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Original Article PULMONOLOGY

The predictive power of albumin-based composite indicators for mortality in patients with aspiration pneumonia

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ABSTRACT

OBJECTIVE: The incidence of aspiration pneumonia (AP) is rising due to an increasing population with chronic conditions. This study investigates the association between albumin-based composite indicators—blood urea nitrogen/albumin (B/A), lactate dehydrogenase/albumin (L/A), and C-reactive protein/albumin (C/A) ratios—and AP-related mortality.

METHODS: In this retrospective study, adult patients diagnosed with AP between 2022 and 2023 were analyzed. Patients' demographics, clinical data, and lab results were recorded. Albumin-based composite indicators were calculated, and outcomes were observed up to 28 days post-admission, categorizing patients as survivors or non-survivors.

RESULTS: The study involved 67 patients, with a median age of 80. The 28-day mortality rate was 38.8% (n=26). There were no substantial demographic or clinical differences between survivors and non-survivors ($p>0.05$). However, non-survivors exhibited notably lower serum albumin levels ($p>0.001$). Additionally, B/A and C/A ratios were significantly higher in non-survivors ($p<0.05$). B/A ratios above 1.03 and C/A ratios above 6.15 correlated significantly with mortality ($p=0.023$ and $p=0.026$).

CONCLUSION: The results indicate that lower serum albumin levels and higher B/A and C/A ratios are significantly linked to AP-induced mortality. These albumin-based indicators may serve as useful markers for early risk assessment and outcome prediction in AP patients.

Keywords: Albumin; aspiration pneumonia; blood urea nitrogen; C-reactive protein; lactate dehydrogenase; mortality.

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Aspiration pneumonia (AP) has recently gained importance due to the aging of the population and the increasing incidence of chronic diseases [1]. Neurologic and esophageal diseases are considered predisposing factors for the development of AP, particularly in older adults [2–4]. Early risk stratification and prediction of disease outcomes are crucial in determining the appropriate treatment strategy for AP [2].

Previous studies have evaluated the effectiveness of various biochemical parameters in predicting mortality in a variety of clinical conditions, including pneumonia, serious viral infections, sepsis, and myocardial infarction [1, 5–9]. Albumin as a negative acute phase reactant can predict the increases in morbidity and mortality risks in critical illnesses. In parallel, albumin-based composite indicators, i.e., the ratio of albumin to other biochemical parameters, including blood urea nitrogen (BUN), C-reactive protein (CRP), and lactate dehydrogenase (LDH), have been one of the most speculated biomarker groups used for predicting mortality in critical diseases mentioned above [1, 7, 10].

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In patients with low hemodynamic status secondary to various clinical situations, BUN level might reflect cardiorenal functions and neurohormonal activation [6, 11, 12]. Several studies reported that LDH can be used as a specific biomarker for lung endothelial damage [10]. LDH is directly related to the extent of cellular damage caused by infections [7]. Therefore, the ratios of these biomarkers to albumin, the most widely studied negative acute phase reactant, might be potentially used for predicting AP-induced mortality.

The prognostic value of the BUN/albumin (B/A) ratio in predicting increased mortality in patients with AP, pneumonia, malignancy, coronavirus disease 2019 (COVID-19), and chronic heart failure has been addressed in the literature [1, 5, 6, 11]. The relationship between serum levels of albumin and LDH and AP-induced mortality has also been studied [13, 14]. Nevertheless, there is still no simple marker that can be used to predict AP-induced mortality and morbidity.

In light of this information, this study was conducted to assess the prognostic powers of BUN, LDH, and CRP biomarkers and the ratios of these biomarkers to albumin in predicting AP-related mortality.

Highlight key points

- The incidence of aspiration pneumonia is increasing with the aging of the population.
- Albumin-based combined indicators are used to predict the mortality of diseases.
- In AP, B/A and C/A elevations were found to be associated with mortality.

MATERIALS AND METHODS

Study Design

This retrospective observational study was conducted with AP patients admitted to 3rd level health practice and research hospital, a tertiary care referral center, between 2022 and 2023. This study was approved by the Kahramanmaras Sutcu Imam University Medical Research Ethics Committee (date: 16.05.2023, number: 05). In this study, the principles of the Helsinki Declaration were adhered to. Written informed consent could not be obtained because it was a retrospective study.

