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ORIGINAL ARTICLE – OPEN ACCESS

Which Parameter is the Most Effective Predictor of Poor Outcomes in Sepsis: C-reactive Protein, Albumin, or C-reactive Protein/Albumin Ratio?

Esra Yakışık Çakır, Işıl Özkoçak Turan

ABSTRACT

Objective: Albumin and C-reactive protein (CRP) values can be indicators of adverse clinical outcomes in sepsis. The purpose of this study was to investigate the diagnostic value of the CRP/albumin ratio in patients with sepsis in an intensive care unit (ICU).

Materials and Methods: This retrospective study examined the records of patients admitted to an ICU for sepsis. The Acute Physiology and Chronic Health Evaluation (APACHE) II score, sex, age, CRP and albumin levels, white blood cell count, and Sepsis-Related Organ Failure Assessment (SOFA) score at ICU admission, duration of mechanical ventilation (MV), ICU stay, presence of bacteremia, and mortality data of the patients were analyzed.

Results: A total of 849 patients diagnosed with sepsis were enrolled in the study. The in-ICU mortality rate was 55% (467/849). The mortality group had notably higher APACHE II scores, duration of MV, ICU stay, SOFA scores, CRP values, and CRP/albumin ratios and lower albumin levels ($p<0.05$). Receiver operating characteristic analysis for mortality prediction yielded area under the curve and cut-off values of 0.820 and >95 mg/L, respectively, for CRP, 0.813 and ≤2.6 g/dL for albumin, and 0.843 and >53.7 for the CRP/albumin ratio.

Conclusion: The results indicated that the CRP/albumin ratio was a more effective parameter than either the CRP or albumin value alone as a predictor of mortality in sepsis patients.

Keywords: Albumin, C-reactive protein, C-reactive protein/albumin ratio, intensive care unit, mortality, sepsis

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Department of Anesthesiology and Clinical of Critical Care, Health Sciences University, Ankara Numune Training and Research Hospital, Ankara, Turkey

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Correspondence
Esra Yakışık Çakır, Health Sciences University, Ankara Numune Training and Research Hospital, Department of Anesthesiology and Clinical of Critical Care, Ankara, Turkey
Phone: +90 312 552 60 00
e-mail: pavulonmouse@hotmail.com

INTRODUCTION

Many patients in intensive care units (ICUs) suffer from a serious and life-threatening response to infection. Sepsis is non-homogeneous disease and a complex clinical syndrome with variable immunological characteristics. It occurs as a result of bacterial invasion of tissues, toxins and enzymes produced by microorganisms, and the response of endogenous cells (1). Despite improved quality of care, the mortality rate for septic patients is still >30% (1, 2). Due to the nonspecific clinical findings and the lack of a definitive risk classification, risk studies for sepsis continue to be important. There is still a need for additional biomarkers that will provide more accurate information regarding the follow-up and clinical outcomes of sepsis (1).

One of the established markers is an elevated C-reactive protein (CRP) level in the presence of infection or inflammation (1, 3). CRP assessment is used in sepsis diagnosis, follow-up, and the evaluation of clinical outcomes. However, a high serum CRP value can also be seen postoperatively and in acute coronary syndromes, malignant tumors, trauma, burns, and autoimmune and rheumatic disorders (4). Therefore, novel biomarkers with high accuracy are needed to diagnose, follow, and evaluate prognosis in sepsis patients (5). Albumin is a protein synthesized in the liver that acts as a modulator of plasma oncotic pressure and transports a variety of ligands, such as bilirubin, fatty acids, and drugs. A low serum albumin concentration may indicate a poor outcome of infection or inflammation in critical patients; however, the role of albumin in critical illness is not yet fully understood (6).

Although CRP and albumin have prognostic value both in inflammation and infectious diseases, the sensitivity and specificity varies. Especially in immunodeficient patients, the use of infection markers may be limited. It has been reported that the CRP/albumin ratio might serve as a marker of clinical outcome (5). However, as yet there is little research comparing the relationship between the CRP/albumin ratio and poor clinical outcomes to that of CRP and albumin measures individually.

