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Original Article

Hypoalbuminemia, a novel prognostic factor for prediction of long-term outcomes in critically ill patients with septic shock

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Abstract: The aim of this study was to explore the cut-off value of serum albumin to predict short and long-term mortality outcomes in patients with septic shock. We performed a retrospective clinical study which analyzed data from adults with septic shock, that were exacted from the Multiparameter Intelligent Monitoring in Intensive Care III (version 1.3) database. The 30-day, 90-day and 1-year mortality rates were compared in patients stratified according to their serum albumin levels. The study included 1034 patients. An optimal cut-off value for serum albumin of 2.45 g/dl was determined using the Youden index. Hypoalbuminemia was defined as an albumin level < 2.45 g/dl. The Kaplan-Meier survival curves showed that a low serum albumin level (< 2.45 g/dl) was associated with poorer survival outcomes. Multivariable Cox regression analysis further revealed that hypoalbuminemia was an independent predictor of short and long-term mortality (30-day mortality hazard ratio [HR]. 1.439, 95% confidence interval [CI]. 1.142, 1.814; 90-day mortality HR 1.448, 95% CI 1.168, 1.795; and 1-year mortality HR 1.389, 95% CI 1.134, 1.702). Serum albumin of 2.45 g/dl was an optimal cut-off value to define hypoalbuminemia and it predicted short and long-term outcomes in patients with septic shock.

Keywords: Serum albumin, septic shock, long-term mortality

Introduction

Despite the advances in modern medical therapeutics, septic shock remains a common life-threatening critical disease that is associated with high mortality [1]. It occurs in more than 230,000 US patients each year, with more than 40,000 US deaths annually [2, 3]. Therefore, understanding the risk factors is important for the management of septic shock. In intensive care units (ICUs), septic shock patients have a high prevalence of serum albumin loss [1, 4]. Serum albumin is the most abundant protein in human serum. It plays an important role in a number of physiological mechanisms including the regulation of the osmotic pressure [5]. More importantly, albumin also plays a central role in the intravascular transport of water-soluble molecules such as hormones, cholesterol, calcium, and drugs [6]. The role of albumin in other mechanisms, including the endothelial glycocalyx and the maintenance of vascular barrier competence, is particularly important in patients with increased capillary leakage such as those with septic shock [6, 7]. As such, the role of albumin in patients with sepsis or septic shock has received significant interest.

Previous studies have revealed that low albumin was an independent risk factor and an indicator of mortality in critically ill patients [8-10]. Low serum albumin may impair immune function, delay wound healing, reduce muscular strength, and lead to the emergence of pressure ulcers [10]. However, different studies often defined hypoalbuminemia using different standards and it was generally defined by a serum albumin < 3.5 g/dl, < 3.0 g/dl or < 2.5 g/

dl in critically ill patients [6, 11-13]. Considering the special clinical circumstances of sepsis, it would be useful to know what the best cut-off level of serum albumin would be in order to define hypoalbuminemia and to use it as a prognostic indicator in patients with septic shock. There are few studies that have explored the effects of albumin levels on the long-term outcomes for adults with septic shock. While mortality in hospitals is falling, long-term mortality after sepsis has remained high as many patients die in the subsequent months [14]. Therefore, the present retrospective study aimed to determine the optimal cut-off value of serum albumin, which could be used to (i) define hypoalbuminemia and (ii) act as a predictor of short or long-term outcomes in patients with septic shock.