Population and Sample

The study's population consisted of all consecutive adult (≥18 years) patients who were admitted to the hospital in the intensive care unit (ICU) or inpatient clinics for chest diseases after they presented to the emergency department with AP. AP was diagnosed based on the following criteria: 1) a history of witnessed or suspected aspiration in patients with previously defined risk factors for oropharyngeal aspiration, including cerebrovascular disorders, impaired swallowing associated with chronic neurological diseases, impaired consciousness, dementia, history of tube feeding [3, 4, 8], 2) a new gravity-dependent pulmonary infiltrate consistent with pneumonia on thoracic imaging, and 3) acute onset of one major symptom or sign, including cough, sputum production or fever or two minor symptoms or signs, including pleuritic chest pain, dyspnea, altered mental status, respiratory rate>20 breaths per minute, signs of pulmonary consolidation, or leukocyte count>$12\times10^3/\mu L$ [4, 14]. In cases suspected of aspiration, a simple water swallowing test was performed to assess the swallowing reflex [4]. The patients with a confirmed diagnosis of AP were included in the study sample. The patients with nosocomial pneumonia diagnosed ≥24 hours after admission and structural destruction of the lungs, such as sequelae of tuberculosis and bronchiectasis, acute hospital admission in the previous 15 days, who were human immunodeficiency virus (HIV) carriers, and received 20 mg/day or more steroid therapy for ≥ four weeks were excluded from the study [3, 14].

Follow-up Procedure

A standardized treatment approach featuring initial antibiotic therapy was used for all patients with AP after hospitalization. Necessary modifications were performed depending on the clinical and microbiological findings of the patient. Accordingly, other therapeutic and supportive measures, including systemic corticosteroids or inotropic drugs, parenteral nutrition, blood transfusion, placement of central venous catheters, nasogastric feeding tube or gastrostomy, invasive or noninvasive mechanical ventilation, and therapeutic bronchoscopy were resorted to at the discretion of the attending physician [4].

Patients were evaluated 28 days after admission until death or discharge. The condition of the patients who were discharged before the 28th day of their hospitalization was queried over the phone on the 28th day.

The Variables in the Research

Patients' demographic (age, gender) and clinical characteristics (comorbidities) were obtained retrospectively from the hospital information system and recorded. The Charlson Comorbidity Index (CCI) was calculated for each patient [15]. The baseline laboratory parameters included white blood cell (WBC) count ($\times 10^3/\mu L$), glucose (mg/dL), creatinine (mg/dL), BUN (mg/dL), serum total protein (mg/dL), albumin (mg/dL), LDH (IU/L), and CRP (mg/dL). The albumin-based composite indicators assessed were B/A, LDH-to-albumin (L/A), and CRP-to-albumin (C/A) ratios.

The pneumonia severity index (PSI) and the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were determined for each patient during their initial admission [16, 17]. The lengths of hospitalization in the ICU or inpatient clinics and the outcome at the end of the 28th day were also recorded for each patient.

Study Groups

Patients 28th at the end of the day, they were grouped according to their last survival status. Accordingly, those who survived for more than 28 days after emergency hospitalization were included in the survivor group, and those who died within 28 days after the first hospitalization were included in the non-survivor group.

Statistical Analysis

The 28-day mortality was the primary outcome of the study. The study's secondary outcomes were the differences between survivor and non-survivor groups in albumin-based composite indicator levels.

Descriptive statistics obtained from the research data are expressed as mean±standard deviation for normally distributed continuous variables, median with minimum-maximum values for non-normally distributed continuous variables, and number and percentage values for categorical variables. Shapiro-Wilk, Kolmogorov-Smirnov and Anderson-Darling tests were used to analyze the normal distribution properties of numerical variables.

To compare differences between categorical variables, Pearson chi-square and Fisher's exact tests were used in 2x2 tables, and Fisher-Freeman Halton test was used in RxC tables.

Respectively, independent samples t-test and Mann-Whitney U test were used to compare two independent groups with and without normal distribution of numerical variables.

In order to determine the optimal cut-off values of the albumin-based composite indicators in predicting AP-induced 28-day mortality, the receiver operating characteristic (ROC) curve analysis was conducted using the DeLong method with the Youden index. The area under the curve (AUC) and the corresponding 95% confidence intervals (CI) were calculated. Positive predictive values (PPV), negative predictive values (NPV), specificity, sensitivity, and positive and negative odds ratios (OR) were calculated according to the optimal cut-off values of the investigated variables with AUC values.

