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Predictive Value of CAR for Renal Survival and Mortality in ICU Patients with AKI Requiring Dialysis

Valor predictivo de la CAR para la supervivencia y mortalidad renal en pacientes de UCI con IRA que requieren diálisis

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RESUMEN

Introducción: Se ha informado que entre el 20% y el 60% de los pacientes internados en la unidad de cuidados intensivos (UCI) desarrollan lesión renal aguda (IRA). A pesar de las prácticas de cuidados críticos y las diferentes terapias de reemplazo renal (TRR) aplicadas en la UCI, los informes indican una alta tasa de mortalidad del 50-60%. Por lo tanto, es evidente la necesidad de contar con un marcador rápido, de bajo costo y fácilmente accesible para usar en exámenes de rutina, especialmente en términos de reducir la mortalidad en la UCI asociada con la IRA. Los parámetros comunes utilizados para medir la inflamación y el pronóstico en pacientes críticamente enfermos son la proteína C reactiva (PCR) y la albúmina. Por otra parte, los niveles altos de PCR y los niveles bajos de albúmina se han asociado con un mal pronóstico y altas tasas de mortalidad, lo que hace que estos dos parámetros estén bien documentados para el uso de marcadores predictivos de mortalidad. En los últimos años, la relación entre estos dos parámetros ha constituido un valor pronóstico novedoso para multitud de enfermedades. **Objetivo**: El presente estudio tuvo como objetivo investigar el valor predictivo de la relación proteína C reactiva/albúmina (CAR) para la supervivencia y mortalidad renal en pacientes de UCI con IRA que requieren diálisis. **Materiales y métodos**: Este estudio retrospectivo incluyó los datos de 219 (119 hombres, 100 mujeres) pacientes de UCI con IRA que requirieron diálisis. La relación CAR se obtuvo dividiendo el nivel de proteína C reactiva (PCR) por el nivel de albúmina. Las puntuaciones APACHE-II, que se utilizan con frecuencia en las unidades de cuidados intensivos para predecir la mortalidad, se compararon con la sensibilidad y especificidad del CAR. El criterio de valoración principal del estudio fue un resultado compuesto de mortalidad en la UCI. El criterio de valoración secundario del estudio fue la supervivencia renal. **Resultados**: Durante el transcurso de la UCI fallecieron 165 (75,3%) pacientes. En nuestro estudio, los análisis ROC mostraron que el CAR se puede utilizar tanto para predecir la supervivencia renal como para predecir la mortalidad en diálisis que requiere IRA en pacientes de la UCI. Se observó que la sensibilidad del CAR fue mayor que la puntuación APACHE-II y la especificidad fue

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similar para predecir la mortalidad en la UCI. **Conclusiones**: Hasta donde sabemos, este es el primer estudio que investiga la relación de CAR con la mortalidad y la supervivencia renal en pacientes de UCI con lesión renal aguda.

Palabras clave: Lesión renal aguda; Proteína C reactiva/albúmina; Mortalidad en UCI; Supervivencia renal

ABSTRACT

Introduction: It has been reported that 20-60% of patients followed in the intensive care unit (ICU) develop acute kidney injury (AKI). Despite the critical care practices and different renal replacement therapies (RRT) applied in the ICU, reports indicate a high mortality rate of 50-60%. Thus, a need for a rapid, low-cost, readily accessible marker to be used in routine examinations is apparent, especially in terms of ICU mortality associated with AKI. Standard parameters used to measure inflammation and prognosis in critically ill patients are C-reactive protein (CRP) and albumin. Separately, high CRP levels and low albumin levels have been associated with poor prognosis and high mortality rates, making these two parameters well-documented for the use of predictive markers of mortality. The ratio between these two parameters has been a novel prognostic value for numerous diseases in recent years. **Objective**: The present study aimed to investigate the predictive value of C-reactive protein/albumin ratio (CAR) for renal survival and mortality in ICU patients with AKI requiring dialysis. **Materials and methods**: This retrospective study included data from 219 (119 males,100 females) ICU patients with AKI who required dialysis. The CAR was obtained by dividing the C-reactive protein(CRP) level with the albumin level. APACHE-II scores, frequently used in intensive care units for predicting mortality, were compared with CAR's sensitivity and specificity. The primary endpoint of the study was a composite outcome of ICU mortality. The secondary endpoint of the study was renal survival. **Results**: During the ICU course, 165 (75.3%) patients died. In our study, the ROC analyses showed that the CAR could be used to predict renal survival and mortality in dialysis-requiring AKI in ICU patients. CAR's sensitivity was higher than the APACHE -II score, and the specificity was similar to predicting ICU mortality. **Conclusion**: To our knowledge, this is the first study to investigate CAR's relationship with mortality and renal survival in ICU patients with acute kidney injury.