Patients and methods

The database and study design

The Medical Information Mart for Intensive Care III (MIMIC-III) is a large database comprising of identified health-related data from over 40,000 patients who have been treated in critical care units of the Beth Israel Deaconess Medical Center, Boston, MA, USA. Data were collected between June 2001 and October 2012 from four ICUs (medical, surgical, coronary care, and neonatal). The database contains comprehensive clinical data including the results of laboratory tests, medications, and International Classification of Disease (ICD)-9 diagnoses obtained from hospital medical information systems for 46,520 ICU patients. To protect patient privacy, all personal data were anonymized and every patient was identified by an integer number called a subject ID. Our access to the database was approved after completion of the NIH web-based training course named ‘Protecting Human Research Participants’ (certification number: 1797305). Patient data were exacted using structure query language with pgAdmin PostgreSQL tools (version 1.20.00). The research protocol of the study was approved by the Ethics Committee of Beth Israel Deaconess Medical Center (number: 1797305).

Study population and definitions

We used ICD-9 code 78.552 to identify patients with septic shock. Inclusion criteria were: (i) men and women ages ≥ 18 years (i) The diagnosis was septic shock at admission; Patients who met the following criteria were excluded: (i) > 5% of data missing or lack of albumin data; (ii) readmission; (iii) patients with chronic renal and hepatic dysfunction, solid tumor, and metastatic cancer.

Data on the following information were extracted from the MIMIC-III database: age, sex, mean arterial pressure on ICU admission, time of ICU admission and discharge, and date of death. All clinical parameters were recorded within 24 h of ICU admission. The date of death for patients who had been discharged from the hospital was obtained from social security death records from the US government. For other patients that died, the date of death was taken to be the date of hospital discharge.

The laboratory measurements included serum albumin, white blood cell count, blood urea nitrogen, serum lactate, serum creatinine, and serum potassium. All laboratory parameters that were extracted from the MIMIC-III database had been measured within 24 h of ICU admission. Scores for the severity of illness were also recorded, including the Simplified Acute Physiology Score II and the; and the Elixhauser comorbidity score was used as a comorbidity estimate [15-17].

The primary endpoint in the study was the 30-day mortality and the secondary endpoints were 90-day and 1-year mortality.

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 20.0 (SPSS Inc., Chicago, IL, USA) for Windows®. An optimal cut-off value for serum albumin of 2.45 g/dl was determined using the Youden index (best pair of sensitivity and specificity for 30-day, 90-day and 1-year mortality from a receiver operating characteristic curve) to categorize: no hypoalbuminemia (≥ 2.45 g/dl) and hypoalbuminemia (< 2.45 g/dl) [11, 18]. Categorical variables were displayed as n (%), continuous variables were summarized as mean ± SD and cut-off values as median and interquartile range (IQR). Comparisons between the two groups were analyzed using Student’s t-test or nonparametric Wilcoxon signed-rank test for continuous variables. Categorical variables

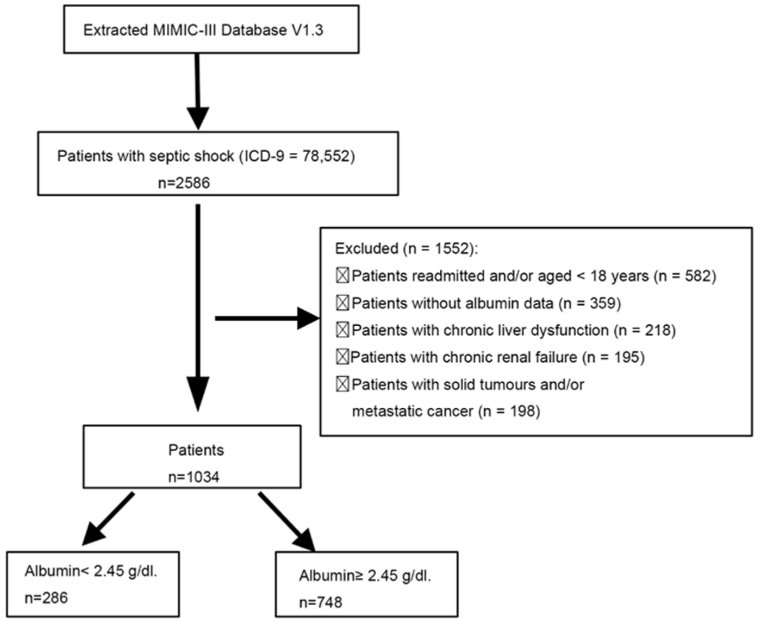

Figure 1. The flow diagram of the patients with septic shock who were included in the study to investigate the role of serum albumin levels. MIMIC-III, Medical Information Mart for Intensive Care III.

were analyzed using χ^2-test or Fisher's exact test.

