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Every Time Prealbumin May Not be an Indicator for Prognosis in Critically Ill Patients

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ABSTRACT

Objective: Prealbumin renamed transthyretin is a protein that is made in the liver and released in the blood and has been used as a beneficial nutritional indicator for long years. It aimed to investigate whether serum prealbumin level is a marker of mortality in patients hospitalized in the intensive care unit.
Methods: This retrospective and single-center study was carried out at level 3 intensive care unit. Data were collected from hospital electronic records and patient file archives. Patient age, gender, acute physiologic and chronic health evaluation score, nutritional risk screening 2002, nutric score, neutrophil-lymphocyte ratio, need for mechanical ventilation and duration, intensive care unit length of stay, comorbid conditions, the situation of nutrition support, causes of enteral feeding intolerance, the situation of protein and energy intake (7 days), laboratory parameters (included prealbumin (0 and 7 days)) at the time of admission to intensive care unit, and mortality status were recorded. Patients were divided into 2 groups as survivors and non-survivors, and the differences between the 2 groups were analyzed for all parameters.
Results: Sixty-three (60%) were female of 105 patients who participated in this study. The mean age was 59 ± 23 years. The mortality rate was 48.6%. The length of stay in the intensive care unit was 30 ± 34 days. The median level of serum albumin (g/dL) on day 1 was 2.7 (2.3-3.2) and on day 7, it was 2.5 (2.1-2.8). The mean level of serum prealbumin (mg/dL) on day 1 was 13.8 ± 6.6 and on day 7, it was 12.5 ± 6.5. Prealbumin (on days 0 and 7) values were not different between survivors and non-survivors (for all $P < .05$). In the binary logistic regression analysis, age and albumin value (on day 7) were found to be independent risk factors for mortality (odds ratio: 1.038 (1.002-1.075), $P = .036$, odds ratio: 1.148 (1.021-1.290), $P = .021$), respectively.
Conclusions: Prealbumin levels did not differ for critically ill patients with and without mortality.

Keywords: Albumin, intensive care unit, prealbumin, prognosis

INTRODUCTION

Malnutrition is characteristic of intensive care unit (ICU) patients.[1] This condition leads to an increase in complications, cost, and length of hospitalization and is considered an independent risk factor for mortality.[2] Nutritional support is very important for critically ill patients; however, the response to them is difficult to monitor and diagnose malnutrition. Advanced age, comorbidities, and pre-existing malnutrition, which are common in many critically ill patients, can exacerbate the condition.[3] These numerous methods, which do not have a clear "gold standard," indicate the difficulty of diagnosing malnutrition in the ICU. Prealbumin is secreted mainly by the liver and choroid plexus. Its short half-life (2 days), small volume of distribution, and uncomplicated measurement make it a good candidate for monitoring rapid changes in metabolic status.[4-5] It is common practice to adjust the amount of calories and protein given to patients according to serum albumin and prealbumin levels during hospitalization. Albumin and prealbumin are negative acute phase reactants and their levels may reflect decreased synthesis due to inflammation rather than nutritional status.[6] Therefore, serum concentrations may be low in critically ill patients, and also there is no strong evidence that increased food intake and control of inflammation in patients lead to increase in serum albumin or prealbumin levels or that increased levels are associated with better outcomes.

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In this study, it was aimed to investigate whether serum prealbumin level is an indicator of mortality in patients hospitalized in the ICU.

METHODS

This retrospective and single-center study was carried out at Training and Research Hospital, Division of Critical Care Unit. The study protocol was approved by the ethics committee of our institution (Date: April 7, 2021; Decision No: 842), and informed consent from patients was not procured because of the retrospective study. Patients were evaluated retrospectively from April 2021 and March 2022. The critically ill patients were excluded if they were not at least 18 years of age and were not expected to remain in the ICU hospitalization for at least 24 hours. One hundred five septic patients followed up in the ICU were included in this study. Demographic and laboratory data were collected from hospital electronic records and patient file archives. Patient age, gender, acute physiologic and chronic health evaluation score (APACHE II), nutritional risk screening (NRS 2002), nutric score, neutr ophil-lymphocyte ratio (NLR), need for invasive mechanical ventilation (IMV) and non-invasive mechanical ventilation (NIMV), IMV duration, the rate of pressure ulcer, length of stay (LOS) in ICU, comorbid conditions, situation of enteral, parenteral, dextrous, and oral nutrition support, causes of enteral feeding intolerance, situation of target protein and energy and protein and energy intake (on day 7), white blood cell (WBC), c-reactive protein (CRP), arterial lactate, procalcitonin, albumin and prealbumin (on days 0 and 7) levels at the time of admission to the ICU, and mortality status were recorded.