The aim of this study was to investigate the usefulness of CRP, albumin, and the CRP/albumin ratio to predict mortality in patients admitted to the ICU due to sepsis.

Table 1. Comparison of demographic and clinical features between mortality and non-mortality cases

Variables	Non-mortality (n=467)	Mortality (n=382)	p
Age (years)[a,b]	65 (23) (49–90) 64±14	67 (21) (54–92) 66±12	0.431
Male sex, n (%)	248 (53.1)	184 (48.2)	0.083
APACHE II score[a,b]	20 (13) (10–35) 20±6	24 (14) (14–47) 25±8	0.001*
SOFA score[a,b]	8 (7) (3–16) 8±6	10 (8) (5–20) 10±7	<0.001*
Vasopressor support, n (%)	159 (34)	228 (59)	0.005*
Dialysis, n (%)	23 (4.9)	54 (14.1)	0.002*
Duration of MV (days)[a,b]	4 (10) (2–41) 5±8	9 (12) (1–44) 10±11	0.001*
ICU stay (days)[a,b]	18 (18) (5–54) 17±15	19 (19) (3–49) 20±15	0.007*
Bacteremia, n (%)	112 (23.9)	107 (28)	0.314
WBC ($X10^3/\mu L$)[a,b]	13.0 (8.5) (1.3–30.6) 13.9±6.5	11.5 (6.4) (1.9–44.6) 14.7±11.9	0.202
CRP (mg/L)[a,b]	53 (46) (12–360) 54±69	158 (120) (23–445) 159±123	<0.001*
Albumin (g/dL)[a,b]	3.1 (1) (1.9–3.9) 3.1±1.1	2.4 (1) (1.0–3.5) 2.3±1	<0.001*
CRP/albumin ratio[a,b]	16.5 (11) (3.5–135) 18.3±24.3	66.6 (38) (7.6–296.4) 69.9±65.3	<0.001*

a: Median (interquartile range) (minimum–maximum); b: Mean±SD; *: P<0.05 was considered significant; SD: Standard deviation; APACHE II: Acute Physiology and Chronic Health Evaluation Score; CRP: C-reactive protein; ICU: Intensive care unit; MV: Mechanical ventilation; SOFA: Sepsis-Related Organ Failure Assessment Score; WBC: White blood cell count. Independent samples were compared using Fisher's exact test or a chi-squared test for categorical variables and a t-test for parametric continuous variables or the Mann-Whitney U test for nonparametric continuous variables

MATERIALS and METHODS

Ethics Approval

Before starting the study, permission was obtained from the local clinical ethics committee on December 21, 2018 (no: E-18-2325).

Patient Data

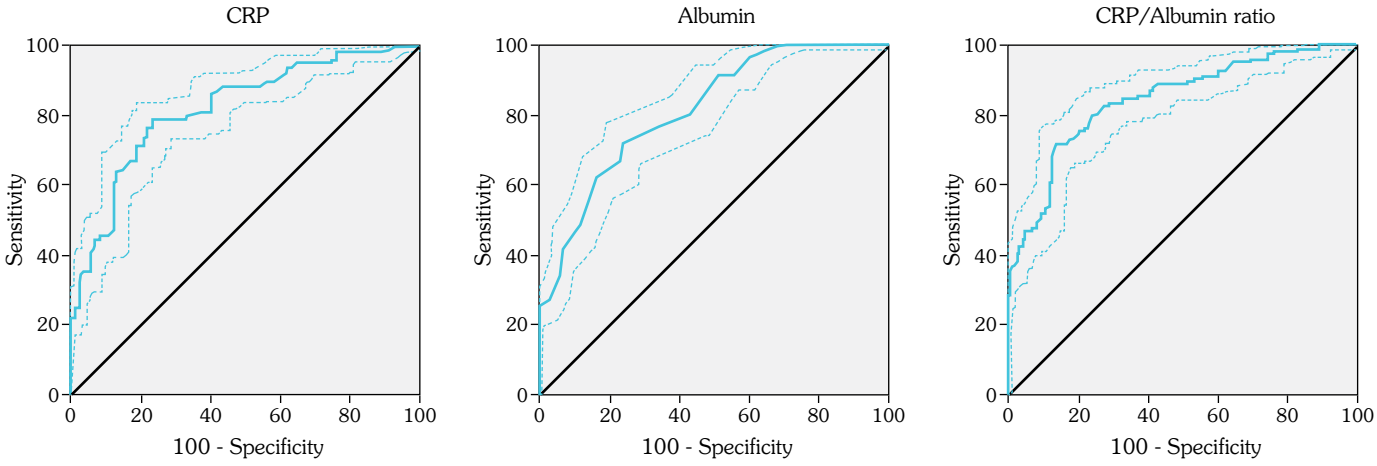
The study used the records of ICU patients diagnosed with sepsis between January 2017 and December 2018 at a single hospital. The ICU is a level 3 facility that treats both surgical and medical patients (total of 96 beds). The diagnosis of sepsis was made using the Third International Consensus Definition of Sepsis and Septic Shock criteria (7). All of the patients with sepsis were treated according to the 2016 International Guidelines for Sepsis and Septic Shock Management (8). Only patients with primary sepsis at the time of admission were enrolled in the study. The Sepsis-Related Organ Failure Assessment (SOFA) score, sex, age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, white blood cell (WBC) count, albumin and CRP levels at ICU admission, duration of mechanical ventilation (MV) support, use of vasopressor, dialysis treatment, length of ICU stay, and presence of bacteremia on admission to the ICU and mortality were recorded and analyzed (9, 10).