In this longitudinal population, the hazard ratio (HR) and 95% confidence interval (CI) for the mortality outcomes were calculated using multivariable Cox proportional hazards regression. In addition, survival rates were analyzed using a log-rank test to determine the mortality outcomes at 30 days, 90 days and 1 year, stratified by serum albumin; and Kaplan-Meier survivals curve are presented. All *P*-values are 2-sided and a *P*-value of < 0.05 was considered statistically significant.

Results

After exclusion of individuals who did not meet the inclusion criteria (n = 1552; **Figure 1**), a total of 1034 eligible patients with septic shock were included in the analyses. There were 359 patients excluded because of a lack of albumin data; and there were no differences observed between them and the included patients in terms of baseline characteristics (data not shown).

According to the cut-off value of serum albumin of 2.45 g/dl, 286 (27.7%) patients were included in the hypoalbuminemia group (< 2.45 g/dl), whereas the remaining 748 (72.3%) patients were without hypoalbuminemia (≥ 2.45 g/dl). The baseline characteristics of the two groups are shown in **Table 1**. Patients with hypoalbuminemia had significantly higher short and long-term mortality rates compared with patients without hypoalbuminemia (P < 0.001 for all comparisons). The proportion of patients; requiring ventilator support, serum lactate, white blood cell count, and the severity of illness scores, were significantly higher and the serum creatinine was significantly lower, among patients with hypoalbuminemia compared with patients without hypoalbuminemia (P < 0.05 for all comparisons).

To identify whether baseline serum albumin plays a causal role in mortality, Cox proportional hazards regression analyses were performed and Kaplan-Meier survival curves were generated. As shown by the results of the univariate analysis presented in **Table 2**, albumin < 2.45 g/dl, age, ventilator support, length of hospital stay, serum creatinine, blood urea nitrogen, serum lactate, serum potassium, and the three scoring systems were all significantly associated with mortality (P < 0.05 for all comparisons; except serum creatinine at 1 year). Patients with serum albumin < 2.45 g/dl were more likely to die within 30 days (HR 1.770; 95% CI 1.416, 2.221; P < 0.001), 90 days (HR 1.695; 95% CI 1.382, 2.079; P < 0.001), and 1 year (HR 1.538; 95% CI 1.269, 1.865; P < 0.001). As shown in **Table 3**, after adjusting for clinical and laboratory characteristics, patients with hypoalbuminemia still showed independent associations with higher risks of short and long-term mortality than patients without hypoalbuminemia. The diagnostic sensitivity, specificity, and area under the curve of serum albumin < 2.45 g/dl for the short and long-term mortality outcomes are shown in **Table 4**.

Figure 2 shows the cumulative incidence of mortality (Kaplan-Meier curves) in the 30-day, 90-day and 1-year periods stratified by the cut-off value of serum albumin of 2.45 g/dl. **Figure 3** shows the ROC curve of 30 days, 90 days,

Table 1. Baseline demographic and clinical characteristics of the two groups of patients with septic shock stratified according to their serum albumin levels (cut-off value 2.45 g/dl)