Jamovi project 2.3.28.0 (Jamovi, version 2.3.24.0, 2023, retrieved from https://www.jamovi.org) and JASP 0.17.1 (Jeffreys's Amazing Statistics Program, version 0.17.2.1, retrieved 2023 from https://jasp-stats.org) software packages were used in statistical analyses. Probability (p) statistics of ≤ 0.05 were considered to indicate statistical significance.

RESULTS

The median age of the 67 patients included in the study was 80 (min. 19, max. 99) years. Most (68.7%) of the patients were male. Hypertension, detected in 37 (55.2%) patients, was the most common comorbidity in the sample. The median CCI score was five, with a maximum value of 12. Malnutrition/dehydration (62.7%) and uncoordinated swallowing reflex (46.3%) were the most common risk factors associated with the development of aspiration. The other demographic and clinical characteristics are shown in Table 1.

Of the 67 patients included in the study, 26 (38.8%) had died within the first 28 days of hospitalization. There was no significant difference in demographic and clinical characteristics between the surviving and non-surviving groups. ($p>0.05$) (Table 1).

Among the risk factors for aspiration, malnutrition/dehydration and uncoordinated swallowing reflex were the most common clinical conditions in both survivor and non-survivor groups (Table 1). There was no significant difference between the survivor and non-survivor groups in the risk factors for aspiration ($p>0.05$).

Patients' laboratory test results are summarized in Table 2. There was no significant difference between the survivor and non-survivor groups in laboratory test re-

Table 1. Demographic and clinical characteristics of the patients

	Overall (n=67) %	Groups based on 28-day mortality		p
		Survivors (n=41) %	Non-survivors (n=26) %	
Age (year), median (min–max)	80.0 (19.0–99.0)	80.0 (19.0–96.0)	80.0 (48.0–99.0)	0.164**
Sex‡				
Female	31.3	34.1	26.9	0.726*
Male	68.7	65.9	73.1	
Addiction for smoking, alcohol, ansd substance, %	22.4	24.4	19.2	0.847*
Comorbidities, %				
Hypertension	55.2	56.1	53.8	0.999*
Diabetes mellitus	13.4	9.8	19.2	0.294*
Chronic renal failure	16.4	12.2	23.1	0.315*
Chronic obstructive pulmonary disease	13.4	14.6	11.5	0.999*
Cardiovascular diseases	20.9	19.5	23.1	0.967*
Cerebrovascular diseases	29.9	31.7	26.9	0.886*
Alzheimer/dementia	34.3	34.1	34.6	0.999*
Others	49.3	56.1	38.5	0.248*
Charlson Comorbidity Index, median (min–max)	5.0 (0.0–12.0)	5.0 (0.0–9.0)	6.0 (0.0–12.0)	
Risk factors for aspiration, %				
Dysphagia	31.3	26.8	38.5	0.465*
Gastroesophageal reflux	16.4	14.6	19.2	0.738*
Uncoordinated swallowing reflex	46.3	46.3	46.2	0.999*
Immobilization/muscular failure	38.8	39.0	38.5	0.999*
Drugs	6.0	4.9	7.7	0.638*
Respiratory problems	9.0	4.9	15.4	0.197*
Cognitive disorders	35.8	34.1	38.5	0.922*
Malnutrition/dehydration	62.7	56.1	73.1	0.254*
Nasogastric feeding	3.0	2.4	3.8	0.999*
Percutaneous endoscopic gastrostomy	3.0	4.9	0.0	0.518*

*: Pearson Chi-Square or Fisher's Exact test; **: Mann-Whitney U test.

sults (p>0.05), except for serum albumin level, which was significantly lower in the non-survivor group than in the survivor group (p>0.001).

Among the albumin-based composite indicators, B/A and C/A ratios were significantly higher in the non-survivor group than in the survivor group (p=0.002 and p=0.029, respectively). On the other hand, there was no significant difference between the survivor and non-survivor groups in the L/A ratio (p=0.069) (Table 2).

There was a significant difference between the groups in the PSI score (p=0.033). There were more patients with a PSI score of four and five than patients with a PSI score of zero to three in both groups. However, the difference between the number of patients with different PSI scores was not statistically significant (p=0.174) (Table 3). Additionally, the median APACHE II score was higher, albeit not significantly, in the non-survivor group than in the survivor group (22 vs. 18, p=0.067).