Evaluation of Serum CRP, Albumin, WBC Level, and Blood Culture

At ICU admission, blood samples were collected into tubes and the WBC count was measured using a Cell-Dyn 3700 analyzer (Abbott Laboratories, Abbott Park, IL, USA) that was calibrated twice daily. Serum was obtained by centrifuging the blood samples at 3000 rpm for 10 minutes at room temperature. The serum CRP concentration was measured using a high-sensitivity turbidimetric immunoassay and a Roche Modular P analyzer (CRP latex HS kit; Roche Diagnostics, Basel, Switzerland). The serum albumin level was determined using colorimetric methods (biuret method and bromocresol green dye kits; Sclavo Diagnostics International, Pian dei Mori, SI, Italy) in a Technicon RA-XT auto analyzer (Technicon, Hobro, Denmark). Bacteremia was defined with a positive blood culture according to analysis with the BD BACTEC FX system (Becton, Dickinson, and Company, Franklin Lakes, NJ, USA).

Data Analysis

The data were analyzed using SPSS Statistics for Windows, Version 17.0 software (SPSS Inc., Chicago, IL, USA). Relationships between parameters were evaluated with Spearman's correlation analysis. The Shapiro-Wilk test was used to determine the distribution of variables. Parametric tests were performed for data with normal distribution; non-normally distributed data were evaluated with non-parametric tests. Independent samples were compared using Fisher's exact test or a chi-squared test for categorical variables. The Mann-Whitney U test was used to assess nonparametric continuous variables and a t-test for parametric continuous variables. Continuous variables were presented using mean±SD and median with interquartile range (IQR) (minimum–maximum) values, categorical variables as frequency and percentage. Receiver operating characteristic (ROC) curve analysis was carried out to determine cut-off values for the CRP/albumin ratio as well as albumin and CRP values as diagnostic screening tests, and the area under the curve (AUC) was calculated. An AUC value of >0.9 was considered to have high accuracy, 0.7–0.9 medium accuracy, and <0.7 low accuracy (11). Both Kaplan-Meier and Cox regression models were performed to measure the effect of variables on mortality. Multivariate logistic regression was performed to determine the effects of each factor. Odds ratio (OR) and the corresponding 95% confidence interval (CI) were computed for the variables. A p value of <0.05 was considered significant.