Statistical Analysis

Continuous variables were tested using Shapiro–Wilk test for normality and data are expressed as median and interquartile range or mean ± standard deviation. Mann–Whitney *U* test was performed to compare distinctions for non-normally distributed variables. Student's *t*-test was performed to compare distinctions for normally distributed variables. Categorical variables were analyzed with a Chi-square test or Fisher's exact test and expressed as numbers (percentages). Binary logistic regression analysis was performed to determine the independent risk factors for mortality. Patients were divided into 2 groups: survivors and non-survivors and the differences between the 2 groups were analyzed for all parameters. The outcomes of the regression analyses were expressed as odds ratio (OR) and 95% CI. A *P* value less than .05 was presumed statistically significant. Statistical analyses were carried out using Statistical Package for the Social Sciences version 22.0. (IBM SPSS Corp.; Armonk, NY, USA).

Main Points

- Prealbumin is a liver-derived protein thought to be significant in the assessment of nutritional deficiency and nutrition support.
- Prealbumin is a negative acute phase reactant, which means that levels decrease during inflammation or infection.
- Although its relationship with mortality in different disease groups has been shown in many studies, it may not always be associated with mortality.

RESULTS

Sixty-three (60%) were female of 105 patients who participated in this study. The mean age was 59 ± 23 years. The mortality rate was 48.6%. The length of stay in ICU was 30 ± 34 days. Acute physiologic and chronic health evaluation score II score was 17 ± 9. Nutritional risk screening 2002 was 4 ± 1. Nutric score was 3 ± 2. Neutrophil-lymphocyte ratio was 14 ± 23. The need for IMV was 63 (60%), and the need for NIMV was 19 (18.1%). Invasive mechanical ventilation duration was 18 ± 33 days. Mean lactate value was 2.5 ± 1.9. The median level of serum albumin on day 0 was 2.7 (2.3-3.2) g/L, and on day 7, it was 2.5 (2.1-2.8) g/L. The mean level of serum prealbumin on day 0 was 13.8 ± 6.6 g/dL, and on day 7, it was 12.5 ± 6.5 g/dL. Enteral nutrition support was 59 (56.2%), parenteral nutrition support was 6 (5.7%), oral nutrition support was 25 (23.8%), and intravenous dextrose support was 9 (8.6%). Among the major causes of enteral feeding intolerance, the most common cause was feeding intolerance (29 (27.6%)) and the next most common cause was diarrhea (16 (15.2%)). While median target protein (g/day) was 118 (107-127), median protein intake (g/day) on day 7 was 90 (67-105). While the mean target energy (kcal/day) was 1709 ± 385, the mean energy intake (kcal/day) on day 7 was 1507 ± 460. The frequency of pressure ulcer was 31 (29.5%). In this study, 30 (28%) patients had hypertension, 20 (19%) patients had diabetes mellitus, and 21 (20%) patients had chronic obstructive pulmonary disease. Non-survivors had higher hypertension and cerebrovascular disease as compared to survivors (for all, $P < .05$). Sex, need for NIMV, IMV duration day, WBC, lactate, CRP, procalcitonin, albumin (on day 0) and prealbumin (on days 0 and 7) values, parenteral, oral, and intravenous dextrose nutrition support, major causes of enteral feeding intolerance, LOS in ICU, mean target energy, median target protein, and median protein intake (day 7) were not different between survivors and non-survivors (for all $P > .05$). Non-survivors had higher APACHE II score (21 ± 9 vs. 14 ± 8, $P=.001$), age (69 ± 16 vs. 49 ± 25, $P=.001$), NRS score (4 ± 1 vs. 3 ± 1, $P=.008$), nutric score (4 ± 2 vs. 2 ± 2, $P=.001$), need for IMV (38 (74.5%) vs. 21 (38.9%), $P=.003$), enteral