Keywords: Acute kidney injury; C-reactive protein/albumin; ICU mortality; Renal survival

INTRODUCTION

Acute Kidney Injury (AKI) is defined as a decrease in renal clearance and glomerular filtration rate (GFR) with disturbances in fluid, electrolyte, and acid-base balance due to a sudden onset of kidney function loss [(1)]. Patients who present with a severe acute clinical picture and require various supportive treatments, such as respiratory and circulatory support, are generally elderly and have a high number of accompanying chronic diseases, requiring care in intensive care units (ICU) [(2)].

It has been reported that 20-60% of patients followed in the ICU develop AKI[(3,4)]. Along with other developing clinical complications, treatments for AKI should be applied and followed closely in terms of effectiveness. Despite the critical care practices and different renal replacement therapies (RRT) applied in the ICU, reports indicate a high mortality rate of 50-60%[(4,5)].

Recent studies have examined endpoints such as short-term survival, hospital mortality, or permanent kidney damage. Various factors, markers, and scoring systems have been investigated in predicting the mortality of patients with AKI hospitalized in the ICU [(6–9)].

C-reactive Protein (CRP) is accepted as an acute phase reactant that increases in various inflammatory processes. It is remarkably known to be widely used for the diagnosis and follow-up of infections. In one study, an association between C-reactive protein and all-cause mortality among critically ill patients with acute kidney injury was investigated, and it was shown that there is a positive correlation between high CRP values and increased mortality [(7)].

Albumin is the hallmark of all plasma proteins as it is involved in the binding and transport capacity of many endogenous and exogenous substances. In addition to its transportive quality, it is also accepted as an indicator of the

nutritional status of patients [10]. Various studies have reported that hypoalbuminemia is a risk factor for the development of acute kidney injury, and it is associated with morbidity, mortality, and increased duration of stay in the ICU [11,12].

The C-reactive protein/albumin ratio (CAR) is a newly defined systemic inflammatory marker that combines CRP and albumin levels [13]. Several previous studies have demonstrated the prognostic value of CAR in patients with sepsis [14,15], acute pancreatitis [16], and COVID-19 pneumonia [17], to name a few diseases for which the ratio was used.

Both inflammatory processes and individuals' fluid-nutritional status are significant factors documented in the development of AKI. Even further, sepsis and malnutrition are frequently observed in the intensive care unit, especially in acute kidney injury patients undergoing dialysis treatment [18]. Considering this data, the present study's objective was to investigate CAR's predictive value for renal survival and mortality in ICU patients with AKI requiring dialysis.

MATERIALS AND METHODS

Study population

This study is a retrospective analysis of patients with AKI requiring dialysis admitted to Health Science University, Sultan II. Abdülhamid Han Training and Research Hospital Intensive Care Unit between June 2017 and June 2020.

In the present study, exclusion criteria included previous dialysis history for acute or chronic renal failure, kidney transplantation, end-stage liver failure, pregnant patients, breastfeeding mothers, and patients requiring dialysis treatment due to drug intoxication. Patients whose CRP and albumin levels were not measured within 48 hours of admission to the ICU were also excluded.

The following parameters were retrieved from the hospital's electronic database: baseline demographic features, comorbidities [i.e., hypertension, diabetes mellitus (DM), coronary artery disease (CAD), chronic kidney disease (CKD), cancer, chronic obstructive pulmonary disease], laboratory values, APACHE-II scores, discharge and mortality status after the follow-up, recovery of renal function, and length of stay in the intensive care unit (days).

Our nephrology unit initiated all of the dialysis treatments; therefore, the indications for dialysis were based on the KDIGO AKI stage 3 classification, including the parameters of uremia, electrolyte abnormality, diuretic unresponsive fluid overload, acid-base imbalance, and sepsis.

The design of the present study was reviewed and approved by both the Ministry of Health Scientific Research Committee and the Local Ethics Committee (approval number: 2022.08.18-31). Subsequently, the study was conducted following the Declaration of Helsinki's "Good Clinical Practice" guidelines. Due to the study's retrospective design, informed consent was not necessary.

Laboratory Analysis

All patients' blood samples were collected within 48 hours of admission to the ICU department. Standard laboratory methods were used to analyze blood samples for complete blood count, serum creatinine, and blood gases. CRP (mg/L) levels were measured using the nephelometry method. Albumin (g/dL) levels were determined using the bromocresol green method. The CAR was obtained by dividing the CRP level by the albumin level.

