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ORIGINAL RESEARCH

Albumin Level is Associated with Short-Term and Long-Term Outcomes in Sepsis Patients Admitted in the ICU: A Large Public Database Retrospective Research

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Objective: This study aimed to explore the relationship between albumin level with short- and long-term outcomes in sepsis patients admitted in the intensive care unit (ICU) based on a large public database to provide clinical evidence for physicians to make individualized plans of albumin supplementation.

Methods: Sepsis patients admitted in the ICU in MIMIC-IV were included. Different models were performed to investigate the relationships between albumin and mortalities of 28-day, 60-day, 180-day and 1-year. Smooth fitting curves were performed.

Results: A total of 5357 sepsis patients were included. Mortalities of 28-day, 60-day, 180-day and 1-year were 29.29% (n = 1569), 33.92% (n = 1817), 36.70% (n = 1966) and 37.71% (n = 2020). In the fully adjusted model (adjusted for all potential confounders), with each 1g/dL increment in albumin level, the risk of mortality in 28-day, 60-day, 180-day and 1-year decreased by 39% (OR = 0.61, 95% CI: 0.54–0.69), 34% (OR = 0.66, 95% CI: 0.59–0.73), 33% (OR = 0.67, 95% CI: 0.60–0.75), and 32% (OR = 0.68, 95% CI: 0.61–0.76), respectively. The non-linear negative relationships between albumin and clinical outcomes were confirmed by smooth fitting curves. The turning point of albumin level was 2.6g/dL for short- and long-term clinical outcomes. When albumin level ≤2.6g/dL, with each 1g/dL increment in albumin level, the risk of mortality in 28-day, 60-day, 180-day and 1-year decreased by 59% (OR = 0.41, 95% CI: 0.32–0.52), 62% (OR = 0.38, 95% CI: 0.30–0.48), 65% (OR = 0.35, 95% CI: 0.28–0.45), and 62% (OR = 0.38, 95% CI: 0.29–0.48), respectively.

Conclusion: Albumin level was associated with short- and long-term outcomes in sepsis. Albumin supplementation might be beneficial for septic patients with serum albumin<2.6g/dL.

Keywords: albumin, mortality, inflammation, sepsis, MIMIC-IV

Introduction

Albumin, as a significant protein and accounting for nearly one half of the total proteins in plasma, plays an important role in various physiological procedures.[1] Albumin not only regulates the acid–base balance and fluid distribution in the body, but also serves as a transporter of many substances including drugs and hormones.[2,3] Previous studies have explored the relationships between albumin level and clinical outcomes in many disorders including malignant tumor,[4] hepatic disease,[5] pancreatitis,[6] infectious disease[7] and even in COVID-19.[8] One study with 100,529 participants and a median follow-up of 8.5 years revealed that with each 1g/dl decrease in plasma albumin, the hazard ratios (HR) for ischemic heart disease, myocardial infarction and stroke were 1.17, 1.25 and 1.46, respectively.[9]

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Albumin also has been identified to have partly anti-inflammatory effects and be beneficial to the patients with sepsis.[10] In sepsis, a recent study showed that when admission serum albumin was ≤ 2.45 g/dL and the lowest serum albumin was ≤ 1.45 g/dL during hospitalization, the probability of survival in hospital declined by 70.6% and 76.4%, respectively.[11] However, few studies have investigated the effects of albumin level on long-term outcomes in sepsis and few definitive randomized controlled trials have been done to explore an outcome benefit of albumin supplementation in sepsis patients.

Hence, we aimed to explore the relationship between albumin level with short- and long-term outcomes in sepsis based on a large public database to provide clinical evidence for physicians to make individualized plans for patients.

Methods

Database and Patients

Medical Information Mart for Intensive Care IV (MIMIC-IV) database (https://mimic.mit.edu/iv/) is a large critical-care database that is an updated version of MIMIC-III. It covers more than 70,000 patients admitted in the intensive care unit (ICU) in a prolonged period time from 2008 to 2019 in Beth Israel Deaconess Medical Center of Boston and contains comprehensively clinical and laboratory data of patients.[12,13] Our retrospective study was based on the MIMIC-IV and the corresponding author (N.D.) passed the Protecting Human Research Participants exam (No.32900964) for obtaining the utility of the database.

