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DOI: 10.17235/reed.2023.9345/2022
Link: PubMed (Epub ahead of print)

Please cite this article as:

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Founding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
ABSTRACT

Introduction: The C-reactive protein (CRP) to albumin ratio is an inflammatory marker that has shown promise in the prognosis of critically ill patients. This study is aimed to assess the value of CRP/albumin ratio to predict severity in acute pancreatitis. Methods: A retrospective study was performed using a prospectively collected database of patients diagnosed with AP admitted to the Department of Gastroenterology between March 2014 and December 2021. Results: Among 722 patients included in the study, 78.67% had mild, 15.65% had moderately severe, and 5.67% had severe acute pancreatitis. The CRP/albumin ratio was significantly associated with severe AP (OR 1.02; 95% CI 1.01–1.03; P < 0.001), and each 10-unit increase in the ratio was associated with a 20% increased likelihood of severe acute pancreatitis. The area under the ROC curve (AUC) value of the CRP/albumin ratio in severe acute pancreatitis was 0.68 (95% CI 0.58-0.77), which was higher than that of the Ranson criteria (0.62). The optimal cut-off value for predicting severe acute pancreatitis was 7.51, with a sensitivity of 63.4% and specificity of 65.6%. Conclusions: Despite its low sensitivity and specificity, the CRP/albumin ratio could be used as a complementary marker to the current scoring systems for the initial assessment of acute pancreatitis prognosis. It is easily obtainable and can provide additional prognostic information to clinicians.

Key words: Acute Pancreatitis, C-Reactive Protein, Serum Albumin, Organ Failure, Biomarkers.

INTRODUCTION

Acute pancreatitis (AP) is one of the most common reasons for consultation in emergency services worldwide, with approximately 275,000 admissions each year only in the United States (1). The global pooled incidence is reported to be 34 cases per 100,000 individuals-year, being North America and Western Pacific the regions with the highest incidence (2). Although its overall mortality rate has fallen over time and is currently around 2%, severe acute pancreatitis (SAP) is still associated with a high mortality rate, which rises up to 50% (1, 3). This significant mortality in severe cases is
related to the development of local complications and organ failure due to systemic inflammatory response syndrome (SIRS) (4, 5). Therefore, one of the most important steps in the management of AP is the early assessment of its severity in order to identify and treat high-risk patients, which improves the outcome and reduces the mortality rate.

C-reactive protein (CRP) is a pentraxin synthesized by the liver in response to inflammatory mediators such as interleukin 6 (IL-6), tumor necrosis factor α (TNFα) and interleukin 1β (IL-1β). The serum levels of this acute-phase protein rise due to infections, inflammatory diseases, trauma and cancer (6). The efficacy of CRP as an outcome predictor in critically ill patients has been corroborated in several prior studies (7, 8). In the same way, serum albumin is another acute-phase protein used as a prognosis marker in the critical care setting. This protein is downregulated by inflammatory signals and its low levels have been correlated with a severe inflammatory response and an increased short-term mortality (9-11).

The CRP/albumin ratio is a novel inflammatory marker that may predict the prognosis of critically ill patients and several cancers (9, 12-14). Nevertheless, there are few studies on the prognostic role of this inflammatory marker in AP. This study aimed to assess the value of CRP/albumin ratio to predict the severity in AP.

**MATERIALS AND METHODS**

**Study design**

A retrospective study was performed from a prospective database of patients diagnosed with AP who were admitted from March 2014 to December 2021 at the Department of Gastroenterology of Hospital Universitario de Valladolid, Spain. The exclusion criteria included age <18 years, recurrent pancreatitis, previous diagnosis of chronic pancreatitis, history of surgery involving the pancreas, history of cancer, pregnancy, patients referred from other hospitals and incomplete data in the electronic medical record. The study followed the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines and was approved by the Ethics Committee of Hospital Universitario de Valladolid with the protocol number PI-22-2929.
Data collection

Data were obtained from electronic medical records of Hospital Universitario de Valladolid. Information collected included patient clinical demographic data, etiology, severity (revised Atlanta criteria, Ranson criteria and Bedside Index of Severity in Acute Pancreatitis [BISAP]), laboratory findings at admission, length of stay, local complications, organ failure, systemic complications, SIRS, intensive care unit (ICU) admission, interventional procedure need and mortality.

