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Nutritional indices may have prognostic value in elderly critically ill patients with sepsis

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ABSTRACT

Aim: Nutritional indicators are associated with adverse outcomes in critically ill elderly patients. In this study, we aimed to evaluate the prognostic potential of prealbumin and albumin in the prediction of mortality in elderly patients with sepsis.

Material and Method: A total of 108 patients who developed intensive care unit-acquired sepsis were divided into two groups: Survivors (n=72) and Non-survivors (n=36).

Results: Patients in the Non-survivors group were often older (68 vs 74) and presented lower prealbumin (15.1 vs 11), and higher Charlson index (4 vs 6), Sequential Organ Failure Assessment (SOFA) score (8.5 vs 10), C-reactive protein (CRP) (68.8 vs 91) and procalcitonin (PCT) (6 vs 8.4) ($p< 0.05$). The area under the curve of PCT was the highest at 0.74. Prealbumin presented the best sensitivity (75%) and 12 mg/dL cut-off value, while PCT had the best specificity (75%) and a cut-off value of 7 ng/mL. Although prealbumin was negatively correlated to SOFA score in a significant way (r=-0.226, p=0.019), White blood cells, CRP, and PCT were positively correlated to SOFA score (r=0.198, p=0.040; r=0.233, p=0.015; r=0.286, p=0.003, respectively). In addition, a weak negative correlation was observed between prealbumin and CRP and PCT (r=-0.203, p=0.037; r=-0.215, p=0.026, respectively). Multivariate analysis showed that a reduction in serum prealbumin levels compared to steady prealbumin greater than 4 mg/dL increased the risk of death by 85% (aHR: 1.85, 95% CI: 1.05-2.56, p=0.029).

Conclusion: Changes in serum prealbumin in the acute phase of sepsis may assist in determining the risk of mortality and in the administration of specific treatment in critically ill elderly patients.

Keywords: Elderly, inflammation, mortality, prealbumin, sepsis

INTRODUCTION

Infection and changes in the immune response in the elderly lead to a severe systemic response to infection in septic patients, severe and often irreversible damage to cells and tissues, and ultimately a life-threatening clinical picture (1). In addition, severe infections in the elderly are sometimes difficult to diagnose due to atypical clinical appearance causing adverse outcomes. Therefore, the incidence of sepsis increases in elderly patients, and advanced age is associated with an increased risk of mortality (2).

Elderly patients, who constitute the majority of critically ill patients in the intensive care unit (ICU), are prone to exposure to acutely stressful clinical situations that add to their chronic illness. Nitrogen losses increase in these patients due to hypermetabolism status, anorexia, and developing malabsorption. Prealbumin (transthyretin) levels can help determine the risk of malnutrition at an early stage and provide nutritional support (3). However, in addition to malnutrition, serum prealbumin levels decrease in conditions such as inflammatory response and ageing (4). The fact that the hepatic synthesis rate of prealbumin is higher compared to that of albumin, its half-life is shorter, and its catabolic rate is predictable suggests that it may be a more reliable indicator than albumin (5). Although nutritional indicators such as prealbumin and albumin have been shown to be associated with adverse outcomes in critically ill elderly patients (3,4,6), whether they have prognostic significance in elderly patients with ICU-acquired sepsis should be further investigated.

In our study, therefore, we aimed to evaluate the relationship of nutritional parameters with clinical outcomes and compare their predictive values with conventional inflammatory markers (White blood cells (WBC), C-reactive protein (CRP) and procalcitonin (PCT)).

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MATERIAL AND METHOD

Study Design

In this cohort study, elderly (age ≥65 years) patients who developed microbiologically proven sepsis at least 48 hours after admission to the General Intensive Care Unit of Konya Numune Hospital were retrospectively analyzed. This study was carried out in accordance with the Declaration of Helsinki between August 2020 and August 2022, with the approval of the ethics committee of Necmettin Erbakan University Non-Interventional Clinical Researches Ethics Committee (Date: 18.11.2022, Decision No: 4054). Written consent was not obtained due to the retrospective design.

Inclusion and Exclusion Criteria

Patients who, according to the definition of SEPSIS-3, developed new-onset sepsis (7) during their treatment in the ICU and who received enteral, parenteral, or both nutritional support were included in the study.