Characteristic	All patients n = 1034	Patients with albumin < 2.45 g/dl n = 286	Patients with albumin ≥ 2.45 g/dl n = 748	Statistical significance
Age, years	65.0 ± 16.2	68.0 ± 16.4	67 ± 16.1	NS
Sex, males	559 (54.1%)	150 (52.4%)	409 (54.7%)	NS
MAP, mmHg	76.5 ± 17.1	73.6 ± 17.5	74.3 ± 16.9	NS
Ventilator support	736 (71.2%)	230 (80.4%)	506 (67.6%)	P < 0.001
CRRT support	67 (6.5%)	23 (8.0%)	44 (5.9%)	NS
In-hospital mortality	362 (35.0%)	127 (44.4%)	235 (31.4%)	P < 0.001
30-day mortality	331 (32.0%)	124 (43.4%)	207 (27.7%)	P < 0.001
90-day mortality	400 (38.7%)	144 (50.3%)	256 (34.2%)	P < 0.001
1-year mortality	467 (45.2%)	156 (54.5%)	311 (41.6%)	P < 0.001
Length of hospital stay, days	11 (6-21)	12 (6-23)	11 (6-21))	NS
Lactate, mg/l	3.1 ± 2.5	3.5 ± 2.9	3.0 ± 2.3	P = 0.017
White blood cell count, x 109/l	13.0 ± 12.0	13.7 ± 17.1	12.6 ± 9.6	P = 0.029
Platelet count, x 109/l	214 (142-307)	226 (134-354)	212 (144-303)	NS
Creatinine, mg/dl	1.4 (1.0-2.3)	0.9 (1.4-2.4)	1.4 (1.0-2.3)	P = 0.035
BUN, mg/dl	30 (19-49)	30 (19-52)	29 (19-49)	NS
Potassium, mmol/l	4.1 ± 0.8	4.1 ± 0.8	4.1 ± 0.8	NS
SAPSII	46 (34-58)	52 (38-65)	44 (33-56)	P < 0.001
Elixhauser comorbidity score	4 (0-9)	5 (0-9)	4 (0-9)	NS
SOFA	7 (4-9)	8 (5-10)	6 (4-9)	P < 0.001

aNormally distributed data presented as mean ± SD (P < 0.05; independent Student's t-test); not normally distributed data presented as median (interquartile range) (P < 0.05; nonparametric Wilcoxon signed-rank test); categorical variables presented as n of patients (%) (P < 0.05; χ^2-test or Fisher's exact test). MAP, mean arterial pressure; CRRT, continuous renal replacement therapy; BUN, blood urea nitrogen; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; NS, no significant between-group difference (P ≥ 0.05).

Table 2. Univariate analysis of the associations between outcomes and clinical and biochemical characteristics in patients with septic shock

Characteristic	Mortality hazard ratio (95% confidence interval)					
	30-day	Statistical significance	90-day	Statistical significance	1-year	Statistical significance
Albumin < 2.45 g/dl	1.770 (1.416, 2.211)	P < 0.001	1.695 (1.382, 2.079)	P < 0.001	1.538 (1.269, 1.865)	P < 0.001
Age	1.024 (1.016, 1.032)	P < 0.001	1.026 (1.019, 1.034)	P < 0.001	1.028 (1.021, 1.035)	P < 0.001
Sex	1.032 (0.831, 1.282)	NS	1.004 (0.825, 1.223)	NS	1.079 (0.899, 1.269)	NS
Ventilator support	3.761 (2.671, 5.295)	P < 0.001	3.044 (2.295, 4.039)	P < 0.001	2.564 (2.010, 3.271)	P < 0.001
Length of hospital stay	0.931 (0.918, 0.946)	P < 0.001	0.972 (0.962, 0.981)	P < 0.001	0.987 (0.980, 0.994)	P < 0.001
Creatinine	1.068 (1.016, 1.123)	P = 0.010	1.051 (1.001, 1.103)	P = 0.046	1.045 (0.998, 1.094)	NS
Blood urea nitrogen	1.007 (1.004, 1.010)	P < 0.001	1.007 (1.004, 1.009)	P < 0.001	1.006 (1.003, 1.009)	P < 0.001
Lactate	1.161 (1.119, 1.205)	P < 0.001	1.144 (1.103, 1.186)	P < 0.001	1.119 (1.079, 1.161)	P < 0.001
Potassium	1.465 (1.305, 1.644)	P < 0.001	1.410 (1.266, 1.571)	P < 0.001	1.439 (1.303, 1.589)	P < 0.001
Elixhauser comorbidity score	1.041 (1.023, 1.059)	P < 0.001	1.045 (1.028, 1.062)	P < 0.001	1.047 (1.031, 1.062)	P < 0.001
SAPSII	1.039 (1.033, 1.045)	P < 0.001	1.036 (1.030, 1.042)	P < 0.001	1.034 (1.028, 1.039)	P < 0.001
SOFA	1.189 (1.153, 1.226)	P < 0.001	1.165 (1.133, 1.199)	P < 0.001	1.146 (1.116, 1.176)	P < 0.001

SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; NS, no significant association (P ≥ 0.05).

and 1 year of serum albumin in patients with septic shock was less than 2.45 g/dl. At 30 and 90 days, the incidence of death was 43.4% (124 of 286) and 50.3% (144 of 286) in the hypoalbuminemia group, respectively; compared with 27.7% (207 of 748) and 34.2% (256 of 748) in the group without hypoalbuminemia, respectively. Patients with septic shock and

Table 3. Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between hypoalbuminemia and mortality of patients with septic shock

Patients with hypoalbuminemia	HR	95% CI	Statistical significance
Short-term mortality			
30-day mortality	1.439	1.142, 1.814	P = 0.002
Long-term mortality			
90-day mortality	1.448	1.168, 1.795	P = 0.001
1-year mortality	1.389	1.134, 1.702	P = 0.002

Adjusted for clinical characteristics of age, sex, length of hospital stay, ventilator support, creatinine, blood urea nitrogen, serum potassium, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment and the Elixhauser comorbidity score.

hypoalbuminemia had an adverse outcome in both short and long-term compared with patients without hypoalbuminemia.

Discussion

The MIMIC database has been used in several studies focused on critically ill patients [19-21]. In this present study, the clinical data were extracted from the electronic medical records based on the MIMIC-III database and analysis of these data demonstrated a potentially interesting relationship between low serum albumin levels and poor prognosis in patients with septic shock. By comparing high and low albumin groups, the present study found that there was a significant difference in the ventilator support used, serum lactate, white blood cell count, serum creatinine, and severity of illness scores between the two groups. The present study demonstrated that a lower serum albumin level appeared to be a strong predictor of short and long-term mortality in patients with septic shock when hypoalbuminemia was defined by a serum albumin < 2.45 g/dl. This cut-off value resulted in a high specificity when predicting 30-day, 90-day and 1-year mortality (76.9%, 77.6%, and 77.0%, respectively).

Albumin is the main serum protein in human body and it plays a role in many aspects of the functioning of the human body [22]. Critically ill patients are commonly accompanied by low serum albumin, with reported incidences as high as 40-50% [12]. Serum albumin is the main determinant of colloid osmotic pressure and a major plasma carrier of many endogenous and exogenous compounds [22]. This multifunctional protein is also an important extracellular non-enzymatic antioxidant, thereby protecting against oxidative stress induced injury [23]. In a comprehensive meta-analysis of 90 studies in adult patients with acute or chronic diseases, a strong dose response relationship was found between serum albumin concentration and outcome [24]. Each 1 g/dl decrease in serum albumin concentration significantly raised the odds of mortality by 137%, prolonged ICU and hospital stay by 28% and 71%, respectively, and increased resource utilization by 66% [24]. The findings of the present study showed that patients with a serum albumin level < 2.45 g/dl had the worse mortality outcomes. This cutoff value has low sensitivity, the specificity is nearly 77%, maybe this factor is not a perfect marker. However, these findings add to the evidence that low serum albumin levels are a strong independent predictor of mortality in patients with septic shock, although it remains unclear whether hypoalbuminemia directly contributes to poor outcomes [11, 18, 25].