Table 2. Laboratory investigations of the patients at the admission

	Groups based on 28-day mortality		p
	Survivors (n=41)	Non-survivors (n=26)	
Leukocyte count (×10³/µl), median (min–max)	12.4 (2.4–30.3)	9.4 (2.3–35.1)	0.266*
Glucose (mg/dL), median (min–max)	123.0 (71.0–356.0)	125.5 (62.0–454.0)	0.528*
Creatinine (mg/dL), median (min–max)	0.9 (0.3–4.7)	1.6 (0.3–4.0)	0.054*
Blood urea nitrogen (mg/dL), median (min–max)	26.0 (8.0–71.0)	43.0 (13.0–106.0)	0.050*
Total protein (mg/dL), median (min–max)	60.9±7.2	58.2±9.0	0.196**
Albumin (mg/dL), median (min–max)	31.7±6.4	24.5±6.1	**<0.001****
Lactate dehydrogenase (IU/L), median (min–max)	303.0 (125.0–794.0)	282.5 (126.0–534.0)	0.699*
C-Reactive protein (mg/dL), median (min–max)	112.0 (5.0–412.0)	115.5 (18.5–414.0)	0.414*
Composite indicators, median (min–max)			
Blood urea nitrogen-to-albumin (B/A) ratio	0.9 (0.2–3.1)	1.7 (0.4–5.7)	**0.002***
Lactate dehydrogenase-to-albumin (L/A) ratio	10.2 (4.4–28.8)	11.9 (6.3–28.8)	0.069*
C-Reactive protein-to-albumin (C/A) ratio	4.1 (0.1–15.6)	5.7 (0.7–19.5)	**0.029***

*: Mann-Whitney U test; **: Independent Samples T-Test.

Table 3. Prognostic variables of the patients

	Groups based on 28-day mortality		p
	Survivors (n=41)	Non-survivors (n=26)	
Pneumonia Severity Index, median (min–max)	4.0 (2.0–5.0)	4.0 (2.0–5.0)	**0.033***
Class1, n (%)	0 (0.0)	0 (0.0)	0.174**
Class2, n (%)	6 (14.6)	1 (3.8)	
Class3, n (%)	6 (14.6)	3 (11.5)	
Class4, n (%)	20 (48.8)	10 (38.5)	
Class5, n (%)	9 (22.0)	12 (46.2)	
APACHE II score, median (min–max)	18.0 (6.0–31.0)	22.0 (7.0–40.0)	0.067*

*: Mann-Whitney U test; **: Fisher Freeman Halton test.

Nasal oxygen support was the most common type of oxygen therapy used in both survivor and non-survivor groups (87.8% and 88.5%, respectively). There was no significant difference between the groups in the rate of patients using different oxygen therapy modalities (p=0.572) (Table 4).

The length of ICU stay was significantly higher in the non-survivor group than in the survivor group (p=0.011). On the other hand, patients in the survivor group stayed significantly longer in other services than the patients in the non-survivor group (p<0.001) (Table 4).

The ROC curve for predicting mortality within the first 28 days following admission is given in Figure 1. The ROC analysis revealed a higher AUC value for the B/A ratio than the C/A ratio in predicting mortality (0.724 vs. 0.659). Accordingly, B/A >1.03 predicted the 28-day mortality with 76.92% sensitivity and 60.98% specificity (p=0.023). Similarly, C/A >6.15 was significantly associated with mortality (p=0.026) (Table 5).

TABLE 4. Comparison of the groups regarding treatment characteristics

	Groups based on 28-day mortality		p
	Survivors (n=41) %	Non-survivors (n=26) %	
Modality for oxygen support, %			0.572**
Nasal oxygen	87.8	88.5	
Non-invasive mechanical ventilation	4.9	0.0	
Mechanical ventilation	7.3	11.5	
Bronchoscopy, yes, n (%)	17 (41.5)	14 (53.8)	0.460**
Length of intensive care stay (day), Median (min–max)	6.0 (1.0–59.0)	12.0 (4.0–28.0)	**0.011***
Length of ward stay (day), Median (min–max)	3.0 (0.0–20.0)	0.0 (0.0–5.0)	<**0.001***

*: Mann-Whitney U test; **: Pearson Chi-Square, Fisher's Exact, or Fisher Freeman Halton test.