Oral alimentation (as total protein and calories may not be measured properly), malnutrition, chronic inflammatory disease, corticosteroid usage, severe immunosuppression, chronic hepatic failure, estimated glomerular filtration rate (eGFR)< 15 mL/kg/m² or renal replacement therapy, missing clinical data, patients who were re-admitted to the intensive care unit and those previously included in the study were excluded from the study.

Demographic and clinical features at the onset of sepsis, comorbidities, biochemical parameters, inflammation profile, disease severity determined by Sequential Organ Failure Assessment (SOFA) score, empirical antimicrobial therapy (initiation of appropriate antimicrobial drugs, including possible pathogens at adequate doses), and microbiological results were evaluated along with the data obtained from medical records.

Study Protocol

Patients admitted to the ICU were screened for sepsis, and routine treatment, including fluid replacement, positive inotropes, antimicrobial agents, and surgery, was applied according to current guidelines to all patients who developed sepsis (8). The nutritional needs of adult critically ill patients were evaluated according to the SCCM/ASPEN guidelines (9). Nutritional parameters (prealbumin, albumin) and inflammation markers (WBC, CRP, PCT) were determined by an AU5800 automated analyzer (Beckman Coulter, California, USA). Serum prealbumin levels were reevaluated in blood samples taken 4 days later.

Sepsis developing 48 hours after ICU admission was defined as ICU-acquired sepsis. Death from any cause within 30 days of sepsis onset was considered 30-day ICU mortality.

The prognostic values of nutritional indicators in elderly sepsis patients were the primary outcome measures, and their associations with systemic inflammation were the secondary outcome measures.

Sample Size

The sample size analysis performed using the G*Power version 3.1 program was based on a similar study by Xie et al. (10). To detect a significant difference in serum prealbumin levels between Survivors and Non-survivors groups, a power analysis was accomplished with the 2-sided Independent Samples t-test using a 0.61 effect size, maximum 5% type I error and 80% power. Considering the 10% drop out rate, the sample size was found to be 72 patients in the Survivors group and 36 patients in the Non-survivors group (108 patients in total).

Statistical Analysis

SPSS software version 26 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Continuous variables were given as mean (SD) or median (IQR), while categorical variables were given as numbers and ratios. Pearson's chi-squared or Fisher's exact tests were used for categorical variables in group comparisons. The Independent Samples t-test was used for continuous variables when normal distribution was shown, and the Mann-Whitney U test was used if not. Mortality predictability of significant laboratory parameters in the univariate analysis was determined by Receiver operating characteristic (ROC) analysis and compared with the values of the area under the curve (AUC). Youden criterion was used to distinguish cut-off values. The SOFA score and the relationship between prealbumin and inflammatory biomarkers (r values) were evaluated with Spearman's correlation coefficient. The association of prealbumin changes with the risk of mortality was analyzed with Cox proportional hazard regression models adjusted for age, sex, and SOFA score. The associations were calculated as unadjusted and adjusted hazard ratios (aHR) with a 95% confidence interval (CI). $p< 0.05$ values were regarded as statistically significant.

RESULTS

A total of 150 patients with clinical signs of sepsis were registered during the study period. The microorganism responsible for the primary infection was detected in 120 (81%) of these 150 patients. Twelve patients died within 4 days of the onset of sepsis. The nutritional indicators and clinical outcomes of 108 patients with microbiologically proven ICU-acquired sepsis were analyzed.

The clinical features of septic patients in the Survivors and Non-survivors groups are shown in **Table 1**. Hypertension, observed in 47% of patients, was the most

common primary underlying disease. Patients in the non-survivors group were often older (68 vs 74), with lower prealbumin (15.1 vs 11), and higher Charlson index (4 vs 6), SOFA score (8.5 vs 10), CRP (68.8 vs 91) and PCT (6 vs 8.4) (p< 0.05). There was no significant difference in clinical outcomes and identified microorganisms between the groups of patients.

ROC analysis was performed to evaluate the predictability of mortality of prealbumin, CRP, and PCT, which are significantly correlated with mortality in sepsis patients. PCT had the highest AUC value, 0.74. Prealbumin with the best sensitivity (75%) and a cut-off value of 12 mg/dL and PCT with the best specificity (75%) and a cut-off value of 7 ng/mL are eligible for ICU mortality predictors. (**Table 2**, **Figure 1**)

The prognostic values of laboratory parameters that in single measurements did not have adequate predictability of mortality due to the relatively low (< 0.80) AUC values were analyzed in their combinations and pairwise comparisons. When these three parameters were evaluated together, although there was no improvement in specificity (70.8%), sensitivity (86.1%), and AUC (0.84) values increased.

