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The Relationship Between Hypoalbuminemia and Mortality in Geriatric Patients with Sepsis

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ABSTRACT

Aim: Albumin can be used as prognostic markers for various clinical results including critical care patients. In our study, we aimed to examine the relationship between albumin and mortality in geriatric patients with sepsis.

Design: Retrospective Study

Materials and Methods: This study included geriatric patients with sepsis treated in the medical intensive care unit of Adana City Training and Research Hospital between January 2018 and December 2020. Two hundred and fifty-two patients were enrolled in the study.

Results: The median acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment, and Charlson Comorbidity Index score were significantly higher in the non-survivors group. According to the laboratory parameters the serum levels of creatinine and, C-reactive protein were significantly higher in the non-survivor group. The serum level of platelets and albumin was significantly higher in the survivor group. In the multivariate analysis, age, APACHE II, platelets, and albumin were determined as significant independent determinants after the correction of the other variables. The lower albumin levels were associated with an increased risk of mortality in geriatric patients with sepsis. In the receiver operating characteristic curve analysis, albumin values of 2.85 and below were predictive for mortality.

Conclusion: Albumin levels can be used as a predictor of mortality in geriatric patients with sepsis. In addition, studies should be planned to evaluate whether the APACHE-2 score and albumin level together can better predict mortality in geriatric patients with sepsis.

Keywords: geriatrics, intensive care unit, mortality, sepsis

Introduction

Albumin is a vital protein for our body and is synthesized solely by the liver. Albumin is excreted in the blood at around 10-15 g per day and it is the most abundant protein in plasma (3.5 g/dL to 5 g/dL). Albumin has some physiologic roles. Human albumin acts as the most important modulator of the oncotic pressure of plasma. So it prevents the leakage of fluids into the extravascular spaces. Albumin also acts on the transport of different substances. Endogenous substances such as fatty acids, ions, bilirubin, and exogenous substances such as drugs; transported by serum albumin. In addition, albumin binds at least 40% of the calcium circulating and is a carrier of hormones like cortisol, testosterone and, thyroxine. The list of drugs transported by albumin includes furosemide, warfarin, methadone, thiopental, methotrexate, propranolol, and many others. Albumin also plays a role in maintaining acid-base balance because it acts as a plasmatic buffer (1-3).

The level of albumin in the plasma may decrease due to liver failure, malnutrition, nephrotic syndrome, chronic kidney failure, protein-losing enteropathy, burns, and sepsis. Low albumin causes many problems in patients, including death. Hypoalbuminemia is not the physiological process of aging however, with aging, diseases that cause hypoalbuminemia are more common. For this reason, hypoalbuminemia and its complications may be seen more frequently in the elderly (4).

Sepsis is associated with increased vascular permeability and capillary leakage that changes the distribution of albumin between intravascular and extravascular compartments. Other than that,

in patients with sepsis, there is also reduced synthesis and increased catabolism of albumin. As a result of these pathophysiological processes, hypoalbuminemia is a risk factor for mortality in patients with sepsis (5).

As a result, the mortality rate increases in both old age and sepsis. We planned to conduct our study in the septic geriatric patient group with a high mortality rate and aimed to examine the relationship between hypoalbuminemia and mortality in this patient group. We also evaluated the scoring systems used worldwide for prognostic evaluation for critically ill geriatric patients with sepsis in our study. In addition, biomarkers were evaluated in our study.

Material and Method

This retrospective study included geriatric patients with sepsis treated in the medical intensive care unit (ICU) of Adana City Training and Research Hospital between January 2018 and December 2020. Hospital is a tertiary regional hospital and has forty medical ICU beds. Sepsis was diagnosed according to the Sepsis-3 criteria (6). All patients aged >64 years who met the criteria were included in the study. The data were obtained from the hospital system. Patients with cancer, patients with liver failure, patients with covid-19, and patients who could not obtain the necessary data for the study were excluded from the study. A total of 2112 patients were reviewed retrospectively from the hospital information system, 252 patients were included in the study.