Sepsis patients admitted in the ICU in MIMIC-IV were included in the study and the definition of sepsis was on the basis of Sepsis 3.0,[14,15] which referred that the infection plus sequential organ failure assessment (SOFA) score ≥2 points. Exclusion criteria included as follow: (1) patients with missing data of albumin; (2) patients with missing data of > 5% variables; (3) age less than 18-year-old.

Data Extraction and Variables

Data extraction in MIMIC-IV was implemented by PgAdmin4 which was applied for running structure query language (SQL).

First, the basic information of each patient including age, gender, marital status, ethnicity, comorbidities, ICU departments, scores of SOFA and chronic health evaluation (APACHEII), length of stay (LOS) in ICU and hospital, and clinical outcomes including (28-day mortality, 60-day mortality, 180-day mortality and 1-year mortality) were extracted.

Second, variables including vital signs and laboratory findings were extracted when patients were admitted in ICU within 24 hours and only the first value of each variable in 24 hours was enrolled in our study. Variables including heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), alanine aminotransferase (ALT), lactate, hematocrit, aspartate aminotransferase (AST), prothrombin time (PT), thrombin time (TT), red blood cell (RBC), white blood cell (WBC), total bilirubin, total calcium, creatinine, urea nitrogen, RBC distribution width (RDW), hemoglobin, hematocrit, bicarbonate, platelet (PLT), anion gap (AG), chloride, sodium, lactate and international normalized ratio (INR) were extracted.

Statistical Analysis

Statistical analysis was performed by EmpowerStats (http://www.empowerstats.com) and the software packages R (http://www.R-project.org).

First, based on the quartiles of albumin level, all the sepsis patients were distributed into four groups (Q1 (≤2.3g/dL, n = 1073), Q2 (2.4–2.7g/dL, n = 1584), Q3 (2.8–3.1g/dL, n = 1261), Q4 (≥3.2g/dL, n = 1439)) (Table 1). Variables were demonstrated and compared as follows: (1) medians for continuous variables, and percentages or frequencies for categories variables; and (2) data analyzed by Chi-squared test and Mann–Whitney *U*-test. Second, univariable analysis for short- and long-term outcomes in sepsis was conducted. Third, relationships between albumin and different clinical outcomes in three models were explored as follows: crude model (adjusted for none), model I (adjusted for age and gender) and model II (adjusted for all potential confounders including age, gender, HR, SBP, DBP, RR, renal disease, CAD, diabetes, hypertension, AG, ALT, AST, PT, TT, RBC, WBC, total bilirubin, total calcium, bicarbonate, creatinine, chloride, lactate, hematocrit, hemoglobin, PLT, RDW, urea nitrogen, sodium, INR, SOFA, and APACHEII). Then, albumin level was changed into the categorical variable as Q1–Q4 and the