The pairwise comparison with ROC curves of these parameters showed no significant difference between the prognostic values of all three parameters (**Table 3**). However, when the combination of the three parameters was compared pairwise with prealbumin, CRP and PCT, the prognostic value was significantly higher (p=0.001, p=0.010, p=0.042, respectively) (data not shown).

Table 1. Clinical characteristics of elderly patients with ICU acquired sepsis

Variables	Total (n=108)	Survivors (n=72)	Non-survivors (n=36)	p value
Age, year	69 (67-76)	68 (66-74)	74 (67-81)	0.028
Gender, male, n (%)	53 (49)	34 (47)	19 (53)	0.586
Underlying condition, n (%)				
Diabetes mellitus	31 (29)	22 (31)	9 (25)	0.547
Hypertension	51 (47)	35 (49)	16 (44)	0.683
Renal disease	17 (16)	10 (14)	7 (19)	0.455
Koroner arter hastalığı	21 (19)	13 (18)	8 (22)	0.606
COPD	23 (21)	14 (19)	9 (25)	0.506
Stroke/serebral hemoraji	19 (18)	11 (15)	8 (22)	0.372
Charlson comorbidity index	4 (3-7)	4 (3-5)	6 (4-8)	<0.001
SOFA score	8.5 (6-10)	8.5 (7-10)	10 (8-11)	<0.001
Mechanical ventilation, n (%)	49 (45)	28(39)	21 (58)	0.056
Vasopressor use, n (%)	57 (53)	34 (47)	23 (64)	0.172
Identified microorganisms, n (%)				
Gram negative bacilli	69 (64)	43 (60)	26 (72)	0.202
Gram positive cocci	55 (51)	39 (54)	16 (44)	0.341
Fungi	11 (10)	5 (7)	6 (17)	0.175
Laboratory findings				
WBC, mm3	12.8±5.4	12.1±5.1	14.2±5.7	0.053
Prealbumin, mg/dL	13.7±5.8	15.1±5.8	11.0±4.8	<0.001
Albumin, g/dL	3.0±0.6	3.1±0.6	2.8±0.5	0.061
C-reactive protein, mg/dL	78.5 (50-99)	68.8 (45-94)	91 (73-114)	0.001
Procalcitonin, ng/mL	7 (4-10)	6 (3-9)	8.4 (6-14)	<0.001
Lactate, mmol/L	2.7±0.9	2.6±0.9	2.9±1.0	0.133
Clinical outcomes				
Appropriate initial treatment, n (%)	66 (61)	48 (67)	18 (50)	0.094
ICU length of stay (days)	14.5±7.4	13.7±7.2	16.2±7.7	0.107
Duration of ICU stay prior to sepsis (days)	7.2±3.5	6.4±3.1	7.8±4.1	0.202

Data shown as mean ± standard deviation, median (interquartile ranges) or n (%). COPD: chronic obstructive pulmonary disease; SOFA: sequential organ failure assessment; WBC: White blood cells; ICU: intensive care unit.

Table 2. Performance of significant parameters in predicting ICU mortality

Variable	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV	NPV
PAB	12 mg/dL	0.72 (0.62-0.80)	75.0	65.3	51.9	83.9
CRP	84 mg/dL	0.70 (0.61-0.79)	66.7	69.4	52.2	80.6
PCT	7 ng/mL	0.74 (0.65-0.82)	66.6	75.0	57.1	81.8
PAB+CRP+PCT		0.84 (0.76-0.90)	86.1	70.8	59.6	91.1

PAB: prealbumin; CRP: C-reactive protein; PCT: procalcitonin; ICU: intensive care unit; AUC: area under the receiver-operating-characteristic curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