Endpoints

The study's primary endpoint was a composite outcome of ICU mortality, defined as death from any cause during the ICU stay. A trained study coordinator who examined the patients' medical records evaluated and confirmed all ICU deaths.

The secondary endpoint of the study was renal survival.

Definitions

Renal survival was defined as a recovery of sufficient kidney function to discontinue dialysis during the hospital stay and at discharge. The Kidney Disease Improving Global Outcomes (KDIGO) classification is based on serum creatinine (SCr) criteria defining AKI and CKD

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Statistical methods

The suitability of continuous numerical variables to the normal distribution was evaluated using scatter plots, Kolmogorov-Smirnov, and Shapiro-Wilk tests. In the presentation of descriptive statistics, mean and standard deviation or median and highest-lowest values were used

for continuous numerical variables according to their conformity with normal distribution, and number and percentage values were used for categorical variables.

The Enter method and Logistic Regression Analysis were used to investigate the effects of patient characteristics on renal survival. The odds ratio (OR) and 95% confidence intervals (95%CI) were calculated in logistic regression analysis.

Enter method and Cox regression analysis were used to investigate the effects of patient characteristics on ICU mortality. Variables with a p-value <0.10 in the univariate Cox regression analysis were included in the multivariate analysis. In the multivariate modeling, the cumulative survival rate graphic during the time at risk (ICU length of stay) was used to compare the statistically significant variables visually. Hazard Ratio (HR) and 95% CI were used to determine the risk of death in Cox Regression analyses.

ROC analysis was used to determine the diagnostic performance of a patient's laboratory parameters in predicting renal survival and ICU mortality. The statistical significance of the area under the curve (AUC) was evaluated in the ROC analysis. The best cut-off point for laboratory parameters with statistically significant diagnostic performance was determined using the Youden Index. The estimation of sensitivity, specificity, and 95% confidence intervals of these parameters were calculated according to the best cut-off point determined. Statistical significance was defined as a p-value <0.05. Analyses were performed using Statistical Package for Social Sciences software, version 20.0 (SPSS; IBM, Armonk, New York, USA).

RESULTS

Two hundred nineteen patients were included in this analysis; 100 (45.7%) of the patients were female, and 119 (54.3%) were male. In terms of age ranges of the sample size, 44 (20.1%) of the patients were between the ages of 18-64, 59 (26.9%) were between the ages of 65-74, 56 (25.6%) were between the ages of 75-84, and 60 (27.4%) were aged 85 and above. Nearly all patients (97.7%) had accompanying comorbid health conditions. To be specific, the most common comorbid disease/health problems of the patients were hypertension (40.6%), CKD (32.4%), DM (30.6%), CAD (24.7%), and chronic heart failure (22.4%) (**Table 1**). The most prevalent causes of acute kidney injury in our study were sepsis and pre-renal causes (hypovolemia, major surgery), respectively.

The mean duration of the patient's ICU stays was 16.5±18.5 days, with the median stay being 11.0 days (1.0-108.0). Patient laboratory values in the first 48 hours of admission to the intensive care unit are presented in **Table 2**.

Table 1: Demographic and clinical characteristics of patients with AKI in the intensive care unit

Characteristics		**All Groups**	
		n	**%**
Age (years)	18-64	44	20,1
	65-74	59	26,9
	75-84	56	25,6
85 and above		60	27,4
Male gender		119	54,3
Comorbidities		214	97,7
Hypertension		89	40,6
CKD		71	32,4
Liver disease*		12	5,5
DM		67	30,6
CAD		54	24,7
CHF		49	22,4
COPD		29	13,2
Malignancy**		23	10,5
Cerebrovascular disease		15	6,8
Dementia		12	5,5
Total		219	100

***CKD**: Chronic kidney disease, **DM**: Diabetes Mellitus, **CHF**: Congestive heart failure **CAD**: Coronary artery disease **COPD**: Chronic obstructive pulmonary disease. ***Patients with end-stage liver failure excluded, ****Patients with advanced malignancies excluded*

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Table 2: Laboratory values in the first 48 hours of admission to the ICU