TABLE 5. Receiver operating characteristic curve analysis showing the cut-off values of B/A and C/A in predicting mortality

	AUC	Sensitivity	Specificity	Cut-off	95% CI	PPV, %	NPV, %	p
Blood urea nitrogen-to-albumin (B/A) ratio	0.724	76.92	60.98	>1.03	0.601–0.826	55.6	80.6	**0.003**
C-reactive protein-to-albumin (C/A) ratio	0.659	46.15	82.93	>6.15	0.533–0.771	63.2	70.8	**0.026**

AUC: Area under the curve; CI: Confidence intervals; PPV: Positive predictive values; NPV: Negative predictive values.

DISCUSSION

The study's findings showed that low albumin and higher B/A and C/A ratios were significantly associated with mortality in patients with AP.

BUN is known to be associated with mortality in various diseases. Chen et al. [12] reported that higher BUN levels were associated with mortality in acute exacerbation of chronic obstructive pulmonary disease (COPD). Additionally, a study conducted in India stated that BUN, albumin, and B/A ratio were significant predictors of in-hospital mortality in COVID-19 patients [6]. In addition to the B/A ratio, another albumin-based composite indicator used to predict mortality in various diseases is the C/A ratio. Nishizawa et al. [3] found that patients with AP had significantly increased CRP and C/A ratio levels compared to the healthy control subjects. Ryu et al. [1] recommended the B/A ratio as a simple and potentially useful prognostic factor in predicting 28-day mortality in AP patients. In the said study, the optimal cut-off value for the B/A ratio was determined as 7.03. In comparison, this study's find-

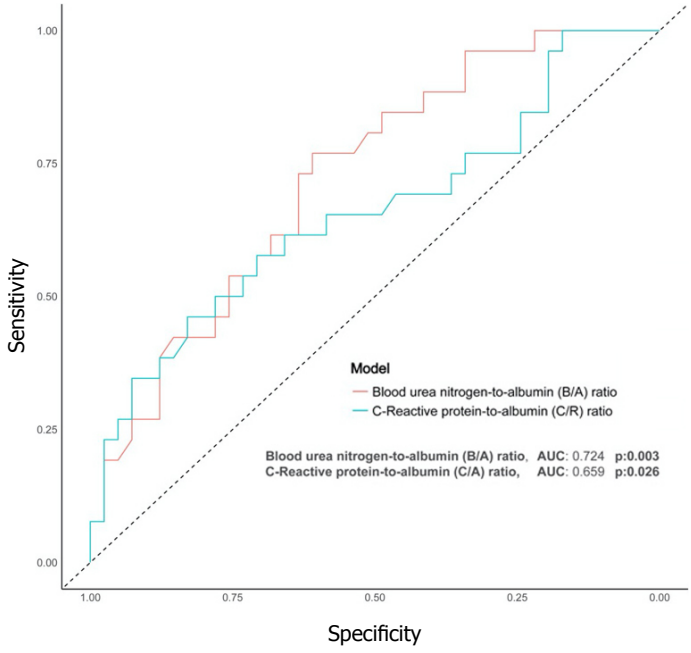

FIGURE 1. Graphical representation of the receiver-operating characteristics curve for predicting mortality within the first 28 days following admission.

ings revealed that increased B/A and C/A ratios were significantly associated with 28-day mortality and that optimal cut-off values of 1.03 and 6.15 can be used to predict mortality in AP patients during the first 28 days of hospitalization. Similar findings were observed in a study conducted with SARS-CoV-2-infected patients admitted to the emergency unit [5]. The difference between the cut-off values determined for the B/A ratio in Ryu et al.'s study [1] and this study (7.03 vs. 1.03) might be attributed to the differences between the units used in the measurements of laboratory parameters. However, further studies are needed to draw generalizable conclusions regarding the use of B/A and C/A ratios to stratify the risk of death in AP.

Cellular injuries from infections or acute respiratory failure usually increase lactate or LDH levels [7, 18]. The use of LDH as a single prognostic factor might be confounding, given the increase in LDH levels in any comorbidity [7]. Serum albumin is a negative inflammatory indicator, and hypoalbuminemia might be used as the denominator for LDH. Jeon et al. [7] reported significantly higher L/A ratios in non-survivors with severe infection requiring intensive care than in survivors. In this study, there were significant differences in serum LDH and albumin levels between survivors and non-survivors. L/A ratio, as an albumin-based composite indicator, was significantly associated with mortality. Sipahioglu and Onuk [10] reported significantly higher L/A and B/A ratios and comparable C/A ratios in surviving COVID-19-related severe acute respiratory distress syndrome patients than in non-survivors. Among the albumin-based composite indicators, they determined that only the L/A ratio was an independent risk factor for mortality.