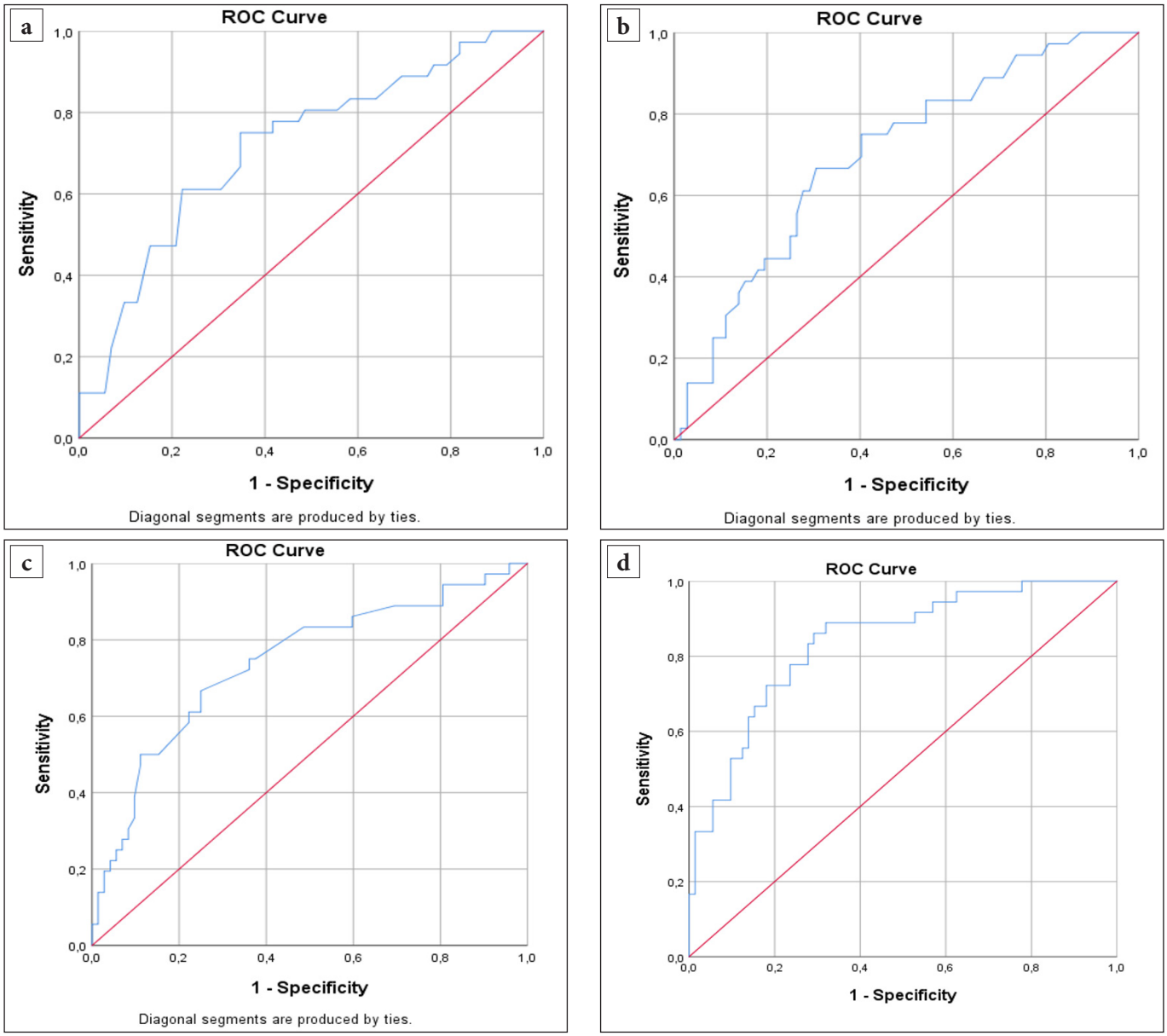

Figure 1. Receiver operating characteristic curves for a) PAB (AUC: 0.72, 95% CI, 0.62-0.80), b) CRP (AUC: 0.70, 95% CI, 0.61-0.79), c) PCT (AUC: 0.74, 95% CI, 0.65-0.82) and d) the combination of PAB, CRP and PCT (AUC: 0.84, 95% CI, 0.76-0.90) in septic patients to predict mortality.