Table 1. Demographic and Clinical Characteristics of the Patients

Variables	Total n = 105	Survivors n = 54	Non-survivors n = 51	*P*
Age, (years)	59 ± 23	49 ± 25	69 ± 16	**.001**
Male, n (%)	63 (60)	34 (63)	29 (56.9)	.524
APACHE II score	17 ± 9	14 ± 8	21 ± 9	**.001**
NRS 2002	4 ± 1	3 ± 1	4 ± 1	**.008**
Nutric score	3 ± 2	2 ± 2	4 ± 2	**.001**
NLR	14 ± 23	15 ± 30	14 ± 10	.811
Need for IMV, n (%)	63 (60)	25 (46.3)	38 (74.5)	**.003**
Need for NIMV, n (%)	19 (18.1)	6 (11.1)	13 (25.5)	.06
IMV duration, days	18 ± 33	33 ± 44	26 ± 17	.322
WBC (10^3/μL)	13 ± 5	13.2 ± 4.8	12.9 ± 6.2	.773
Lactate (mmol/L)	2.5 ± 1.9	2.5 ± 2.1	2.5 ± 1.6	.962
CRP (mg/dL)	82 ± 81	79 ± 76	84 ± 87	.763
Procalcitonin (μg/L)	7 ± 28	9 ± 36	5 ± 14	.427
Albumin (g/dL), 0 day	2.7 (2.3-3.2)	2.9 (2.5-3.2)	2.7 (2.2-3.1)	.09
Albumin (g/dL), 7 day	2.5 (2.1-2.8)	2.6 (2.4-2.9)	2.2 (1.9-2.6)	**.001**
Prealbumin (mg/dL), 0 day	13.8 ± 6.6	14.6 ± 6.2	13 ± 7.1	.202
Prealbumin (mg/dL), 7 day	12.5 ± 6.5	13.5 ± 5.8	11.5 ± 7.2	.122
Enteral nutrition support, n (%)	59 (56.2)	21 (38.9)	38 (74.5)	**.001**
Parenteral nutrition support, n (%)	6 (5.7)	3 (5.6)	3 (5.9)	.943
Oral nutrition support, n (%)	25 (23.8)	14 (25.9)	11 (21.6)	.600
Dextrose support, n (%)	9 (8.6)	5 (9.3)	4 (7.8)	.600
Major causes of enteral feeding intolerance (0-7 day), n (%)				
Diarrhea	16 (15.2)	10 (19.6)	6 (11.1)	.226
Gastrointestinal bleeding	8 (7.6)	3 (5.6)	5 (9.8)	.480
Feeding intolerance	29 (27.6)	12 (22.2)	17 (33.3)	.203
Nausea/vomiting	15 (14.3)	7 (13)	8 (15.7)	.690
Ileus	2 (1.9)	1 (1.9)	1 (2)	1.000
Target protein (g/day)	118 (107-127)	117 (106-127)	120 (109-127)	.417
Protein intake (g/day), 7 day	90 (67-105)	90 (64-108)	90 (70-105)	.982
Target energy (kcal/day)	1709 ± 385	1761 ± 446	1654 ± 304	.156
Energy intake (kcal/day), 7 day	1507 ± 460	1600 ± 445	1410 ± 461	**.034**
Pressure ulcer, n (%)	31 (29.5)	11 (20.4)	20 (39.2)	**.034**
Comorbidities, n (%)				
COPD	21 (20)	11 (20.4)	10 (19.6)	.922
CAD	14 (13.3)	5 (9.3)	9 (17.6)	.206
HTN	30 (28.6)	8 (14.8)	22 (43.1)	**.001**
CVD	9 (8.6)	1 (1.9)	8 (15.7)	**.014**
DM	20 (19)	7 (13)	13 (25.5)	.102
LOS in ICU, days	30 ± 34	33 ± 44	26 ± 17	.249

APACHE II, acute physiologic and chronic health evaluation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; n, number; NIMV, non-invasive mechanical ventilation; NLR, neutrophil-lymphocyte ratio; NRS, nutritional risk screening; WBC, white blood cell; y, year.

Table 2. Multivariable Binary Logistic Regression Modeling of Parameters for Mortality

Variables	OR	95% CI	*P*
Age	1.038	1.002-1.075	**.036**
Albumin, 7 day	1.148	1.021-1.290	**.021**
APACHE II score	1.055	0.950-1.173	.308
Need for IMV	1.834	0.550-6.097	.323
NRS 2002	1.010	0.626-1.623	.972
Nutric score	1.267	0.717-2.236	.415
Enteral nutrition support	2.325	0.677-8.000	.180
Energy intake, 7 day	1.000	0.999-1.002	.460
Pressure ulcer	1.041	0.331-3.277	.945
HTN	1.176	0.333-4.629	.746
CVD	2.624	0.217-31.250	.447
ARF	1.782	0.583-5.464	.310

APACHE II, acute physiologic and chronic health evaluation; ARF, acute renal failure; CVD, glomerular filtration rate; HTN, hypertension; IMV, invasive mechanical ventilation; NRS, nutritional Risk Screening; OR, odds ratio.

nutrition support (38 (74.5%) vs. 25 (46.3%), *P*=.001), and the frequency of pressure ulcer (20 (39.2%) vs. 11 (20.4%), *P*=.034) as compared to non-survivors. Survivors had higher albumin (on day 7) (2.6 (2.4-2.9) vs. 2.2 (1.9-2.6) *P*=.001) and mean energy intake (on day 7) (1600 ± 445 vs. 1410 ± 461, *P*=.034) as compared to non-survivors. Detailed demographic characteristics were described in Table 1. In the binary logistic regression analysis, age and albumin value (on day 7) were found to be independent risk factors for mortality (OR: 1.038 (1.002-1.075), *P*=.036, OR: 1.148 (1.021-1.290), *P*=.021), respectively (Detailed demographic characteristics were described in Table 2).