Variables	AUC	95% CI	p	Cut-off level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CRP, (mg/L)	0.820	0.793–0.846	<0.001	>95	79	76	73	81
Albumin, (g/dL)	0.813	0.785–0.839	<0.001	≤2.6	72	76	71	77
CRP/albumin ratio	0.843	0.817–0.867	<0.001	>53.7	79	86	80	80

AUC: Area under the curve; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value

Figure 1. Receiver operative characteristic curves for CRP, albumin, and the CRP/albumin ratio to predict mortality in patients with sepsis in an intensive care unit

RESULTS

Of a total of 1805 adult patients, 956 patients were excluded and the remaining 849 sepsis patients were enrolled in the study. Patients who died in the ICU were classified in the mortality group (n=382, 45%) and patients who were discharged were included in the non-mortality group (n=467, 55%). The mortality group had significantly higher APACHE II and SOFA scores; longer MV duration, use of vasopressor, dialysis treatment, and ICU stay; higher CRP levels and CRP/albumin ratios, and significantly lower albumin levels compared with the non-mortality group (p<0.05). There was no significant difference in gender, age, bacteremia rate, or WBC count (p>0.05) (Table 1).

ROC analysis for mortality prediction revealed AUC and optimal cut-off values of 0.820 and >95 mg/L, respectively, for CRP, 0.813 and ≤2.6 g/dL for albumin, and 0.843 and >53.7 for the CRP/albumin ratio. Figure 1 shows the AUC, CI, p value, sensitivity, and specificity results for the CRP/albumin ratio and the albumin, and CRP levels. After adjusting for confounding factors, the predictive value of death in the ICU of albumin, CRP, and the CRP/albumin ratio was significant (OR: 1.27, 95% CI: 1.12–1.46, p<0.001; OR: 1.24, 95% CI: 1.13–1.58, p<0.001; OR: 1.58, 95% CI: 1.01–2.51, p<0.001, respectively). Cox regression analysis and the Kaplan-Meier test indicated that the CRP/albumin ratio may be a marker of ICU mortality in sepsis patients.

DISCUSSION

The results of the present study demonstrated that the sepsis patients who died had a longer MV duration and ICU stay, higher SOFA and APACHE II scores, higher CRP levels and CRP/albumin ratios, and lower albumin levels than those who survived. The CRP and albumin levels and the CRP/albumin ratio predicted mortality in septic patients with moderate accuracy based on the AUC values (0.7–0.9). The cut-off values for mortality were identified as CRP: >95 mg/L, albumin: ≤2.6 g/dL, and CRP/albumin ratio: >53.7 (11). The most effective parameter for mortality prediction was the CRP/albumin ratio, which had the highest AUC (0.843), followed by CRP (0.820) and albumin (0.813). The mortality rate due to sepsis was high in our study, which may have been due to the advanced age and high presence of comorbidities in our patient population.

CRP is both produced and secreted by hepatocytes (5, 12). CRP is stimulated by cytokines and is a useful monitor the effects of antibiotics, in response to inflammation and infection. In addition, CRP measurement is both easily performed and less costly than other cytokine assays (1, 13). A change in CRP in the first 48 hours after a patient is admitted to the ICU is a significant sign. It is a useful indicator to decide whether additional diagnostic procedures are necessary, or to continue or modify therapeutic interventions (1).

It has been demonstrated that the CRP level and APACHE score were correlated with mortality rate in sepsis patients (14). Consistent with our results, it has previously been reported that non-surviving patients have higher SOFA scores and APACHE-II scores, as well as longer MV duration and ICU stay (5, 9, 10). Gans et al. (15) observed that complications of infection after abdominal surgery were more frequent in patients with a CRP level >159 mg/L. A CRP >95 mg/L was a predictor of death in our study of patients with sepsis. This difference in the cut-off value may be related to the patients' primary diagnosis and other inflammatory factors. Therefore, CRP elevation may not be a sufficient parameter for early detection of adverse outcomes in patients in the ICU for diagnostic or therapeutic reasons (16). This supports the need for new laboratory parameter studies.