The association between low serum albumin and high risk of mortality in patients with septic shock may have several explanations. First of all, albumin is a carrier for several endogenous and exogenous compounds, with antioxidant and anti-inflammatory properties, and it is the main protein responsible for plasma colloid osmotic pressure, all of which would be beneficial for haemodynamic stability [13, 26]. Albumin can combine with large amounts of free fatty acids in the blood to protect them from lipid peroxidation damage and it can reduce or eliminate the toxicity of internal or external toxic substances by binding with them, which in turn reduces endothelial damage, and further reduces the risk of complications and mortality [27, 28]. Two meta-analyses that included studies in patients with sepsis reported a trend toward decreased mortality with albumin resuscitation fluid for sepsis compared with non-albumin fluids [29, 30]. Secondly, older patients are far more likely to develop sepsis, and also they are more likely to have comorbid conditions, such as malnutrition. A recent study indicated that malnutrition and inflammatory activation could contribute to the

Table 4. Diagnostic sensitivity, specificity, and area under the curve (AUC) of serum albumin < 2.45 g/dl for predicting short and long-term mortality in patients with septic shock

	30-day motility	90-day mortality	1-year mortality
Sensitivity	37.5%	36.0%	33.4%
Specificity	76.9%	77.6%	77.0%
AUC of ROC (95% CI)	0.583 (0.545-0.629)	0.580 (0.544-0.616)	0.555 (0.520-0.590)

ROC, receiver operating characteristic; CI, confidence interval.