Creatinine(mg/dL)	Mean±SD	3,6±2,1
	Median (Min-Max)	3,1 (0,7-12,9)
CRP (mg/L)	Mean±SD	146,8±96,4
	Median (Min-Max)	143,0 (2,2-442,0)
Albumin (g/dL)	Mean±SD	2,5±0,7
	Median (Min-Max)	2,4 (1,1-4,5)
pH	Mean±SD	7,29±0,13
	Median (Min-Max)	7,30 (6,70- 7,61)
HCO_3 (mEq/L)	Mean±SD	19,1±6,4
	Median (Min-Max)	19,1 (3,3-41,2)
Hb (g/dL)	Mean±SD	10,0±2,1
	Median (Min-Max)	9,6 (5,1-17,0)
Neutrophil(/mm³)	Mean±SD	12306,3±7761,3
	Median (Min-Max)	10690,0 (90,0-54300,0)
Lymphocyte(/mm³)	Mean±SD	1237,0±1719,0
	Median (Min-Max)	926,0 (5,0-19260,0)
Platelet (/mm³)	Mean±SD	209079,2±109674,9
	Median (Min-Max)	200000,0 (11000,0-762000,0)
CAR	Mean±SD	66,7±49,2
	Median (Min-Max)	60,3 (0,8-245,6)

***CRP**: C-reactive protein, **HCO3**: Bicarbonate, **Hb**: Hemoglobin, **CAR**: CRP/Albumin Ratio*

The univariate logistic regression analysis observed that the patients' sociodemographic characteristics, as well as their diseases and health problems, did not have a statistically significant effect on renal survival. **Table 3** presents the demographic and clinical characteristics of patients' renal survival.

Table 3: Demographic and clinical characteristics of patients on renal survival

Characteristics		**Renal Survival, n (%)**	**OR (95% CI)**	***p****
Age(years)	18-64	13 (29,5)	R	
	65-74	14 (23,7)	0,74 (0,31-1,79)	0,507
	75-84	22 (39,3)	1,54 (0,67-3,58)	0,312
	85 and above	22 (36,7)	1,38 (0,60-3,18)	0,448
Gender	Female	37 (37,0)	R	
	Male	34 (28,6)	0,68 (0,39-1,20)	0,185
Hypertension	No	38 (29,2)	R	
	Yes	33 (37,1)	1,43 (0,81-2,53)	0,224
CKD	No	45 (30,4)	R	
	Yes	26 (36,6)	1,32 (0,73-2,40)	0,358
Liver disease*	No	67 (32,4)	R	
	Yes	4 (33,3)	1,05 (0,30-3,59)	0,945
DM	No	46 (30,3)	R	
	Yes	25 (37,5)	1,37 (0,75-2,51)	0,305
CHF	No	53 (32,1)	R	
	Yes	18 (33,3)	1,06 (0,55-2,03)	0,869
CAD	No	54 (31,8)	R	
	Yes	17 (34,7)	1,14 (0,58-2,23)	0,700
COPD	No	63 (33,2)	R	
	Yes	8 (27,6)	0,77 (0,32-1,83)	0,551
Malignancy**	No	65 (33,2)	R	
	Yes	6 (26,1)	0,71 (0,27-1,89)	0,494
Cerebrovascular disease	No	65 (31,9)	R	
	Yes	6 (40,0)	1,43 (0,49-4,17)	0,518
Dementia	No	67 (32,4)	R	
	Yes	4 (33,3)	1,05 (0,30-3,59)	0,945

CKD**: Chronic kidney disease, **DM**: Diabetes Mellitus, **CHF**: Congestive heart failure, **CAD**: Coronary artery disease, **COPD**: Chronic obstructive pulmonary disease. ** Patients with end-stage liver failure excluded, *******Patients with advanced malignancies excluded*

Creatinine (AUC: 0.587, p=0.035), CRP (AUC: 0.676, p<0.001), albumin (AUC: 0.628, p=0.003), pH (AUC: 0.638, p<0.001), HCO3 levels (AUC: 0.606, p=0.008), CAR (AUC: 0.663, p<0.001) and APACHE II score (AUC: 0.598 and p=0.035) were found to have statistically significant diagnostic performance in predicting renal survival. The area under the curve of various parameters for predicting renal survival in the ICU is presented in **Table 4**.

Table 4: Area under the curve of various parameters for predicting renal survival

Variable	AUC	*P*	Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)
Creatinine (mg/dL)	0,587	**0,035**	≤3,07	62,0(49,7-73,2)	56,8(48,4-64,9)
CRP (mg/L)	0,676	**<0,001**	≤154,7	74,7(62,9-84,2)	53,4(45,0-61,6)
Albumin (g/dL)	0,628	**0,003**	>3,08	35,2(24,2-47,5)	90,5(84,6-94,7)
pH	0,638	**<0,001**	>7,32	62,0(49,7-73,2)	63,5(55,2-71,3)
HCO_3 (mEq/L)	0,606	**0,008**	>21,6	46,5(34,5-58,7)	73,0(65,1-79,9)
CAR	0,663	**<0,001**	≤32,09	52,1(39,9-64,1)	83,1(76,1-88,8)
APACHE II	0,598	**0,035**	≤19	32,8(21,3-46,0)	88,4(81,0-93,7)