Albumin is an acute-phase protein that is rapidly down-regulated by inflammatory signals, so changes in the albumin level are associated with the extent of the inflammatory response and can be used as an early predictor of clinical outcomes (5). Hypoalbuminemia develops in sepsis due to decreased hepatic synthesis, increased leakage into the interstitial compartment, and catabolism (17, 18). In cases of sepsis, severe disease, or trauma, both an immune response and increased capillary leakage occur, leading to albumin escaping into the interstitial area. Albumin also plays a substantial role in the immune response against pathogens and the destructive effect of immune dysregulation (18). The protective effect of an elevated serum albumin level is related to mechanisms such as vasodilation, anti-apoptosis and anti-antioxidant activity, increased binding to toxins, and reduced platelet aggregation (19, 20). Arnau-Barrés et al. (21) found that albumin had the potential to be a strong determinant of prognosis and mortality in older adults with sepsis. They reported that an albumin level <2.6 g/dL was a prognostic factor for mortality, which is similar to our findings. The albumin level upon ICU admission appeared to be an important indicator of mortality in the present study, however, additional research is needed to further explain this relationship

The ability to reliably interpret individual albumin and CRP results is limited, however, the CRP/albumin ratio may be a stronger, unifying marker that positively correlates with infection: A higher ratio indicates greater inflammation (5). A CRP/albumin ratio >20 has been associated with higher rates of postoperative complications and wound site infection in abdominal surgery patients (22). Ranzani et al. (23) reported an AUC value of 0.612, 0.621, and 0.590 for the CRP/albumin ratio, albumin, and CRP, respectively, measured at discharge as predictors of predicts 90-day mortality in a study of 334 sepsis patients admitted to the ICU. Llop-Talaveron et al. (19) determined that the CRP/albumin ratio had an AUC of 0.807 for mortality prediction among patients on parenteral nutrition. Basile-Filho et al. (5) found that the CRP/albumin ratio had the highest AUC value (0.731), followed by CRP (0.708) and albumin (0.697), for the prediction of hospital mortality. In the present study, these parameters also demonstrated moderate accuracy (AUC: 0.7–0.9) in mortality prediction, and the CRP/albumin ratio was the most effective.

In a series that examined a large number postoperative patients admitted to an ICU (n=11,832), Oh et al. (24) determined a CRP/albumin ratio threshold value of >17.5 for 30-day mortality and >15.8 for 1-year mortality. The patient groups in that study were similar in age to those in our study. The higher cut-off value of >53.7 for mortality in our study can likely be attributed to the fact that our patient group only had sepsis. The Oh et al. (24) patient group included medical, surgical, neurologic, and emergency cases, which represents substantial diagnostic heterogeneity.

Although the CRP/albumin ratio is a more effective marker of mortality than CRP or albumin alone, the degree of reliability and optimal cut-off value varies among diagnostic groups. Therefore, although the present study features the largest ICU case series of any sepsis study, analysis of large case series with different diagnostic patient groups, including sepsis, are required to validate our results.

The addition of the CRP/albumin ratio to the APACHE II and SOFA scoring systems used to predict mortality might increase their effectiveness and reliability. In recent studies, the CRP/albumin ratio has been shown to be an effective parameter to predict clinical outcomes and mortality in cancer, cardiovascular disease, and coronavirus 19 patients (25–28). To the best of our knowledge, there has been no other study that evaluated the relationship between the CRP/albumin ratio and poor clinical outcomes in comparison with CRP and albumin alone in ICU patients with sepsis. In our study, the CRP/albumin ratio more effectively predicted mortality in sepsis patients than the individual variables.

Our study has some limitations due to its retrospective nature. Since the patients' admittance values were analyzed, changes occurring during follow-up and their effect on clinical outcomes could not be interpreted. In addition, underlying diseases that might impact the patients' outcomes could not be evaluated. Finally, our results cannot be generalized because they are based on single-center data.

CONCLUSION

The results of this study of CRP and albumin markers in the largest series of sepsis patients admitted to an ICU revealed that while albumin and CRP values were predictors of sepsis mortality, the CRP/albumin ratio was more effective than either variable alone. CRP and albumin are affected by various inflammatory factors and have limited utility as predictors of mortality. The ratio may have significant value. Further studies on this topic are needed to validate our findings.

Ethics Committee Approval: The Health Science University, Ankara Numune Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 21.12.2018, number: E-18-2325).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – EYÇ; Design – EYÇ; Supervision – IÖT; Resource – EYÇ; Materials – EYÇ; Data Collection and/or Processing – EYÇ; Analysis and/or Interpretation – IÖT; Literature Search – EYÇ; Writing – EYÇ; Critical Reviews – IÖT.

Conflict of Interest: The authors have no conflict of interest to declare.

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