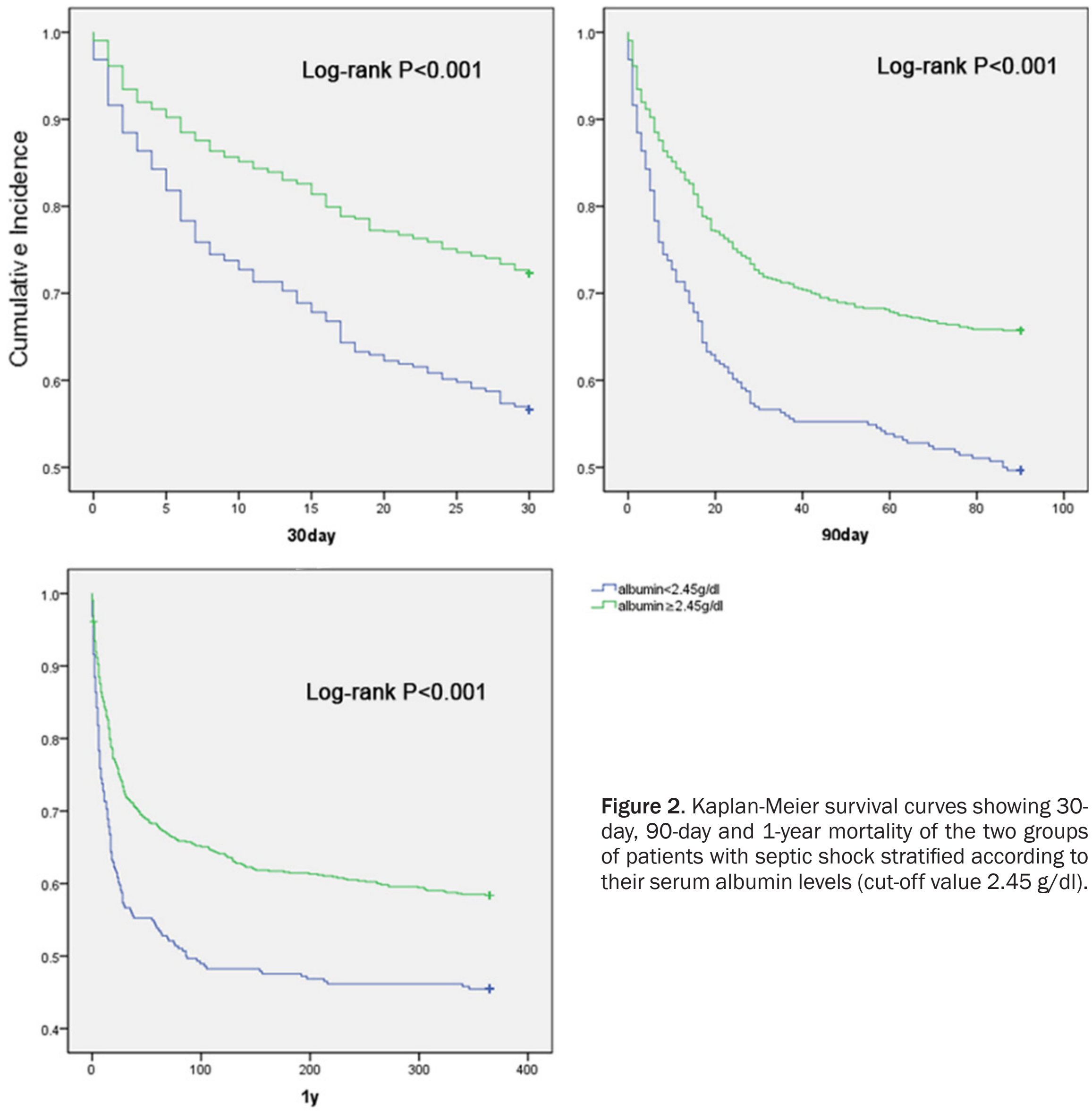

Figure 2. Kaplan-Meier survival curves showing 30-day, 90-day and 1-year mortality of the two groups of patients with septic shock stratified according to their serum albumin levels (cut-off value 2.45 g/dl).

cause of hypoalbuminemia in patients [31]. Hypoalbuminemia generally acts as a nutritional marker, patients with malnutrition at ICU admission are more likely to die [32].

This present study showed that the serum albumin level at admission can be used as an independent predictor of 30-day, 90-day and 1-year mortality in patients with septic shock. To the best of our knowledge, previous studies that have evaluated the prognostic significance of serum albumin in septic patients mainly focused on 28- to 30-day mortality [10, 11, 33, 34]. This present study focused on the long-