Table 1 Baseline Characteristics of the Study Population

	Albumin (g/dL) (Quartiles)				
Variables	**Total**	**Q1 (≤2.3)**	**Q2 (2.4–2.7)**	**Q3 (2.8–3.1)**	**Q4 (≥3.2)**
Number	5357	1073	1584	1261	1439
Age(years)	66.00 (55.00–76.00)	64.00 (54.00–75.00)	66.00 (55.00–76.00)	66.00 (56.00–77.00)	66.00 (55.00–76.00)
Gender (n,%)					
Male	3068 (57.27%)	572 (53.31%)	893 (56.38%)	744 (59.00%)	859 (59.69%)
Female	2289 (42.73%)	501 (46.69%)	691 (43.62%)	517 (41.00%)	580 (40.31%)
Comorbidities (n,%)					
Hypertension	1105 (20.63%)	235 (21.90%)	317 (20.01%)	268 (21.25%)	285 (19.81%)
CAD	489 (9.13%)	81 (7.55%)	134 (8.46%)	129 (10.23%)	145 (10.08%)
Renal disease	239 (4.46%)	54 (5.03%)	59 (3.72%)	50 (3.97%)	76 (5.28%)
Diabetes	164 (3.06%)	23 (2.14%)	52 (3.28%)	47 (3.73%)	42 (2.92%)
Vital signs					
HR (beats/min)	97.00 (83.00–112.00)	100.00 (85.00–114.00)	99.00 (84.00–114.00)	96.00 (81.00–112.00)	96.00 (81.00–110.00)
RR (beats/min)	21.00 (17.00–25.00)	21.00 (17.00–26.00)	21.00 (17.00–25.00)	20.00 (17.00–25.00)	21.00 (17.00–25.00)
SBP (mmHg)	111.00 (97.00–128.00)	109.00 (96.00–125.00)	110.00 (97.00–127.00)	111.00 (96.00–127.00)	113.00 (98.00–132.00)
DBP (mmHg)	63.00 (53.00–74.00)	62.00 (52.00–73.00)	63.00 (52.00–73.00)	63.00 (53.00–74.00)	63.00 (53.00–77.00)
Laboratory variables					
ALT (IU/L)	30.00 (17.00–67.00)	27.00 (15.00–58.00)	31.00 (17.00–69.00)	31.00 (17.00–75.00)	29.00 (17.00–67.00)
AST (IU/L)	45.00 (25.00–103.00)	45.00 (25.00–104.00)	47.00 (26.00–103.00)	45.00 (24.00–102.00)	41.00 (24.00–101.00)
PT (s)	15.40 (13.30–20.10)	16.00 (13.90–20.40)	15.65 (13.50–19.90)	15.10 (13.20–19.80)	14.80 (12.80–20.55)
TT (s)	32.90 (28.70–40.70)	34.60 (29.50–43.20)	33.25 (28.90–41.00)	32.40 (28.50–39.40)	32.30 (28.20–39.90)
RBC (*10^{12}/L)	3.44 (2.92–3.99)	3.25 (2.78–3.71)	3.34 (2.87–3.84)	3.49 (2.98–4.00)	3.72 (3.12–4.22)
WBC (*10^{9}/L)	12.30 (7.60–18.30)	13.30 (8.10–19.80)	12.80 (7.70–19.10)	12.00 (7.40–17.60)	11.40 (7.50–16.70)
Total bilirubin (umol/L)	13.68 (6.84–32.49)	13.68 (6.84–37.62)	13.68 (6.84–34.20)	11.97 (6.84–27.36)	13.68 (6.84–32.49)
Total calcium (mmol/L)	2.00 (1.87–2.15)	1.90 (1.75–2.02)	1.97 (1.85–2.10)	2.02 (1.90–2.15)	2.12 (2.00–2.25)
Creatinine (umol/L)	123.76 (79.56–203.32)	114.92 (70.72–203.32)	114.92 (79.56–203.32)	123.76 (79.56–203.32)	123.76 (88.40–194.48)
Urea nitrogen (mmol/L)	4.64 (2.98–7.96)	4.98 (2.98–8.13)	4.81 (2.98–8.13)	4.81 (3.15–7.96)	4.48 (2.82–7.63)
RDW (%)	15.60 (14.20–17.50)	16.00 (14.60–18.00)	15.70 (14.30–17.50)	15.50 (14.20–17.20)	15.30 (14.00–17.20)
Hemoglobin (g/dL)	10.20 (8.70–11.80)	9.60 (8.20–11.10)	10.00 (8.60–11.40)	10.30 (8.90–11.90)	11.00 (9.20–12.50)
Hematocrit (%)	31.50 (27.10–36.20)	29.90 (25.70–34.20)	30.55 (26.50–35.00)	32.00 (27.70–36.50)	34.00 (28.80–38.30)
Bicarbonate (mmol/L)	21.00 (18.00–25.00)	20.00 (17.00–24.00)	21.00 (18.00–24.00)	21.00 (18.00–25.00)	22.00 (19.00–25.00)
PLT (*10^{9}/L)	182.00 (115.00–265.00)	189.00 (108.00–295.00)	181.00 (113.00–262.50)	180.00 (119.00–259.00)	180.00 (118.00–252.00)
AG (mmol/L)	16.00 (13.00–19.00)	15.00 (12.00–18.00)	15.00 (13.00–18.00)	16.00 (13.00–19.00)	17.00 (14.00–20.00)
Chloride (mmol/L)	103.00 (98.00–107.00)	104.00 (99.00–109.00)	103.00 (99.00–108.00)	103.00 (98.00–108.00)	101.00 (96.00–105.00)
Sodium (mmol/L)	138.00 (134.00–141.00)	137.00 (133.00–141.00)	138.00 (134.00–141.00)	138.00 (135.00–141.00)	137.00 (134.00–141.00)
INR	1.40 (1.20–1.90)	1.50 (1.30–1.90)	1.40 (1.20–1.80)	1.40 (1.20–1.80)	1.40 (1.20–1.90)
Lactate (mmol/L)	2.00 (1.40–3.20)	2.20 (1.40–3.50)	2.00 (1.40–3.00)	1.90 (1.30–3.10)	2.00 (1.40–3.20)
Scoring systems (IQR)					
APACHEII	12.00 (9.00–15.00)	12.00 (10.00–16.00)	12.00 (9.00–15.00)	12.00 (9.00–15.00)	12.00 (9.00–15.00)
SOFA	3.00 (2.00–5.00)	3.00 (2.00–5.00)	3.00 (2.00–5.00)	3.00 (2.00–4.00)	3.00 (2.00–5.00)
Clinical outcomes (days)					
LOS in ICU	5.40 (2.44–11.84)	6.77 (3.05–13.09)	5.26 (2.58–11.52)	4.64 (2.18–10.74)	5.30 (2.23–11.91)
LOS in hospital	12.92 (7.05–22.71)	14.27 (7.68–23.85)	13.02 (7.39–22.57)	11.77 (6.64–20.70)	12.74 (6.98–23.26)
28-day mortality (n,%)	1569 (29.29%)	440 (41.01%)	446 (28.16%)	325 (25.77%)	358 (24.88%)
60-day mortality (n,%)	1817 (33.92%)	487 (45.39%)	512 (32.32%)	376 (29.82%)	442 (30.72%)
180-day mortality (n,%)	1966 (36.70%)	521 (48.56%)	553 (34.91%)	409 (32.43%)	483 (33.56%)
1-year mortality (n,%)	2020 (37.71%)	525 (48.93%)	571 (36.05%)	424 (33.62%)	500 (34.75%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; WBC, white blood cells; PLT, platelet; RDW, red blood cell distribution width; RBC, red blood cells; PT, prothrombin time; TT, thrombin time; AG, anion gap; INR, international normalized ratio; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; LOS, length of stay; ICU, intensive care unit; IQR, interquartile ranges.