Definition of variables and outcome

The patients were separated into two groups as the survivor group who were discharged or transferred within 28 days of the first diagnosis and the non-survivor group who died within 28-days of the first diagnosis. In addition to the basic characteristics of the patients, first-day results of the hematological and biochemical analysis, including serum lactate, creatinine, C-reactive protein (CRP), and procalcitonin levels were also scanned. According to the results of the first day, sequential organ failure assessment (SOFA) score, acute physiology, and chronic health evaluation II (APACHE II) score, and Charlson comorbidity index (CCI) were calculated for each patient.

Statistical Analysis

Categorical variables were reported as numbers (%) and differences between groups were assessed using the chi-square test. Continuous variables were expressed as medians and interquartile range (IQR), and differences between groups were compared while using Mann–Whitney U test. A logistic regression analysis was conducted to identify variables associated with mortality. All statistically significant variables were included in the univariate analysis. All variables with a P value of less than 0.1 in univariate analyses were included in the multivariate analysis. Sensitivity, specificity, and receiver operating characteristic (ROC) with the area under the curve (AUC) were calculated to investigate the diagnostic test performance for albumin to predict mortality in sepsis patients. Optimal cut-off values were determined by Youden's index. All analyses were 2-tailed and conducted by R Statistical Software (version 5.3.0) and GraphPad Prism 8.0 (GraphPad Inc., CA, USA). p-value <0.05 was considered statistically significant. Estimated values are given with 95% confidence intervals (CI).

Results

252 patients were enrolled in the study. The baseline characteristics and outcomes of the patients are summarized in Table 1. The median age was 75 years (IQR 69–82) and 41.3% were male.

Table 1. Baseline characteristics and laboratory findings of total patients, survivors, and non-survivors

	Total (n= 252)	Survivors (n= 166)	Non-survivors (n= 86)	p
Age (Years)	75(69-82)	75(69-79)	75(74-82)	**0.005**
Sex				0.053
Male	104(41,3)	62(37.3)	62(37.3)	
Female	148(58.7)	104(62.7)	44(51.2)	
Prognostic scores				
APACHE-II	19(14-24)	16(13-20)	25(19-28)	**<0.001**
SOFA	6(3-9)	6(3-8)	6(4-10)	**0.018**
CCI	6(4-9)	6(4-8)	6(5-9)	**0.041**
Laboratory tests				
Wbc (x 10/µL)	11.7(8.4-16.3)	11(7.6-16)	12(9.4-16.2)	0.113
Hb (g/dL)	9.5(8.6-11.8)	9.8(8.6-11.9)	9.5(8.4-11)	0.124
Plt (x 10/µL)	186(141-284)	205(141-300)	171(122-262)	**0.037**
Na (mmol /L)	139(131-141)	139(134-141)	136(128-143)	0.132
K (mmol /L)	3.9(3.4-4.4)	3.8(3.3-4.7)	4.1(3.4-4.4)	0.112
Cr (g/dL)	1.59(0.9-2.4)	1.4(0.9-2.2)	1.6(1.1-2.5)	**0.042**
ALT (u/L)	44(24-86)	42(25-80)	62(24-96)	0.134
CRP (mg/L)	51(29-74)	44(25-68)	61(39-87)	**0.003**
PCT (g/L)	9.1(2.1-20)	6.4(1.9-21)	11.8(5.8-19)	0.096
Albumin (g/dL)	2.9(2.2-3.1)	3(2.6-3.1)	2.6(2.2-2.9)	**<0.001**

K: potassium, **Na:** sodium, **APACHE-II score:** Acute Physiology and Chronic Health Evaluation 2 score, **CCI:** Charlson comorbidity index, **Cr:** Creatinine **CRP:** C-reactive protein, **Hb:** hemoglobin, **PCT:** procalcitonin, **Plt:** platelet count, **SOFA:** Sequential Organ Failure Assessment, **WBC:** white blood cell.

Table 2. Odds ratios obtained by unadjusted univariate and adjusted multivariate logistic regression analysis for mortality in sepsis patients

	Univariate			Multivariate		
Variables	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (years)	1.041	1.009-1.074	0.011	1.062	1.015-1.111	0.009
APACHE-II score	1,276	1,197-1,359	<0,001	1.298	1.204-1.399	<0,001
SOFA score	1,105	1,022-1,196	0,013	--	--	--
CCI	1.118	1.006-1.242	0,038	--	--	--
Plt (x 10^3/µL)	0.998	0.995-1.000	0.043	0.996	0.993-0.999	0.012
Creatinine (mg/dL)	1.143	0,956-1,367	0.142	--	--	--
C-reactive protein (mg/L)	1,010	1.002-1.018	0,012	1.012	1.001-1.023	0.29
Albumin (g/dL)	0,211	0,117-0,382	<0,001	0.276	0.132-0.581	0.001

APACHE-II score: Acute Physiology and Chronic Health Evaluation 2 score, **CCI:** Charlson comorbidity index, **Plt:** platelet count, **SOFA:** Sequential Organ Failure Assessment.

