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Title: Which parameter is the most effective in predicting poor outcomes in sepsis: C-reactive protein, albumin, or C-reactive protein/albumin ratio?

Running Title: Sepsis and C-reactive protein/albumin ratio

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ABSTRACT

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

Materials and Methods: Our retrospective study worked out patients admitted to the ICU for sepsis. The patients’ acute physiology and chronic health evaluation (APACHE) II scores, sex, age, CRP, albumin levels, white blood cell, and sepsis-related organ failure assessment (SOFA) scores at ICU admission, mechanical ventilation (MV) stay, ICU stay, bacteremia, and mortality were enrolled.

Results: A total of 849 patients diagnosed with sepsis were involved in our study. The in-ICU mortality rate was 55% (467/849). The mortality group had remarkably higher APACHE II scores, duration of MV duration, ICU stay, SOFA scores, CRP level, and CRP/albumin ratio and lower albumin level (p<0.05). In the analysis of receiver operating characteristics for mortality prediction, the area under rotation and cut-off values were 0.820 and> 95 mg / L for CRP, 0.813 and ≤2.6 g/dL for albumin, and 0.843 and >53.7 for CRP/albumin ratio.

Conclusion: In this study, it was found that the CRP / albumin ratio was a more effective parameter than CRP or albumin alone in predicting mortality in sepsis patients.

Keywords: Albumin; C-reactive protein; C-reactive protein/albumin ratio; Sepsis; Intensive care unit; Mortality

INTRODUCTION

The majority of patients in intensive care units (ICUs) suffer from serious and life-threatening infectious diseases. Sepsis is non-homogeneous disease and a complex clinical syndrome with variable immunological characteristics. It occurs as a result of the effects of bacterial invasion of tissues, the 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 over 30% (1,2). Due to the nonspecific clinical findings and the lack of a definitive risk classification, risk studies on sepsis are still ongoing. Therefore, in addition to existing biomarkers, there is a need for new biomarkers that provide more accurate information regarding the follow-up and clinical outcomes of sepsis (1).

One of the established markers is C-reactive protein (CRP) level increases in the presence of infection or inflammation (1,3). CRP assessment is used in sepsis diagnosis, follow-up, and evaluation of clinical outcomes. However, elevated serum CRP can also be seen postoperatively and in acute coronary syndromes, malignant tumors, trauma, burns, and autoimmune and rheumatic disorders (4). For this reason, 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 and plays a role in blood oncotic pressure as a transport molecule for bilirubin, fatty acids, and drugs. Low serum albumin concentrations may indicate poor outcomes of infection or inflammation in critical patients (6). However, the effect of albumin on critical illness is not yet understood (6).

Although CRP and albumin have prognostic value both in inflammation and infectious diseases, their sensitivity and specificity are variable. Especially in immunodeficient patients, the use of infection markers may be limited. Recently, it was reported that the CRP / albumin ratio could be used as a marker of clinical outcome (5). However, there is insufficient study evaluating the relationship between CRP/albumin ratio and poor clinical outcomes compared to CRP and albumin alone.

The aim of this study was to investigate the usefulness of CRP, albumin, and CRP / albumin ratios for ICU admission in predicting mortality in patients admitted to the ICU due to sepsis.

**MATERIAL and METHODS**

**Ethical approval**

The study was retrospectively worked out patients who were hospitalized in the ICU and diagnosed with sepsis between January 2017 and December 2018. The ICU includes both the
surgical and medical patient population. Before starting the study, permission was obtained from the local clinical ethics committee (registration number: E-18-2325, date: 21/12/2018).

**Patient data**

The ICU is level 3 and both the surgical and medical patient population (total of 96 beds) is being treated. The diagnosis of sepsis was made in accordance with the criteria of the Third International Consensus Definition of Sepsis (7). All patients with sepsis were treated reference to the 2016 International Guidelines for Sepsis and Septic Shock Management (8). Only patients with primary sepsis at the time of admission were involved in our study. The patients’ sepsis-related organ failure assessment (SOFA) scores, sex, age, acute physiology and chronic health evaluation (APACHE) II scores, white blood cell (WBC), albumin and CRP levels at ICU admission, mechanical ventilation (MV) support period, use of vasopressor, dialysis treatment, ICU stay, presence of any bacteremia on admission to the ICU and mortality were recorded (9,10).

**Determination of serum CRP, albumin, and WBC levels and blood culture**

At ICU admission, blood samples were collected into tubes and WBC count was measured using a Cell-Dyn 3700 (Abbott, 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. Serum CRP concentrations were measured by high-sensitivity turbidimetric immunoassay using a Roche Modular P analyzer (CRP latex HS, Roche kit, Roche Diagnostics, GmbH, Mannheim, Germany). Serum albumin levels were determined by using colorimetric methods (Biuret, Brom Cresol Green: Sclavo kits) in Technicon RA-XT auto analyzer. Bacteremia was defined as a positive blood culture by BACTEC FX (Becton Dickinson, Becton Dickinson, Sparks, Sparks, MD, USA).