Study definitions and classifications

According to the revision of the Atlanta classification, the diagnosis of AP required at least two of the following features: abdominal pain consistent with AP, biochemical evidence of pancreatitis (amylase or lipase at least three times greater than the upper limit of normal), and/or characteristic findings on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) or transabdominal ultrasonography (15).

The severity of pancreatitis was classified as mild (MAP) (absence of organ failure and the absence of local or systemic complications), moderately severe (MSAP) (presence of transient organ failure and/or local or systemic complications within 48 h) and SAP (presence of persistent organ failure, involving one or more organs and lasting > 48 h) (15, 16).

A score ≥2 points for one of three organs (respiratory, cardiovascular or renal system) of the modified Marshall scoring was defined as organ failure (17). Systemic complication was defined as an exacerbation of a pre-existing co-morbidity such as heart failure, coronary artery disease, chronic lung disease or chronic kidney disease precipitated by AP. Whereas a local complication refers to the presence of acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis (15).

SIRS was defined as the presence of two or more of the following criteria: temperature >38°C or <36°C, heart rate>90 beats/minute, respiratory rate>20 breaths/minute or partial pressure of CO2 <32 mmHg, leucocyte count >12,000 or <4000/microliters or
>10% immature forms (15, 18).

In this study, mortality was defined as any event resulting in the death of the patient during their hospital admission or within 90 days after their discharge. Upon admission to the emergency department, all patients underwent CRP and albumin value measurement. Additionally, routine imaging was performed on all patients via CECT or transabdominal ultrasonography. For patients suspected to have complications, repeat imaging was performed.

**Statistical analysis**

In cases of a normal distribution, continuous variables were expressed as the mean ± standard deviation (SD) and the median and interquartile range for a non-normal distribution. Categorical variables were expressed as frequencies and proportions. Chi-square or 2-tailed Fisher’s exact test were applied for categorical data. For continuous variables, the groups were compared by using one-way analysis of variance (ANOVA) with Bonferroni post-hoc correction or Kruskal–Wallis test according to the result normality test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using both univariable and multivariable logistic regression analysis to assess the predictiveness of the CRP/albumin ratio for SAP. The following variables were included in the multivariable analysis: age, hypertension and diabetes. These covariables were chosen based on their p-value < 0.1 by the Wald test. To evaluate the accuracy of the CRP/albumin ratio in predicting SAP, patients were classified into two groups: MAP/MSAP and SAP groups. The receiver operative characteristic (ROC) curve was generated for both CRP/albumin ratio and Ranson criteria. The optimal cut-off point of CRP/albumin ratio for predicting SAP was calculated using Youden's index. Statistical analyzes were calculated by using IBM® SPSS® Statistics 21.0.

**RESULTS**

Among the 936 patients with AP admitted to the gastroenterology department throughout the study period, 722 patients were included in the current study, as shown in the flow diagram (Fig. 1). Of these patients, 384 (53.2%) were female. The mean age was 68.5 ±16.9 years. Biliary was the most frequent etiology of AP (62%). Regarding lifestyle habits, 16.2% were smokers and 23.5% drank alcohol. Baseline
patient and admission characteristics are summarized in Table 1.

Based on the revised Atlanta Classification, 568 (78.67%) patients were classified as MAP, 113 (15.65%) as MSAP and 41 (5.67%) as SAP. Ranson score, BISAP, organ failure, local complications, systemic complications, SIRS, length of hospital stay, ICU admission, interventional procedure need and mortality were significantly higher in the SAP group (Table 2). Seventeen patients with MSAP and 6 with SAP required interventional procedures, with endoscopic drainage being the most frequently used modality (56.2%) followed by percutaneous catheter drainage (43.8%).

On multivariable logistic regression analysis, CRP/albumin ratio remained a significant predictor of SAP, with a 20% increase in the likelihood of SAP for each 10-unit increase in the ratio (OR 1.02; 95% CI 1.01–1.03; P < 0.001) (Table 3). The area under the ROC curve (AUC) of CRP/albumin ratio in SAP was 0.68 (95% CI 0.58-0.77; P< 0.001) and was higher than that of the Ranson criteria, 0.62 (95% CI 0.53-0.71; P=0.008). According to Youden's index the optimal cut-off point that discriminates between SAP and MAP/MSAP was 7.51 (sensitivity 63.4%, specificity 65.6%, positive predictive value 10.0% and negative predictive value 96.7%) (Figure 2).