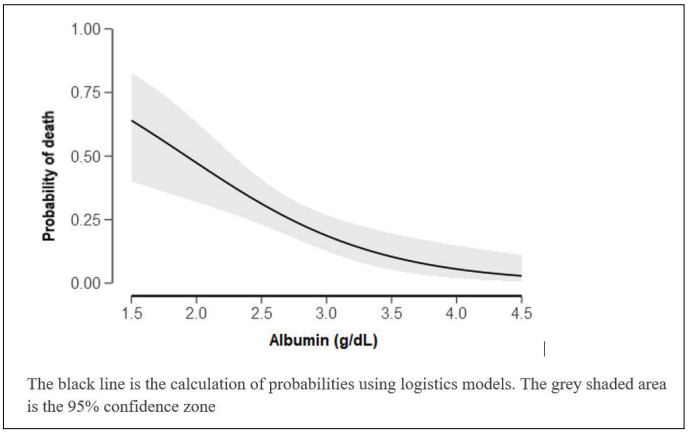

Figure 1. Changes in albumin level which can the probability of death in geriatric patients with sepsis.

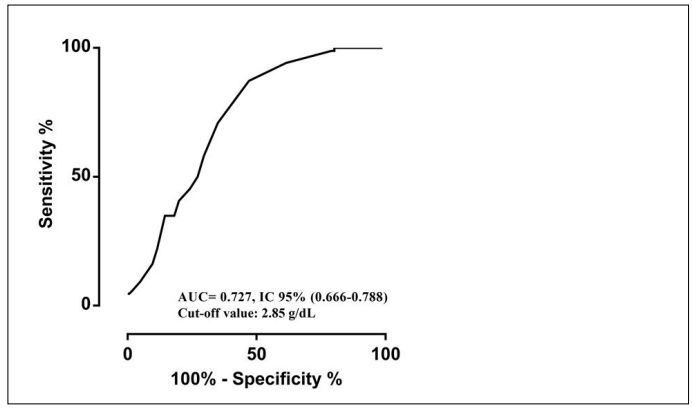

Figure 2. ROC curve of serum albumin level for the estimation of mortality in septic patients.
***AUC** = area under the curve,*
***ROC** = receiver operating characteristic,*
***CI** = confidence intervals*

The survivors' group included 166 patients and non-survivors, 86 patients. The mortality rate was determined as 34.1%. The groups had similar characteristics in terms of gender distribution (p> 0.05). When the groups were analyzed in terms of age, the non-survivor group consisted of older individuals (p< 0,05). The median APACHE II (p<0.001), SOFA (p< 0.05), and CCI score (p<0.05) were higher in the non-survivors group. According to the laboratory parameters the serum levels of creatinine (p<0.05) and, CRP (p<0.05) were significantly higher in the non-survivor group. The serum level of platelets (p<0.05) and albumin (p<0.05) was significantly higher in the survivors. The median of the other parameters was similar in both groups.

The results of the univariate-multivariate logistic regression analysis applied to show predictive factors in respect of mortality are shown in Table 2. In the multivariate analysis, age (OR: 1.062 CI: 1.015-1.111 p=0.009), APACHE II (OR: 1.298; CI: 1.204-1.399; p<0.001), platelets (OR: 0.996; CI: 0.993- 0.999; p= 0.012) and albumin (OR: 0.276; CI: 0.132- 0.581; p= 0.001) were determined as significant independent determinants after correction of the other variables. The lower albumin levels were associated with an increased risk of mortality in geriatric patients with sepsis (Figure1). The ROC curve to assess Albumin level as a predictor of mortality is shown in Figure 2. The AUC for albumin was 0.727 at a 95% CI of 0.666–0.788 (P< 0.001) with sensitivity of 71% and specificity of 66%. Albumin values of 2.85 and below were predictive for mortality.