***AUC**: Area under curve, **CI**: Confidence interval, **CRP**: C-reactive protein, **HCO3**: Bicarbonate, **Hb**: Hemoglobin, **CAR**: CRP/Albumin Ratio*

When determining the best cut-off values for renal survival, the CRP cut-off value as ≤154.7 mg/L was found to have a sensitivity of 74.7% and a specificity of 53.4%; albumin had a sensitivity of 35.2% and a specificity of 90.5% for the cut-off point of >3.08 g/dL; CAR had a sensitivity of 52.1% and a specificity 83.1% for the cut-off point of ≤32.09; and lastly, the sensitivity of the APACHE II score when the cut-off value of ≤19 was calculated to be 32.8% and the specificity was 88.4% for predicting renal survival. ROC curves of CRP, albumin, CAR, and APACHE II levels are presented in **Figure 1**.

In the univariate logistic regression analysis, the patient's age, disease, and health problems did not have a statistically significant effect on ICU mortality (**Table 5**).

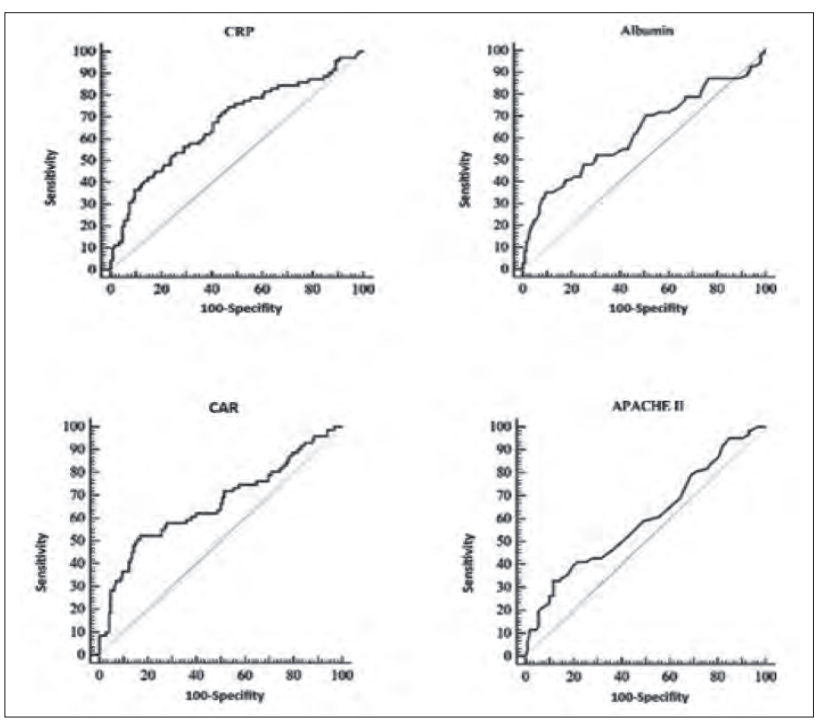

Figure 1: ROC curves of CRP, albumin, CAR and APACHE II for predicting renal survival

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Table 5: Univariate analysis of the demographic and clinical characteristics on ICU mortality

Characteristics		**ICU mortality, n (%)**	**HR (95% CI)**	***p****
Age (years)	18-64	32 (72,7)	R	
	65-74	47 (79,7)	1,18 (0,75-1,86)	0,480
	75-84	41 (73,2)	0,84 (0,53-1,33)	0,456
	85 and above	45 (75,0)	1,15 (0,73-1,80)	0,560
Gender	Female	74 (74,0)	R	
	Male	91 (76,5)	1,42 (1,04-1,94)	**0,029**
Hypertension	No	102 (78,5)	R	
	Yes	63 (70,8)	0,85 (0,62-1,17)	0,313
CKD	No	115 (77,7)	R	
	Yes	50 (70,4)	0,77 (0,55-1,07)	0,119
DM	No	114 (75,0)	R	
	Yes	51 (76,1)	0,78 (0,56-1,09)	0,149
CHF	No	123 (74,5)	R	
	Yes	42 (77,8)	1,28 (0,90-1,83)	0,175
CAD	No	127 (74,7)	R	
	Yes	38 (77,6)	1,11 (0,77-1,60)	0,564
COPD	No	143 (75,3)	R	
	Yes	22 (75,9)	0,78 (0,49-1,22)	0,274
Malignancy**	No	146 (74,5)	R	
	Yes	19 (82,6)	0,95 (0,59-1,53)	0,824
Cerebrovascular disease	No	152 (74,5)	R	
	Yes	13 (86,7)	1,06 (0,60-1,87)	0,846
Dementia	No	153 (73,9)	R	
	Yes	12 (100,0)	1,51 (0,84-2,73)	0,171
Liver disease***	No	157 (75,8)	R	
	Yes	8 (66,7)	1,04 (0,51-2,12)	0,915
Renal survival	No	129 (87,2)	2,23 (1,54-3,24)	**<0,001**
	Yes	36 (50,7)	R	
Total		165 (75,3)		