**DISCUSSION**

The prompt identification of patients with AP that could potentially develop a complicated form of this inflammatory disease is key to reduce its mortality by starting an appropriate treatment at an early stage. For this reason, many scores have been proposed in order to predict the prognosis in AP. Nevertheless, such scores have several limitations, including the need to wait 48 hours for an adequate assessment (e.g., Ranson criteria) or being complex to use, due to the large number of parameters that it takes into account (e.g., APACHE II). This situation has led to the investigation of new, simpler, rapid and cost-effectiveness prognostic markers. (19).

The CRP/albumin ratio is an easily calculable biomarker that has gained relevance in recent years in the study of the prognosis of several malignancies and inflammatory diseases. The higher CRP and lower albumin levels have been related to a higher inflammatory status (20). This marker has been associated with poor prognosis in critically ill patients. For instance, Ranzani et al. reported that CRP/albumin ratio could
be used as independent factors to predict long-term mortality in septic patients after ICU discharge being more accurate than CRP alone (9).

Regarding AP, only a few studies have investigated the prognostic value of the CRP/albumin ratio. Kaplan et al. conducted a retrospective study and found a positive correlation between the CRP/albumin ratio, Ranson score, and Atlanta classification. They observed that 26.3% of patients with a CRP/albumin ratio >16.28 had SAP (21). In the current study, we determined an optimal cut-off of 7.51, which could predict the occurrence of SAP with an AUC of 0.68. This AUC value was higher than that obtained using the Ranson criteria (AUC=0.62). Approximately 63% of patients with CRP/albumin ratio >7.51 developed SAP. Yılmaz et al. reported a cut-off value of 8.51 in SAP, which is slightly higher than our results. (22). Karabuga et al. found that the CRP/albumin ratio was significantly higher in patients with SAP than those with MAP, as assessed by the BISAP score, with a sensitivity of 71.43% and specificity of 70.88% (23). A recent systematic literature review, which analyzed three studies involving 956 patients, revealed a positive correlation between the CRP/albumin ratio at admission and the development of SAP, prolonged hospitalization and increased mortality rate (24). Some possible explanations of these findings could be that interleukin-6 and other inflammatory cytokines are disproportionately released in AP reducing the albumin synthesis by the liver. Additionally, the increased capillary permeability secondary to endothelial cell damage due to these cytokines leads to an excessive extravasation of albumin into the interstitial space, decreasing colloid osmotic pressure, which has been associated with the development of respiratory failure and acute kidney injury (25, 26). On the other hand, CRP is not only an inflammatory marker but also may play a significant pathogenic role in endothelial damage during AP. CRP has been associated with a down-regulation of nitric oxide synthesis by endothelial cells in critically ill patients, which decreases the antioxidant defenses resulting in apoptosis of endothelial progenitor cells (27). This situation could lead to microvascular alterations and finally organ failure and death (28).

Our investigation has a significant strength in that it represents, to the best of our knowledge, the study with the largest sample size for evaluating the correlation between CRP/albumin ratio and the severity of AP. Nevertheless, this study has several
limitations that need to be considered. First, there might be information bias due to the retrospective design of the study. Second, this study was carried out in a single center, which may limit the generalizability of the present results. Third, we did not record the time elapsed from the onset of symptoms to the measurement of CRP and albumin in our database, which could potentially influence the results. Finally, the present research excluded patients with incomplete data in the medical records, which might have led to selection bias. Due to these limitations, we suggest to carrying out multicenter, prospective studies in order to corroborate our results and establish the optimal cut-off value of the CRP/albumin ratio.

In summary, our results illustrated that the CRP/albumin ratio, despite its low sensitivity and specificity, could be used as a complementary marker to the classical scores in the initial assessment of the prognosis of acute pancreatitis. This marker is a cost-effective, easy to measure and valuable tool that could be used by physicians to recognize high-risk patients in order to implement an early and appropriate treatment. However, more research is needed to support the potential of this biomarker as a reliable predictor of acute pancreatitis outcomes.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

SOURCES OF FUNDING

None.

