Moreover, in the multivariate analysis using the Cox regression model, after discounting confounding factors, there was an independent relationship between CAR and APACHE II and mortality only, rather than other inflammation-based prognostic scores. However, the predictive value for mortality of APACHE II (AUC-ROC  $> 0.947$ ), which has been traditionally used as the prognostic score in the determination of ICU mortality, was found to be superior to that of CAR (AUC-ROC  $> 0.676$ ).

C-reactive protein is a marker of the inflammatory response and has been widely researched in cardiovascular and infectious diseases in particular to monitor therapeutic success. However, its role as a marker of clinical results in critically ill patients is unclear and debatable (4). Although a low albumin level has been associated with nephrotic syndrome, liver cirrhosis, or to explain the problem at a sufficiently advanced degree of heart failure and nutritional disorders, the fall in serum albumin concentration in these patients suggests that this process, which is possibly mediated by cytokines, is the result of acute or chronic inflammation (5). Several studies have associated hypoalbuminemia and high CRP levels with a prolonged hospitalization period, higher in-hospital mortality rates in elderly patients, and critical care patients (16-19). In this respect, the findings of the current study are consistent with the literature. In the non-survivor group, the CRP level was determined to be high and the albumin level was low. The CRP and albumin levels of the patients in the first 24 hours were related to mortality.

There were some potential limitations to this study. Primarily, this was a retrospective, single-center study with a small sample, so the clinical and survival comparisons could have been affected by selection bias. Therefore, there is a need for prospective, multi-center studies with larger cohorts to overcome these problems.

In conclusion, CAR is a strong, independent prognostic marker for the prediction of mortality in ICU patients. There is a high predictivity value associated with the APACHE II score with 100% success in showing clinical mortality for ICU patients with anticipated mortality. However, as CAR is a single parameter with similar rates to APACHE II, which is calculated from multiple parameters of specificity and sensitivity of mortality prediction rates, the value of this low-cost and easily accessible method is increased. In the future, the addition of CAR to the calculation of the disease severity score should be considered.

### AUTHOR CONTRIBUTIONS:

Concept: HAF, AST; Design: HAF, AST, ME; Supervision: HAF, AST; ; Data Collection and/or Processing: HAF, ME; Analysis and/or Interpretation: HAF, ME; Literature Search: HAF, AST; Writing Manuscript: HAF, ME; Critical Review: HAF, AST, ME.

**Ethics Committee Approval:** Adiyaman University Non-Interventional Clinical Research Ethics Committee. Decision Date: 17/04/2018, Number of Decision: 2018 / 3-8

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** Authors have no conflicts of interest to declare.

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