DISCUSSION

In this study, the files of a total of 105 patients hospitalized in the tertiary ICU were reviewed retrospectively, and it was planned to investigate the effects of parameters, primarily prealbumin, on mortality. When the prealbumin values of the patients at the time of hospitalization and on the seventh day were examined, it was observed that there was no relationship with mortality and that age and seventh day albumin level were independent risk factors for mortality. It has been shown in the studies that advanced age and hypoalbuminemia have a poor prognosis in patients hospitalized in the ICU.[7-11] In a study evaluating the 90-day mortality of septic patients, mean albumin values of the patients who died were 2.2 g/dL, and it has been reported that the cut-off value for mortality is 2.5 g/dL.[12] Vincent et al[13] reported that hypoalbuminemia adversely affects the entire clinical spectrum, mortality, morbidity, and ICU LOS in critically patients. Hypoalbuminemia occurs with decreased albumin synthesis secondary to inflammatory mediator release after acute phase processes, leakage from vascular capillaries, and renal losses following renal damage. Because albumin plays significant roles in the human body, such as maintenance of osmotic pressure, acid-basic balance, and transport of substances, decreased serum concentrations of albumin may be associated with death.[14] There have been numerous studies investigating the relationship between prealbumin and prognosis. Cheng et al[15] reported that the rate of infection and mortality increased and the length of hospital stay was prolonged in trauma patients with low prealbumin levels in the ICU. Another study, by Avram et al[16] reported that serum prealbumin was an independent risk factor for mortality in patients with peritoneal dialysis. Yang et al[17] observed that serum prealbumin levels were independently associated with mortality in critically ill patients who were severely burned. Zuo et al[18] reported that decreased prealbumin level is an independent prognostic factor of in-hospital mortality, ICU admission, and mechanical ventilation for older adults aged ≥ 65 years with COVID-19.[18] Zu et al[19] documented that the preoperative lower prealbumin group (<140 mg/L) was a prognostic risk for patients with gastric cancer. When the articles examining the relationship between prealbumin and mortality were searched on PubMed, it was seen that there was 1 article that was similar to our results. In the study by Lim et al. prealbumin levels were investigated on days 0 and 7 by including patients who received parenteral nutrition for more than 7 days in the ICU. At the end of 7 days, the patients were divided into two groups as increasing and decreasing the prealbumin value. There was no statistical difference between the groups in terms of mortality as a prognostic marker (*P*=.673).[20] Since prealbumin has a shorter half-life (2 days) than albumin and a more fast ratio of hepatic synthesis, a predictable catabolic ratio, and a rapid rising with adequate protein intake, it can also be an indicator of prognostic index in tumors, malnutrition, trauma, surgery, cirrhosis, burns, and critically ill patients as demonstrated in the aforementioned studies. When our results were examined, it was determined that both 0 and 7 days' prealbumin levels of the patients were lower than the reference prealbumin values in the studies (prealbumin values below 15 and 18 mg/dL were evaluated as low in the studies).[21, 22] Although nutritional support was given, prealbumin values on the seventh day decreased in both groups. Table 1 shows that target energy and protein levels could not be reached at the

end of the seventh day. Although the prealbumin value did not show the nutritional status sensitively enough, the fact that the patients were not given sufficient nutritional support may have prevented the increase in the prealbumin value. Statistically, the inability to detect prealbumin as a risk factor for mortality can be explained by the absence of an increase in the prealbumin value on the seventh day.

Limitations

The study was conducted in a single center and further our study population was relatively heterogeneous (e.g., cardiothoracic, neurosurgical, trauma, and pulmonary patients). Second, bias was inevitable because of the limited number of patients involved. There are a large number of variables that affect prealbumin levels that have not been looked at in the study (e.g., malnutrition status, renal and live function, type and extent of surgery, corticosteroid use, and other causes of inflammation). This preliminary results of 105 patients presented that prealbumin may not be an indicator of prognosis in critically ill patients. We predict that as a result of increasing the number of patients, a different outcome may be obtained in terms of prognosis.

Prealbumin level may not always give an idea about the prognosis in patients hospitalized in the ICU. The results may be unexpected, especially if there are many poor situations that may affect the prognosis and prealbumin values. Seeing more than one intermittent prealbumin value rather than a single value is important in terms of interpreting the results. We are of the opinion that it would be more accurate to determine the prognosis according to the increase or decrease in the prealbumin value in the follow-up.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gazi Yaşargil Training and Research Hospital (Date: April 07, 2021, Decision No: 842).

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