relationships with clinical outcomes in three models were also explored. Fourth, after adjusted for all potential confounders, the smooth fitting curves were constructed for illuminating the associations of albumin level and different clinical outcomes by a generalized additive model. Fifth, two models including model I (linear model) and model II (two-segment nonlinear model)

were compared. The P value of the log-likelihood ratio test determined the better model. If P>0.05, it indicated that the better was linear model. If not, the nonlinear model was selected and the turning point of albumin level was confirmed by recursive algorithm. Finally, the subgroups analyses between albumin level and different variables by stratified models were investigated.

Results

General Information and Baseline Variables of the Cohort

In our study, a total of 5357 sepsis patients were included and the associated flow chart is displayed in Figure 1. The median age of the cohort was 66 and males accounted for 57.27% in total (Table 1). ALmost half (43.61%) of the patients were married and 66.34% were white (Supplementary Table 1). Around a fifth (20.63%) of the patients had hypertension and nearly one half were admitted in Medical ICU(MICU) department (Supplementary Table 1). The median days of LOS in ICU and hospital were 5.40 and 12.92, respectively. The median scores of SOFA and APACHEII were 3.00 and 12.00, respectively. Mortalities of 28-day, 60-day, 180-day and 1-year were 29.29% (n = 1569), 33.92% (n = 1817), 36.70% (n = 1966) and 37.71% (n = 2020). In Table 1, different variables were also compared and analyzed between four groups based on quartiles of serum albumin levels. In Q1 group (serum albumin ≤2.3g/dL), the mortalities of the 28-day, 60-day, 180-day and 1-year were all the highest compared with Q2-Q4 groups, which were 41.01%, 45.39%, 48.56% and 48.93%, respectively.

Univariate Analyses for Short- and Long-Term Outcomes in Sepsis

In Table 2, univariate analyses for mortalities of 28-day, 60-day, 180-day and 1-year in sepsis were performed. Variables including age, CAD, renal disease, RR, PT, TT, total bilirubin, total calcium, creatinine, urea nitrogen, RDW, AG, INR, lactate, SOFA, and APACHEII were positively associated with mortalities of the short- and long-term. Variables including diabetes, RBC, hemoglobin, hematocrit, chloride, sodium and albumin were negatively associated with mortalities of the short- and long-term.