Table 3. Comparison of ROC curves

	PAB vs. CRP	PAB vs. PCT	CRP vs. PCT
Difference between areas	0.019	0.022	0.041
Standard error	0.079	0.073	0.077
95% confidence interval	-0.136 to 0.173	-0.121 to 0.165	-0.111 to 0.192
Z statistic	0.235	0.301	0.524
Significance level	p = 0.814	p = 0.764	p = 0.600

PAB: prealbumin; CRP: C-reactive protein; PCT: procalcitonin; ROC: Receiver operating characteristic analysis

The relationship in sepsis patients between inflammatory markers and the SOFA score, which is an indicator of disease severity, was evaluated by bivariate analysis. Prealbumin was significantly negatively correlated with SOFA score (r=-0.226, p=0.019), while WBC, CRP, and PCT were positively correlated with SOFA score (r=0.198, p=0.040; r=0.233, p=0.015; r=0.286, p=0.003, respectively). Compared to other biomarkers, the correlation between PCT and SOFA score was more clear (**Table 4**). In addition, a weak negative correlation was observed between prealbumin and CRP and PCT (r=-0.203, p=0.037; r=-0.215, p=0.026, respectively) (data not shown).

Table 4. The relationship between SOFA scores and inflammatory biomarkers

		WBC	Prealbumin	Albumin	CRP	PCT	Lactate
SOFA	rs*	0.198	-0.226	-0.145	0.233	0.286	0.121
	p	0.040	0.019	0.134	0.015	0.003	0.213

*Spearman correlation. SOFA: sequential organ failure assessment; WBC: White blood cells; CRP: C-reactive protein, PCT: procalcitonin

Table 5. Risk relationship between categories of change in prealbumin and mortality

Categories (mg/dL)	Unadjusted		Model 1*		Model 2†	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
< -4 (n=25)	1.89 (1.09-2.58)	0.026	1.76 (1.03-2.51)	0.044	1.85 (1.05-2.56)	0.029
-4 to < 4 (n=55)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥ 4 (n=28)	0.70 (0.37-1.21)	0.244	0.65 (0.32-1.11)	0.512	0.67 (0.30-1.19)	0.282

*Model 1 adjusted for age and gender. †Model 2 adjusted for age, gender and Sequential Organ Failure Assessment score. HR: hazard ratio; CI: confidence interval

Prealbumin changes associated with mortality were calculated by Cox hazard regression. The multivariate analysis, adjusted for age, sex, and SOFA score, showed that, compared to steady prealbumin levels, a decrease in serum prealbumin above 4 mg/dL increased the risk of death by 85%, (aHR: 1.85, 95% CI: 1.05-2.56, p=0.029) (**Table 5**).

DISCUSSION

In this study, the observed reductions in serum prealbumin levels in critically ill patients with sepsis were associated with adverse outcomes. In elderly patients with ICU-acquired sepsis, prealbumin values demonstrated similar prognostic significance to conventional inflammatory markers such as CRP and PCT.

Although the nutritional parameters prealbumin and albumin were previously defined as indicators of nutritional intake, subsequent studies in acutely stressed patient groups have shown that they are also affected by conditions such as inflammatory response, surgery, trauma, and ageing (4,11,12). The decrease in nutritional markers in acute stress situations can be explained by several mechanisms independent of nutrition. First, cytokines such as tumour necrosis factor (TNF), interleukin-1, and interleukin-6 secreted in case of inflammation (e.g., infectious disease) increase the synthesis of acute phase proteins and decrease hepatic synthesis of other proteins, including prealbumin and albumin (12,13). Second, in the other cytokine-related mechanism, TNF and secondary eicosanoid metabolites cause capillary leakage, causing hepatic proteins to pass into the extravascular compartment (14). Third, by playing a nonspecific role in host defence, it ensures the clearance of toxic metabolites induced by infection and is consumed during this process (15). In our study, the higher levels of CRP and PCT, which are established inflammatory markers in the Non-survivors group, and the negative correlation of prealbumin with these markers were consistent with the aforementioned mechanisms. In conclusion, inflammation in the early stage of sepsis in critically ill patients may be more effective on nutritional markers, which are negative acute phase reactants, than nutrient intake or replacement therapy (16,17).

Compared to albumin, with a short metabolic half-life (2 days), stronger correlation with the inflammatory response, and, due to its higher affinity for ligands, increased detoxification capacity, prealbumin is considered a better indicator than serum albumin in assessing malnutrition and predicting mortality in critically ill patients. (5,18-20). Our multivariate analysis, including the SOFA score, which is positively associated with the mortality of septic patients, sheds light on the interaction of disease severity with prealbumin levels in the elderly population (21). In our study, a more significant decrease in serum prealbumin was noticed in patients who died, and this relationship remained statistically significant even when adjusted for disease severity. In addition, the correlation analysis observed a weak negative correlation between prealbumin levels and disease severity. This suggests that, in addition to being an indicator of disease severity, prealbumin levels in critically ill patients may also be significantly affected by other factors in their prognostic potential.