AVAILABILITY OF DATA

The data in the current study are available from the corresponding author upon reasonable request.

AUTHORS CONTRIBUTIONS

Involved in the conception, analysis of data and draft of the manuscript: JFPG and RCZI. Involved in the acquisition of data: MLRR and MARR. Revised manuscript critically for important intellectual content: MLRR and LFS. All authors contributed to the article and approved the submitted version.
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Table 1. Baseline clinical characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>n=722</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (± SD)</td>
<td>68.5 (±16.9)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>338 (46.8)</td>
</tr>
<tr>
<td>Female</td>
<td>384 (53.2)</td>
</tr>
</tbody>
</table>
BMI, mean (± SD) 27.7 (±4.7)
WC (cm), mean (± SD) 100.5 (± 13.7)

Etiologies, n (%)  
- Biliary 448 (62)
- Alcohol 56 (7.8)
- ERCP 26 (3.6)
- Idiopathic 149 (20.6)
- Others 43 (6)
- Diabetes mellitus, n (%) 118 (16.3)
- Hypertension, n (%) 385 (53.3)
- Alcoholism, n (%) 170 (23.5)
- Smoker, n (%) 116 (16.2)

Abbreviations: BMI, Body mass index; WC, waist circumference; ERCP, Endoscopic retrograde cholangiopancreatography.

**Table 2.** Comparison of clinical outcomes and laboratorial data between severity categories in patients with acute pancreatitis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>MAP (n=568)</th>
<th>MSAP (n=113)</th>
<th>SAP (n=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranson Score, median (IQR)</td>
<td>1 (1-2)</td>
<td>2 (1-2)</td>
<td>2 (1-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BISAP, median (IQR)</td>
<td>1 (0-1)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SIRS, n (%)</td>
<td>105 (18.5)</td>
<td>71 (62.8)</td>
<td>34 (82.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Variable</td>
<td>Non-adjusted analysis</td>
<td>Adjusted analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-----------------------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95%CI)</td>
<td>P value</td>
<td>OR (95%CI)</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Length of stay (days), median (IQR)</td>
<td>5 (4-7)</td>
<td>12 (8-20)</td>
<td>10 (3-25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>27 (65.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/dL), median (IQR)</td>
<td>3.7 (3.4-4.0)</td>
<td>3.5 (3.1-3.8)</td>
<td>3.4 (3.1-3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/L), median (IQR)</td>
<td>11 (3.7-38.0)</td>
<td>28.9 (6.5-93.0)</td>
<td>48 (13.5-142.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP/albumin, median (IQR)</td>
<td>2.8 (1.0-10.7)</td>
<td>8.0 (1.9-26.0)</td>
<td>15.7 (3.9-44.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; BISAP, Bedside Index of Severity in Acute Pancreatitis; SIRS, systemic inflammatory response syndrome; ICU, intensive care unit; CRP, C-reactive protein.

Comparison among the three groups.

The significance for pairwise comparisons was calculated using the Bonferroni adjustment. *P* < 0.05, compared with MAP; *P* < 0.05, compared with MSAP

Table 3. Univariable and multivariable analysis to assess the relationship between CRP/albumin ratio and severe acute pancreatitis.
<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.041 (1.017-1.067)</td>
<td>0.001</td>
<td>1.030 (1.002-1.059)</td>
<td>0.033</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.864 (1.382-5.933)</td>
<td>0.005</td>
<td>1.860 (0.824-4.197)</td>
<td>0.135</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.967 (0.956-4.045)</td>
<td>0.066</td>
<td>1.578 (0.737-3.379)</td>
<td>0.241</td>
</tr>
<tr>
<td>BMI</td>
<td>1.046 (0.981-1.115)</td>
<td>0.166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP/albumin ratio</td>
<td>1.024 (1,015-1,033)</td>
<td>&lt;0.001</td>
<td>1.023 (1.014-1.032)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, Body mass index; CRP, C-reactive protein.

P value of the model <0.005; Nagelkerke R2 0.154

**Figure 1.** Flow diagram of patient selection.
**Figure 2.** Receiver operating characteristic curve for CRP/albumin ratio and Ranson criteria to predict severe acute pancreatitis.