Relationship Between Albumin and Different Clinical Outcomes in Three Models

In Supplementary Table 2, three models were constructed to explore the relationship between albumin level and clinical outcomes: crude model adjusted for none, model I adjusted for age and gender, and model II adjusted for all potential confounders. In model II, with each 1g/dL increment in albumin level, the risk of mortality in 28-day, 60-day, 180-day and 1-year decreased by 39% (OR = 0.61, 95% CI:0.54–0.69), 34% (OR = 0.66, 95% CI:0.59–0.73), 33% (OR = 0.67, 95% CI: 0.60–

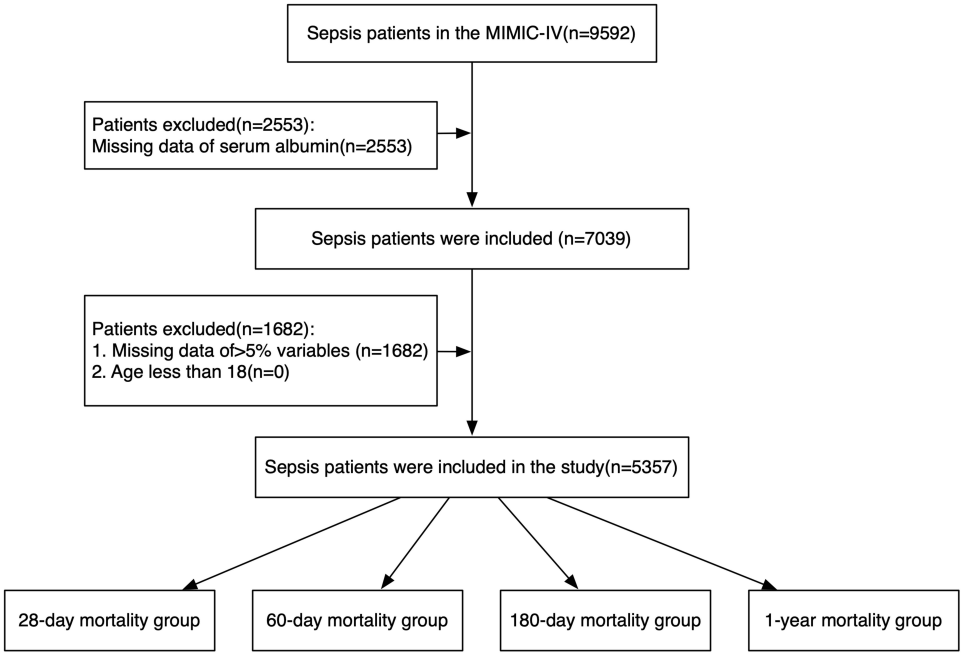

Figure 1 Flow chart and study design.