Malnutrition is common in hospitalized elderly patients. Kubrak et al. (22) demonstrated in a study on acute care patients that the incidence of malnutrition in hospitalized elderly patients was between 42% and 91%. The increased risk of malnutrition and inflammation in elderly patients with decreased prealbumin levels adversely affects the prognosis (4,6). In our study, it can be thought that the potential effects of malnutrition on immune dysregulation were limited by providing the necessary nutritional support during the ICU stay (23). Therefore, the older age and increased comorbidity index of the patients in the Non-survivor group may contribute to adverse outcomes by leading to deterioration in immune functions related to ageing, underlying disease and frailty.

Li et al. (6) found that serum prealbumin was associated with mortality in a study conducted on elderly patients with severe pneumonia. Qin et al. (24) indicated that CRP and PCT have prognostic significance in elderly patients with sepsis caused by pulmonary infection. In our study, serum PCT presented the highest AUC (0.74) and specificity (75%), while serum prealbumin had the highest sensitivity (75%). The AUCs of all three biomarkers had a fair discriminative ability (< 0.80) and similar prognostic value in differentiating Survivors and Non-survivors groups. However, the combination of prealbumin, CRP, and PCT, in which we evaluated the prognosis of the septic patients, reached a significantly higher AUC (0.84) than the individual measurements.

These findings suggest that prognostic predictability in elderly patients with ICU-acquired sepsis may be increased by multimarker evaluation of the parameters.

The present study showed a significant negative correlation between serum prealbumin and the established inflammatory markers CRP and PCT. In addition, the correlation of prealbumin with PCT, which is a superior biomarker compared to CRP in the diagnosis of sepsis, was more evident (25). Therefore, prealbumin, in addition to a nutritional protein, may be an inflammatory marker for infections in elderly patients. These results showing the potential effects of the acute phase response in the early phase of sepsis on nutritional markers are consistent with previous studies.

In addition to baseline measurements, changes in prealbumin levels are also used in the assessment of mortality risk. Rambod et al. (26) studied the relationship between prealbumin levels and mortality in outpatients receiving hemodialysis treatment. In patients with initial prealbumin levels between 20-40 mg/dL, decreases in prealbumin levels above 10 mg/dL over a 6-month period were independently associated with mortality. Nichols et al. (27) evaluated the relationship between serum prealbumin and clinical outcomes in critically ill patients. In the study in which the median baseline prealbumin levels were 11.6 mg/dL, a decrease of 1.3 mg/dL in prealbumin levels evaluated with measurements made with 3-day intervals was associated with mortality. In our study, the mean prealbumin level at the onset of sepsis was 13.7 mg/dL, and reductions above 4 mg/dL measured at 4-day intervals increased the mortality risk by 85%, which was consistent with the previous study. However, the smaller absolute decrease due to lower baseline prealbumin compared to the study of Rambod can be explained by the higher severity of the disease in critically ill patients and the significantly shorter time between the measurements of prealbumin.

This study had several limitations. First, due to the single-centre nature of our study, our results cannot be generalized to other ICUs. Second, advanced age, comorbidities, and increased disease severity in sepsis patients in the ICU may cause differences in prognosis-related cut-off values of inflammatory parameters. Third, the retrospective design of the study may affect the serum levels of prealbumin and albumin, resulting in the inability to evaluate the nutritional status of patients when enrolled in the study due to the lack of data such as total protein or body mass index. Fourth, because of examining the prognosis of patients in the ICU only, our data do not include information on the association of nutritional indicators with long-term clinical outcomes.

CONCLUSION

In elderly patients, prealbumin values at the onset of sepsis have a similar and moderate prognostic ability as CRP and PCT. Prealbumin changes may help identify the increased risk of mortality in elderly patients with nosocomial infections and receive specific treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Necmettin Erbakan University Non-Interventional Clinical Researches Ethics Committee (Date: 18.11.2022, Decision No: 4054).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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