***CKD**: Chronic kidney disease, **DM**: Diabetes Mellitus, **CHF**: Congestive heart failure, **CAD**: Coronary artery disease, **COPD**: Chronic obstructive pulmonary disease . *Cox Regression Analysis was performed, **Patients with advanced malignancies excluded, ***Patients with end-stage liver failure excluded*

On the other hand, it was found that the ICU mortality of males was higher compared to the mortality of female patients (HR:1.42) (p=0.029), and the ICU mortality of patients with an absence of renal survival was higher than patients with renal survival (HR:2.23) (p<0,001). Of the 219 patients, 165 (75.3%) were renal non-survivors, and 54 (24.7%) were renal survivors. On the multivariate analysis, renal survival was the only variable that remained significant in ICU mortality (OR:2.26 and p<0,001) (**Table 6**).

Figure 2 shows the comparison of ICU mortality of patients according to the presence of renal survival.

Creatinine (AUC: 0.620, p=0.008), CRP (AUC: 0.879, p<0.001), albumin (AUC: 0.880, p<0.001), pH (AUC: 0.594 and p=0.022), neutrophil levels (AUC: 0.630) and p=0.002), NLR (AUC: 0.634, p=0.002), CAR (AUC: 0.91, p<0.001), and APACHE II score (AUC: 0.904, p<0.001) were found to have statistically significant diagnostic performance in predicting ICU mortality. The area under the curve of various parameters for predicting ICU mortality is presented in **Table 7**.

Table 6: Multivariate analysis of the demographic and clinical characteristics on ICU mortality

Characteristics		Corrected HR (95% CI)	p*
Gender	**Female**	**R**	
	Male	**1,34 (0,98-1,83)**	**0,068**
Renal survival	**No**	**2,26 (1,56-3,28)**	**<0,001**
	Yes	**R**	

***Cox Regression Analysis was performed*

Figure 2: Comparison of ICU mortality of patients according to the presence of renal survival

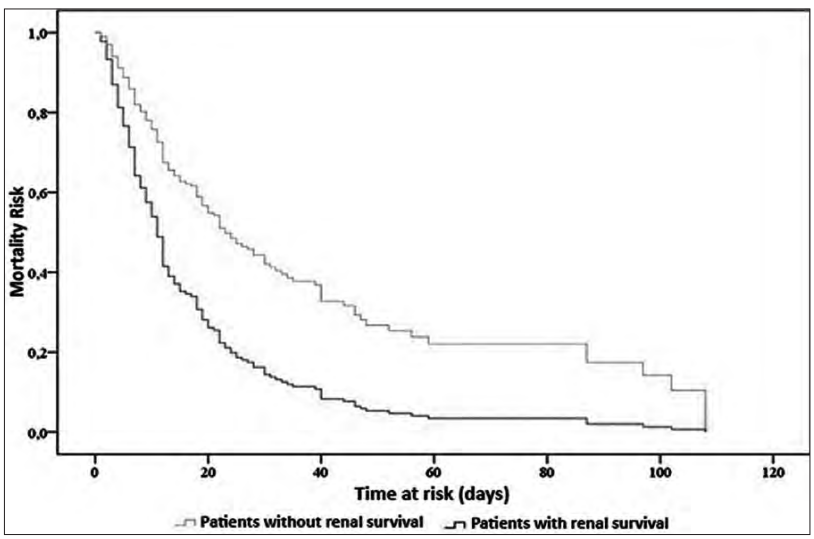

Table 7: Area under the curve of various parameters for predicting ICU mortality

Variable	AUC	*p*	Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)
Creatinine (mg/dL)	0,620	**0,008**	>3,28	58,2 (50,3-65,8)	63,0 (48,7-75,7)
CRP (mg/L)	0,879	**<0,001**	>98,5	82,4 (75,7-87,9)	87,0 (75,1-94,6)
Albumin (g/dL)	0,880	**<0,001**	≤2,65	79,4 (72,4-85,3)	85,2 (72,9-93,4)
pH	0,594	**0,022**	≤7,18	24,9 (18,5-32,2)	94,4 (84,6-98,8)
Neutrophil (/mm³)	0,630	**0,002**	>10500	58,2 (50,3-65,8)	70,4 (56,4-82,0)
CAR	0,911	**<0,001**	>33,46	89,7 (84,0-93,9)	85,2 (72,9-93,4)
APACHE II	0,904	**<0,001**	>29	83,6 (76,2-89,4)	89,7 (75,8-97,1)