Table 2 Univariate Analysis for Short-Term and Long-Term Outcomes in Sepsis

Variables	Univariable (OR,95% CI) (28-Day Mortality)	Univariable (OR,95% CI) (60-Day Mortality)	Univariable (OR,95% CI) (180-Day Mortality)	Univariable (OR,95% CI) (1-Year Mortality)
Age (years)	1.02 (1.01, 1.02)	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)
Gender				
Male	Ref.	Ref.	Ref.	Ref.
Female	0.99 (0.88, 1.12)	1.07 (0.95, 1.19)	1.02 (0.91, 1.14)	1.00 (0.89, 1.11)
Hypertension				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.95 (0.82, 1.10)	0.90 (0.78, 1.04)	0.89 (0.78, 1.03)	0.88 (0.77, 1.01)
CAD				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.13 (0.93, 1.38)	1.23 (1.02, 1.49)	1.26 (1.04, 1.52)	1.30 (1.07, 1.56)
Diabetes				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.62 (0.43, 0.91)	0.68 (0.48, 0.97)	0.71 (0.50, 0.99)	0.70 (0.50, 0.98)
Renal disease				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.38 (1.05, 1.81)	1.48 (1.14, 1.92)	1.61 (1.24, 2.09)	1.59 (1.23, 2.06)
HR (beats/min)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
RR (beats/min)	1.01 (1.01, 1.02)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
SBP (mmHg)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
DBP (mmHg)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
ALT (IU/L)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
AST (IU/L)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
PT (s)	1.02 (1.01, 1.02)	1.02 (1.01, 1.02)	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)
TT (s)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
RBC (*10^{12}/L)	0.82 (0.76, 0.89)	0.78 (0.73, 0.85)	0.78 (0.73, 0.84)	0.77 (0.72, 0.83)
WBC (*10^{9}/L)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
Total bilirubin (umol/L)	1.06 (1.04, 1.07)	1.06 (1.05, 1.08)	1.06 (1.04, 1.07)	1.06 (1.04, 1.07)
Total calcium (mmol/L)	1.06 (1.00, 1.12)	1.10 (1.04, 1.17)	1.12 (1.06, 1.19)	1.13 (1.07, 1.20)
Creatinine (umol/L)	1.06 (1.03, 1.09)	1.05 (1.02, 1.08)	1.05 (1.02, 1.09)	1.06 (1.03, 1.10)
Urea nitrogen (mmol/L)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
RDW (%)	1.14 (1.12, 1.17)	1.17 (1.14, 1.19)	1.17 (1.15, 1.20)	1.17 (1.15, 1.20)
Hemoglobin (g/dL)	0.96 (0.93, 0.98)	0.94 (0.92, 0.97)	0.94 (0.92, 0.96)	0.94 (0.91, 0.96)
Hematocrit (%)	0.99 (0.98, 1.00)	0.98 (0.98, 0.99)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)
Bicarbonate (mmol/L)	0.99 (0.98, 1.00)	1.00 (0.98, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
PLT (*10^{9}/L)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
AG (mmol/L)	1.05 (1.04, 1.06)	1.04 (1.03, 1.05)	1.04 (1.03, 1.05)	1.04 (1.03, 1.05)
Chloride (mmol/L)	0.98 (0.97, 0.98)	0.98 (0.97, 0.98)	0.97 (0.97, 0.98)	0.98 (0.97, 0.98)
Sodium (mmol/L)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.98 (0.98, 0.99)	0.99 (0.98, 0.99)
INR	1.17 (1.12, 1.23)	1.17 (1.12, 1.23)	1.15 (1.10, 1.21)	1.15 (1.10, 1.21)
Lactate (mmol/L)	1.20 (1.17, 1.24)	1.19 (1.16, 1.23)	1.17 (1.14, 1.20)	1.17 (1.14, 1.20)
Albumin (g/dL)	0.67 (0.61, 0.74)	0.72 (0.66, 0.79)	0.74 (0.67, 0.81)	0.75 (0.69, 0.82)
SOFA	1.21 (1.18, 1.25)	1.21 (1.18, 1.25)	1.20 (1.17, 1.24)	1.21 (1.18, 1.25)
APACHEII	1.09 (1.07, 1.10)	1.08 (1.07, 1.10)	1.08 (1.07, 1.10)	1.08 (1.07, 1.10)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; WBC, white blood cells; PLT, platelet; RDW, red blood cell distribution width; RBC, red blood cells; PT, prothrombin time; TT, thrombin time; AG, anion gap; INR, international normalized ratio; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; OR, odds ratio; CI, confidential interval.

0.75), and 32% (OR = 0.68, 95% CI:0.61–0.76), respectively. In addition, albumin level was changed into the categorical variable as Q1–Q4 and the relationships with clinical outcomes in three models were also explored. In model II, the values of OR in Q4 group for all clinical outcomes were the lowest: 0.42 for 28-day mortality (95% CI:0.34–0.51), 0.47 for 60-day mortality (95% CI:0.38–0.57), 0.47 for 180-day mortality (95% CI:0.38–0.57,), and 0.48 for 1-year mortality (95% CI:0.40–0.59).