However, there are no studies on the prognostic power of the L/A ratio in AP patients. This study's findings did not support the use of the L/A ratio to predict mortality in AP patients, probably because of comparable LDH levels in the survivor and non-survivor groups. Large-scale studies are needed to determine the prognostic impact of the L/A ratio in AP.

Previous studies reported poor nutritional status as a predictive factor for survival in AP. Poor nutritional status, indicated by low body mass index (BMI) and serum albumin levels, negatively affects the development, refractoriness, and severity of infectious disease [19]. BMI and serum albumin levels are reportedly related to life expectancy in older populations [19, 20]. Ito et al. [21] determined that BMI values of less than 19.9 kg/m^2 were associated with higher mortality rates in elderly Japanese patients with AP. Nevertheless, the mean BMI values in the survival and non-survivor groups were 19.5 kg/m^2 and 16.1 kg/m^2, respectively. It might be difficult to generalize this finding to the populations living in Western countries with relatively higher BMI values. In comparison, in this study, anthropometric data used to calculate the BMI values of the patients were not available. Therefore, serum albumin level was the only parameter used to evaluate the nutritional status of the patients included in this study. Low serum albumin levels were significantly associated with 28-day mortality in the study group, in line with the literature [2, 4, 13]. The evaluation of the nutritional status using either serum albumin levels or relevant composite indexes is vital in predicting the survival of patients with AP.

The impact of malnutrition on the development of mortality in patients with AP may be time-dependent; that is, the negative effect of malnutrition may be more pronounced as the duration of chronic disease increases. Bosch et al. [14] investigated the prognostic factors of AP-induced mortality in older people with dementia and found that older age, being more dependent on care, lower serum albumin levels, and lymphocyte counts were associated with six-month mortality. Cabre et al. [22] found that lymphopenia and malnutrition were associated with 30-day and 12-month mortality. In comparison, only the 28-day mortality rate was investigated, and no grouping was made based on dementia.

Yanagita et al. [19] found that the Geriatric Nutritional Risk Index (GNRI) score, an indicator of nutritional disorder-related complications, was an independent early predictor of 90-day survival. In this study, non-survivors had significantly lower serum albumin levels than survivors. Then again, parameters such as serum albumin level, current weight, and ideal weight are included in the GNRI. In comparison, in this study, patients' GNRI scores could not be calculated due to the lack of patients' anthropometric data.

The pneumonia severity in patients with dysphagia or aspiration is another predictive factor. In general, mortality is expected to increase proportionally as pneumonia severity increases, as reflected by higher PSI scores [23]. Modification of the treatment according to the severity of the disease reportedly reduces in-hospital mortality rates [19]. In contrast, this study's findings did not reveal a significant relationship between PSI

scores and AP-induced mortality. In addition, the use of PSI in AP patients has been a matter of debate. Ryu et al. [1] detected significant differences in PSI scores between the survived and non-survived AP patients. Yet, they attributed these results to the fact that PSI is primarily affected by age and comorbid conditions. It is also difficult to calculate PSI scores in a timely manner. Hence, biochemical markers and composite indicators consisting of these markers may prove more useful as they may allow rapid decision-making.

The study's single-center, retrospective design was its primary limitation. The study's retrospective nature made it difficult to collect patients' demographic and clinical data. The study's small sample size was another limitation. Thirdly, if a comprehensive assessment of nutritional status could be made using several composite indices, it would have made a more holistic assessment together with the study's findings possible.

Conclusion

It was determined that low serum albumin levels and higher B/A and C/A ratios were significantly associated with 28-day in-hospital mortality. Evaluating the nutritional and inflammatory statuses of patients with AP is important in stratifying the mortality risk. In this context, multicenter, large-scale, prospective studies are needed to support the findings of this study, which indicated that B/A and C/A ratios are easily calculated and objective biomarkers that can be calculated to predict the risk of death in patients with AP.

Ethics Committee Approval: The Kahramanmaras Sutcu Imam University Medical Research Ethics Committee granted approval for this study (date:16.05.2023, number: 05).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: No conflict of interest was declared by the authors.

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