Discussion

Because of high morbidity or mortality in critically ill, a rapid clinical assessment of the severity of sepsis is an important strategy to improve results. To assess morbidity and mortality of sepsis in ICU, the scoring systems and biomarkers are usually used in ICU (7). In our study, we aimed to investigate the prognostic value of albumin levels in geriatric patients with sepsis. We found that low albumin levels are an independent risk factor for mortality in geriatric patients with sepsis. In addition, age, APACHE-2 score, and low platelet levels were also found to be independent risk factors for mortality in geriatric patients with sepsis in our study.

As stated in the literature, previous studies found a relationship between albumin levels and mortality in patients with stroke, myocardial infarction, or hip fracture (8-10). Also in the literature;

the result of ''hypoalbuminemia is a poor predictor of survival after percutaneous endoscopic gastrostomy in elderly patients with dementia'' was also reached (11). In addition, an inverse relationship between hypoalbuminemia and acute-phase proteins was found in hospitalized elderly patients with community-acquired pneumonia (12). Hannan, J.L. et al found an association between low albumin levels and hospital mortality in patients older than 60 years (13). S. Tal et al. found that hypoalbuminemia and age were associated with mortality in hospitalized elderly patients, similar to our study (14).

In studies involving critically ill patients, hypoalbuminemia was also associated with poor outcomes. Murray, M.J. et al found that the serum albumin levels negatively correlated with the length of ICU and hospital stay and the duration of mechanical ventilation. (15). Gloub et al. also showed that the non-surviving patient group had lower albumin levels than the surviving patient group in the surgical ICU(16).

Serum albumin also has prognostic value for critically ill patients with sepsis patients. Because albumin levels reflect patients' nutritional status, liver function, and previous general health. Also, hypoalbuminemia has been observed since the early stages of sepsis because the underlying inflammatory state via increased interleukin-1 or tumor necrosis factor causes decreased albumin production by the liver (17). As a result, sepsis causes hypoalbuminemia or worsens if the patient has the previous hypoalbuminemia. In support of these hypotheses, Arnau-Barrés et al. found in their study that albumin levels were associated with mortality in elderly sepsis patients. They showed that albumin level < 2.6 g/dl was independently associated with 30-day mortality. In their study, they also found independent associations of CCI, CRP level, and inadequate initial antibiotic therapy with 30-day mortality (18). In our study, we showed that albumin value < 2.85 g/dl is an independent risk factor for mortality. The results show compatibility with these aspects.

APACHE-2 and SOFA scoring systems are widely used in the world for the estimation of mortality in intensive care units because their accuracy has been accepted (19, 20). In our study, we found statistically significantly higher APACHE-2 and SOFA scores in the non-surviving group, which was consistent with the literature. We also found APACHE-2 as an independent risk factor. Albumin level is not included in the APACHE-2 scoring system. However, according to our study, both are independent risk factors for mortality in geriatric patients with sepsis. For this reason, according to the results of our study, we can recommend that studies can be conducted to evaluate APACHE-2 and albumin levels together for predicting mortality in elderly patients with sepsis.

There are some limitations in the study that should be discussed. First of all our study is that it is a single-center retrospective study. Secondly, we only take one measurement during hospitalization in the ICU, and we do not look at the serial measurement values in ICU stays. In addition, there were insufficient patients in some sub-groups for the source of sepsis. Therefore, a statistical analysis of the source of sepsis was not conducted.

Conclusion

In conclusion, albumin levels can be used as a predictor of mortality in elder patients with sepsis. However, this result is to be strengthened by prospective multicenter studies. Also, according to our study, age, APACHE-2 score, and low platelet levels are independent risk factors for mortality in geriatric patients with sepsis. In addition, studies should be planned to evaluate whether the APACHE-2 score and albumin level together can better predict mortality in geriatric patients with sepsis.

AUTHOR CONTRIBUTIONS:

Concept: ME; **Design:** ME; **Supervision:** ME, HAF; **Data Collection and/or Processing:** ME; **Analysis and/or Interpretation**: HAF; **Literature Search:** ME, HAF; **Writing Manuscript**: ME; **Critical Review:** ME, HAF.

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Informed Consent: Retrospective study

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