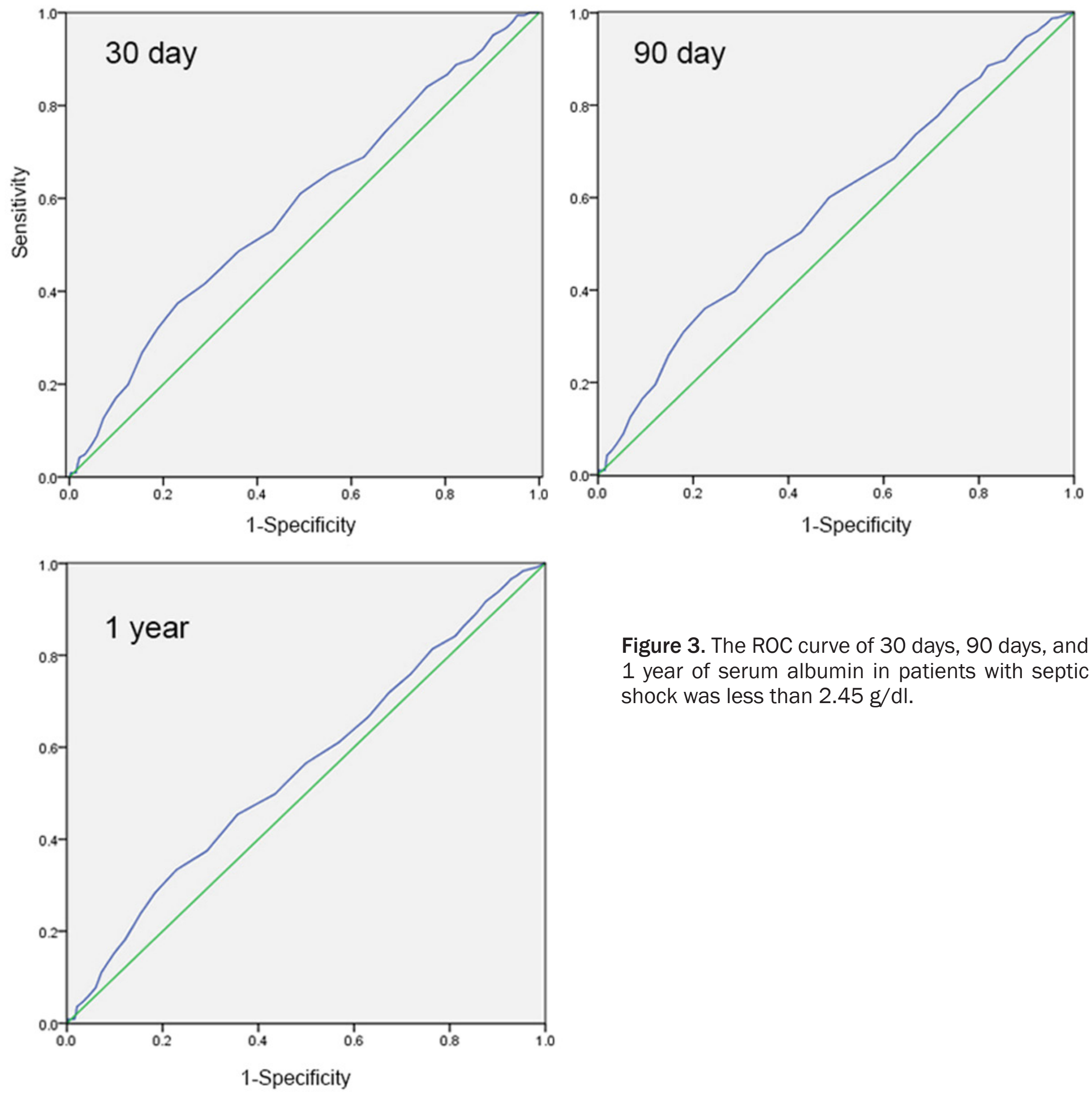

Figure 3. The ROC curve of 30 days, 90 days, and 1 year of serum albumin in patients with septic shock was less than 2.45 g/dl.

term outcomes in patients with septic shock as this might be indicative of residual inflammation. A previous study demonstrated that nearly 20% patients who survive sepsis have a late death, which can't be explained by their health status before sepsis [34]. This present study selected a long-term mortality endpoint and found that septic patients with hypoalbuminemia still had an adverse outcome in the longer term.

This present study had several limitations. First, although the MIMIC-III database included more than 40,000 patients, few patients with septic shock met the inclusion criteria so the sample size was small, which limited the statistical power of the analyses. Secondly, this cut-off value 2.45 g/dl has high specificity; however, the sensitivity is low. Third, the patients with septic shock in this present study were all extracted from ICU electronic records. Patients whose disease was managed in hospital wards or emergency departments were not included in the study. Forth, serum albumin levels were only recorded at ICU admission, and a series of measurements during the ICU stay might have been more valuable for the evaluation of the relationship between serum albumin and prognosis.

Conclusion

A higher serum albumin level (≥ 2.45 g/dl) was associated with a decreased risk for 30-day, 90-day and 1-year mortality in patients with septic shock. A serum albumin of 2.45 g/dl was the optimal cut-off value to define hypoalbuminemia. It appears to be a novel independent predictor for short and long-term outcomes in critically ill patients with septic shock in ICUs.

Disclosure of conflict of interest

None.

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