***AUC**: Area under curve, **CI**: Confidence interval, **CRP**: C-reactive protein, **CAR**: CRP/Albumin Ratio*

In terms of predicting ICU mortality, the cut-off values for the following parameters were calculated: CRP with the cut-off point of >98.5 mg/L had a sensitivity of 82.4% and a specificity of 87.0%; albumin with the cut-off point of ≤2.65 g/dL had a sensitivity of 79.4% and a specificity of 85.2%; CAR with the cut-off point of >33.46 had a sensitivity of 89.7% and a specificity of 85.2%; lastly, the sensitivity of the APACHE II score for the best cut-off point of >29 was 83.6% and the specificity was 89.7% for ICU mortality (**Figure 3**).

Prior to our study, the CRP/albumin ratio in AKI patients treated only in in-patient wards was studied, where ICU patients were excluded from the study [27]; conversely, the CRP/albumin ratio in ICU patients of other systemic diseases, such as pancreatitis or cardiovascular disease has been reported. However, the CRP/albumin ratio in AKI patients, particularly those treated in the ICU, has not been reported. Thus, it is important to highlight the importance of this

study as it is, to the best of our knowledge, the first in the literature to examine the relationships between CRP/albumin ratio with renal survival and mortality of patients in the ICU, specifically with AKI requiring dialysis.