**Data analysis**

The data of our study were analyzed with the SPSS 17.0 statistical program. Relationships between parameters were evaluated with Spearman’s correlation analysis. Shapiro-Wilk test was worked out to determine the distribution of variables of patient data. If the data were...
normally distributed, parametric tests were performed. If we found any abnormality, non-parametric tests were performed. Independent samples were compared using Fisher’s exact test or chi-square test for categorical variables. We performed a Mann-Whitney U test on nonparametric continuous variables and a t-test on parametric continuous variables. Continuous variables were presented using mean ± standard deviation and median Inter Quantile Range (IQR), (minimum–maximum) values, categorical variables as frequency and percentage distribution. Receiver operating characteristic (ROC) curve was carried out to determine cut-off values for CRP/albumin ratio, albumin, and CRP as diagnostic screening tests and area under the curve (AUC) were calculated. AUC values >0.9 were described as high accuracy, 0.7-0.9 as medium accuracy, and <0.7 as low accuracy (11). Both Kaplan–Meier and Cox regression models were performed to measure the effect of variables on mortality. Multivariate logistic regression was worked to determine the effects of each factor. Odds ratio (OR) and the corresponding 95% confidence interval were computed for the variables. If the p values were <0.05, it was considered significant.

RESULTS

Of a total of 1805 adult patients, 956 patients were excluded and the remaining 849 sepsis patients were admitted to this study. Patients who death in the ICU were evaluated as the mortality group (n=382, 45%), while patients who were discharged were included in the non-mortality group (n=467, 55%). The mortality group had significantly higher APACHE II scores, MV duration, use of vasopressor, dialysis treatment, SOFA scores, ICU stay, CRP level, and CRP/albumin ratio and significantly lower albumin level compared to the non-mortality group (p<0.05). It was determined that the results were similar in terms of gender, age, bacteremia rate and WBC count of the patients (p>0.05) (Table 1).

According to ROC analysis for mortality prediction, the AUC and optimal cut-off values were 0.820 and >95 mg/L for CRP, 0.813 and ≤2.6 g/dL for albumin, and 0.843 and >53.7 CRP/albumin ratio, respectively. Figure 1 shows the AUC, confidence interval, p value, sensitivity, specificity for CRP/albumin ratio, albumin, and CRP. After adjusting for
confounding factors, albumin, CRP, and CRP / albumin ratio were showed to be significant predictors of death in ICU (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). In the Cox regression test and the Kaplan Meier test, CRP/albumin ratio still appears as a marker associated with death.

**DISCUSSION**

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

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 is both easily-performed and less costly than other cytokine assays (1,13). The changes in CRP are significant in the first 48 hours, after patients are admitted to the ICU. It is also useful in deciding whether additional and additional diagnostic procedures are necessary and to continue and modify therapeutic interventions (1).

It was shown that CRP level and APACHE score were correlated with mortality rate in sepsis patients (14). Consistent with our results, it was previously noted that non-surviving patients, due to their more serious condition, have SOFA scores and APACHE-II scores, as well as longer MV duration and ICU stay (5,9,10). Gans et al. (15) it has been observed that in patients with CRP levels above 159 mg / L, complications of infection after abdominal surgery are more frequent. In our study, CRP greater than 95 mg / L was determined a marker of death in patients.
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could not be interpreted. In addition, underlying diseases that may impact the patients’ outcomes could not be evaluated. Finally, our results cannot be generalized because they are based on single-center data.

**CONCLUSIONS**

In this study including the largest series of sepsis patients admitted to the ICU, albumin and CRP were found to be effective predictors of sepsis mortality. However, CRP/albumin ratio was better to CRP and albumin alone in predicting death rate in patients with sepsis, as CRP and albumin are affected by various inflammatory factors and have limited utility in mortality prediction. Further studies on this topic are needed to validate our findings.

**References**

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**Figure legends**

Figure 1. ROC curves for CRP, albumin, and CRP/albumin ratio predicting mortality in patients with sepsis in the intensive care unit.
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Table 1. Comparison of demographic and clinical features between mortality and non-mortality cases

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

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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 chi-square test for categorical variables and t-test for parametric continuous variables or Mann–Whitney U-test for nonparametric continuous variables.

*P < 0.05 was considered significant.

\(^a\) Median (Inter Quantile Range) (minimum-maximum), \(^b\) Mean ± standard deviation.