A Non-Linear Relationship Between Albumin Level and Clinical Outcomes

In Table 3, two models including model I (the linear model) and model II (two-segment non-linear model) were constructed and compared. For all four types of clinical outcomes, the P values of the log-likelihood ratio test were all <0.05, which demonstrated that model II was a better fit to depict the relationship between albumin level and clinical outcomes. The turning point of albumin level for clinical outcomes was 2.6g/dL. On the left side (≤2.6g/dL), with each 1g/dL increment in albumin level, the risk of mortality in 28-day, 60-day, 180-day and 1-year decreased by 59% (OR = 0.41, 95% CI:0.32–0.52), 62% (OR = 0.38, 95% CI:0.30–0.48), 65% (OR = 0.35, 95% CI: 0.28–0.45), and 62% (OR =

Table 3 The Threshold Effect for Analysis Between Albumin and Clinical Outcomes

	Number (%)	OR (95% CI)
28-day mortality		
Model I: The linear model	5357 (100%)	0.61 (0.54, 0.69)
Model II: Two-segment non-linear model		
The turning point of albumin (g/dL)		
≤2.6 (slope 1)	2318 (43.27%)	0.41 (0.32, 0.52)
>2.6 (slope 2)	3039 (56.73%)	0.79 (0.66, 0.94)
Slope 2 to slope 1		1.93 (1.35, 2.75)
Predicted at 2.6		−1.01 (−1.11, −0.91)
P for the log-likelihood ratio test		<0.001
60-day mortality		
Model I: The linear model		0.66 (0.59, 0.73)
Model II: Two-segment non-linear model		
The turning point of albumin (g/dL)		
≤2.6 (slope 1)	2318 (43.27%)	0.38 (0.30, 0.48)
>2.6 (slope 2)	3039 (56.73%)	0.90 (0.76, 1.07)
Slope 2 to slope 1		2.39 (1.69, 3.37)
Predicted at 2.6		−0.85 (−0.94, −0.75)
P for the log-likelihood ratio test		<0.001
180-day mortality		
Model I: The linear model		0.67 (0.60, 0.75)
Model II: Two-segment non-linear model		
The turning point of albumin (g/dL)		
≤2.6 (slope 1)	2318 (43.27%)	0.35 (0.28, 0.45)
>2.6 (slope 2)	3039 (56.73%)	0.97 (0.82, 1.14)
Slope 2 to slope 1		2.73 (1.95, 3.84)
Predicted at 2.6		−0.75 (−0.85, −0.66)
P for the log-likelihood ratio test		<0.001
1-year mortality		
Model I: The linear model		0.68 (0.61, 0.76)
Model II: Two-segment non-linear model		
The turning point of albumin (g/dL)		
≤2.6 (slope 1)	2318 (43.27%)	0.38 (0.29, 0.48)
>2.6 (slope 2)	3039 (56.73%)	0.96 (0.82, 1.13)
Slope 2 to slope 1		2.55 (1.82, 3.58)
Predicted at 2.6		−0.70 (−0.79, −0.60)
P for the log-likelihood ratio test		<0.001

Notes: Model I and II adjusted for: age; gender; HR; SBP; DBP; RR; renal disease; CAD; diabetes; hypertension; AG; ALT, AST, PT; TT; RBC; WBC; total bilirubin; total calcium; bicarbonate; creatinine; chloride; lactate; hematocrit; hemoglobin; PLT; RDW; urea nitrogen; sodium; INR; SOFA; APACHEII.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; WBC, white blood cells; PLT, platelet; RDW, red blood cell distribution width; RBC, red blood cells; PT, prothrombin time; TT, thrombin time; AG, anion gap; INR, international normalized ratio; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; OR, odds ratio; CI, confidential interval.