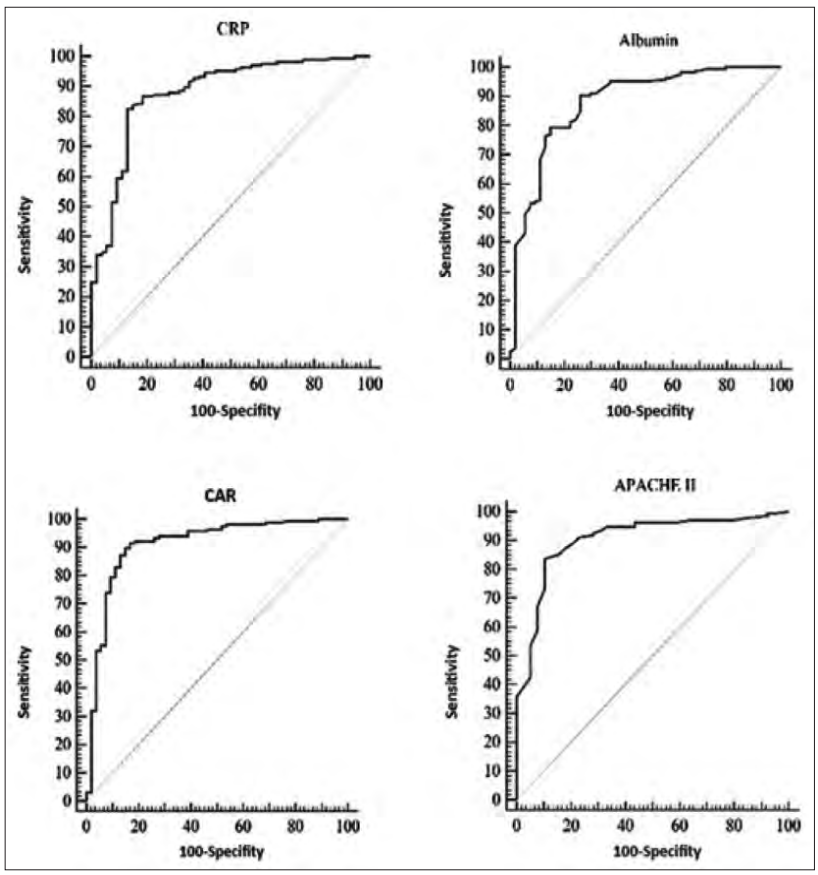

Figure 3: ROC curves of CRP, albumin, CAR and APACHE II levels

DISCUSSION

Before discussing our study's CRP to albumin ratio (CAR) findings, it is important to briefly relook each parameter separately. The incidence of AKI in patients who receive care in the ICU is reported as an average of 36%, further demonstrating that the development of AKI in ICU patients is considered one of the meaningful factors associated with high mortality despite the advances in dialysis technology and advanced life support [19,20]. Critically ill patients who develop AKI for various reasons and survive eventually require lifelong RRT [21]. Although the pathogenesis of AKI cannot be fully explained, studies have shown that circulating inflammatory mediators are higher in patients with AKI. Specifically, CRP is the most studied inflammatory mediator as it increases ROS production, stimulates endothelial cell apoptosis, and leads to endothelial dysfunction, ultimately progressing to AKI. In recent years, accumulating evidence has shown that CRP is not only an inflammation biomarker but also an important mediator contributing to the pathogenesis of diseases. More importantly, an increase in inflammatory response affects the repair and proliferation mechanisms of the renal tubular cells, causing the affected renal tissue to progress to fibrosis [22–24].

Albumin, a protein synthesized in the liver, is both an indicator of malnutrition and a negative acute phase reactant, where hypoalbuminemia is known to indicate systemic inflammatory response seen in varying underlying conditions such as kidney disease or liver disease [25]. Furthermore, albumin has been found to have antioxidant, anti-inflammatory, and protective effects on the kidneys, in addition to its well-known properties in the transport of molecules and regulation of osmotic pressure. Thus, hypoalbuminemia results in renal damage due to the inability to effectively remove toxic substances or regulate the decrease in intravascular volume, resulting in

concomitant renal hypoperfusion [26]. In a study by Shao et al., hypoalbuminemia was found to be an independent risk factor for both the development of AKI in critically ill patients and the progression of developing AKI to chronic renal failure [12].

Combining these two mechanisms, both inflammatory processes and the nutritional status of individuals are important in the development of AKI in critically ill patients. While CRP and albumin individually serve as indicators of systemic disease, relying on them alone yields lower predictive power for prognosis or mortality outcomes. Wang et al. investigated risk factors in critically ill patients with AKI. They found that a high CAR value was an independent risk factor in predicting hospital mortality, 2-year all-cause mortality, and lower renal survival [18]. In another recent study, high CAR was associated with lower survival in acute kidney injury patients aged 80 years and older requiring dialysis [27]. From the perspective of evaluating patients' inflammatory processes and nutritional status in combination, we investigated CAR in patients requiring dialysis for AKI to predict renal survival and ICU mortality.

In our study, the ROC analyses showed that the CAR could be used to predict renal survival and mortality in dialysis-requiring AKI in ICU patients. Particularly for ICU mortality, CAR's sensitivity with a cut-off point of >33.46 was 89.7%, and its specificity was 85.2%. On the other hand, the sensitivity of the APACHE-II score - frequently used in intensive care units- with the cut-off point >29 was 83.6%, and the specificity was 89.7%. CAR's sensitivity was higher than the APACHE -II score, and the specificity was similar.

In our study, patients with concomitant CKD were not excluded. If patients with concomitant chronic kidney disease (CKD) had been excluded from the study, the sensitivity and specificity of creatinine as an indicator of renal survival may have differed. However, it is crucial to acknowledge that the study population consisted of intensive care unit (ICU) patients presenting severe acute clinical conditions requiring respiratory and circulatory support. Notably, 79.9% of the patients were over 65 years of age and had stage 2 CKD or higher. Excluding patients with concomitant CKD from such a study population would substantially reduce the sample size, hindering our ability to achieve the desired sample size. Furthermore, in the study, those with previous dialysis histories for acute or chronic renal failure were excluded to avoid potential misinterpretation of the study results.

Although the present study showed the predictive value of the CAR in patients with AKI, the retrospective nature of the study, which might include selection bias and a relatively small sample size from a single center, should be acknowledged as a potential limitation; however, the strict inclusion and exclusion criteria and the level of statistical significance strengthen the findings. The other strength of our study is that the RRT decision of patients followed up in the intensive care unit with AKI can only be initiated by our nephrology unit, which provides standardization. In this context, evaluating patients' demographic, clinical, and laboratory characteristics is crucial to determining mortality risk factors and identifying new prognostic markers. Additionally, large-scale randomized studies on the utility of the CAR are needed.

CONCLUSION

The results suggest that CAR might be a clinically valuable marker in ICU patients with AKI. A rapid, low-cost, readily accessible marker like CAR can be used in routine examinations, such as the APACHE-II score, to predict mortality in intensive care units. To the best of our knowledge, this is the first study to investigate CAR's relationship with mortality and renal survival in ICU patients with AKI.

Ethics Committee Approval

All procedures followed the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients included in the study.

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