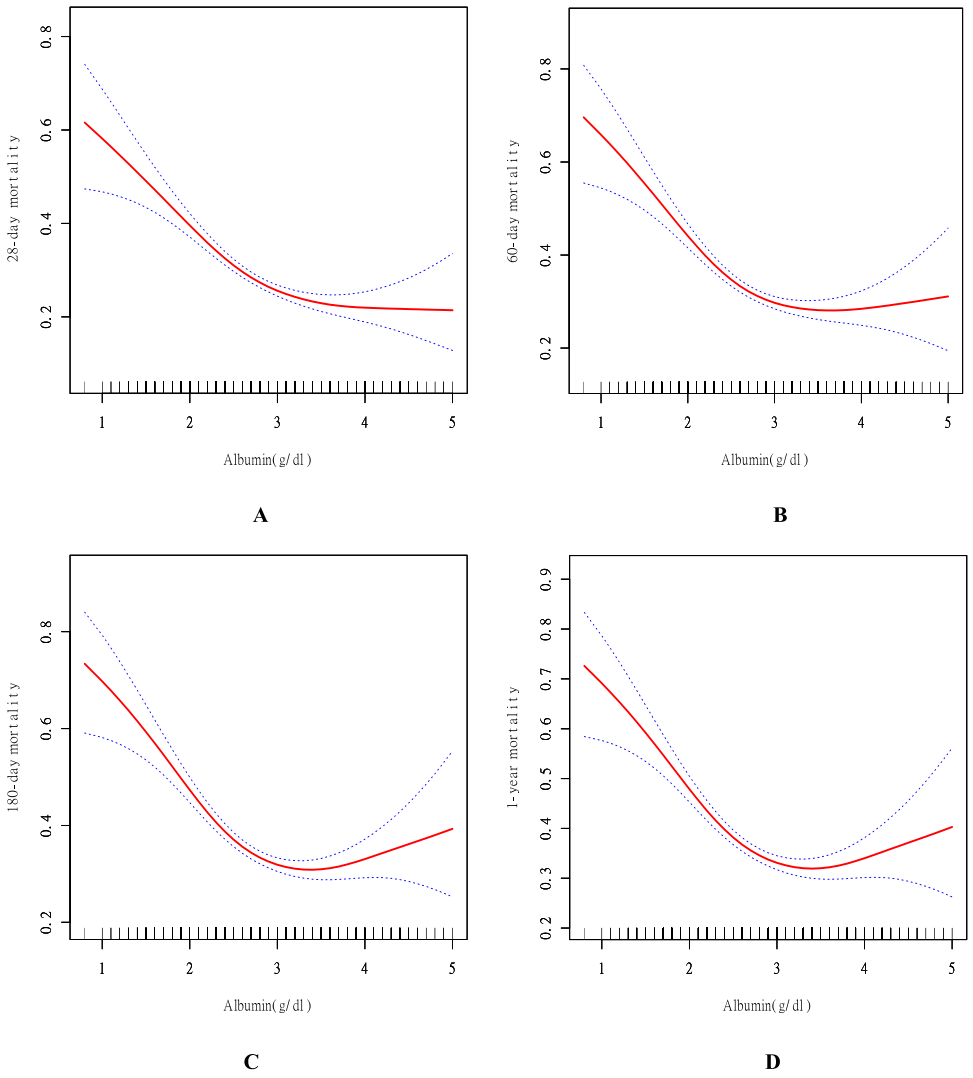

Figure 2 Smooth fitting curves demonstrated the non-linear relationships between albumin level and mortalities of 28-day (**A**), 60-day (**B**), 180-day (**C**) and 1-year (**D**).

0.38, 95% CI: 0.29–0.48), respectively. On the right side (>2.6g/dL), the risk of 28-day mortality still significantly declined (OR = 0.79, 95% CI:0.66–0.94), while for mortalities of 60-day (OR = 0.90, 95% CI:0.76–1.07), 180-day (OR = 0.97, 95% CI:0.82–1.14), and 1-year (OR = 0.96, 95% CI:0.82–1.13), the risk declined insignificantly.

The four smooth fitting curves were performed in Figure 2. For 28-day mortality, the significantly negative non-linear relationship was confirmed. For mortalities of 60-day, 180-day and 1-year, the non-linear relationships were still found.

Kaplan–Meier Analysis for Cumulative Hazard of Mortality

Figure 3 highlighted that in Q1 group (≤2.3g/dL), there was a significantly higher cumulative hazard of 1-year mortality by Kaplan–Meier analysis. In Supplementary Figure 1, Kaplan–Meier analysis for cumulative hazard of mortalities of 28-day (A), 60-day (B) and 180-day (C) in sepsis based on quartiles of albumin level (Q1–Q4) were demonstrated.

Subgroup Analysis

In Supplementary Table 3, the subgroups analyses between albumin level and different variables by stratified models were explored. Patients who got higher levels of total bilirubin (≥23.9umol/L) and total calcium (≥2.20mmol/L) and lower levels of chloride (≤99mmol/L) and RBC (≤$3.09*10^{12}$/L) had increased risk of short-term and long-term mortalities.

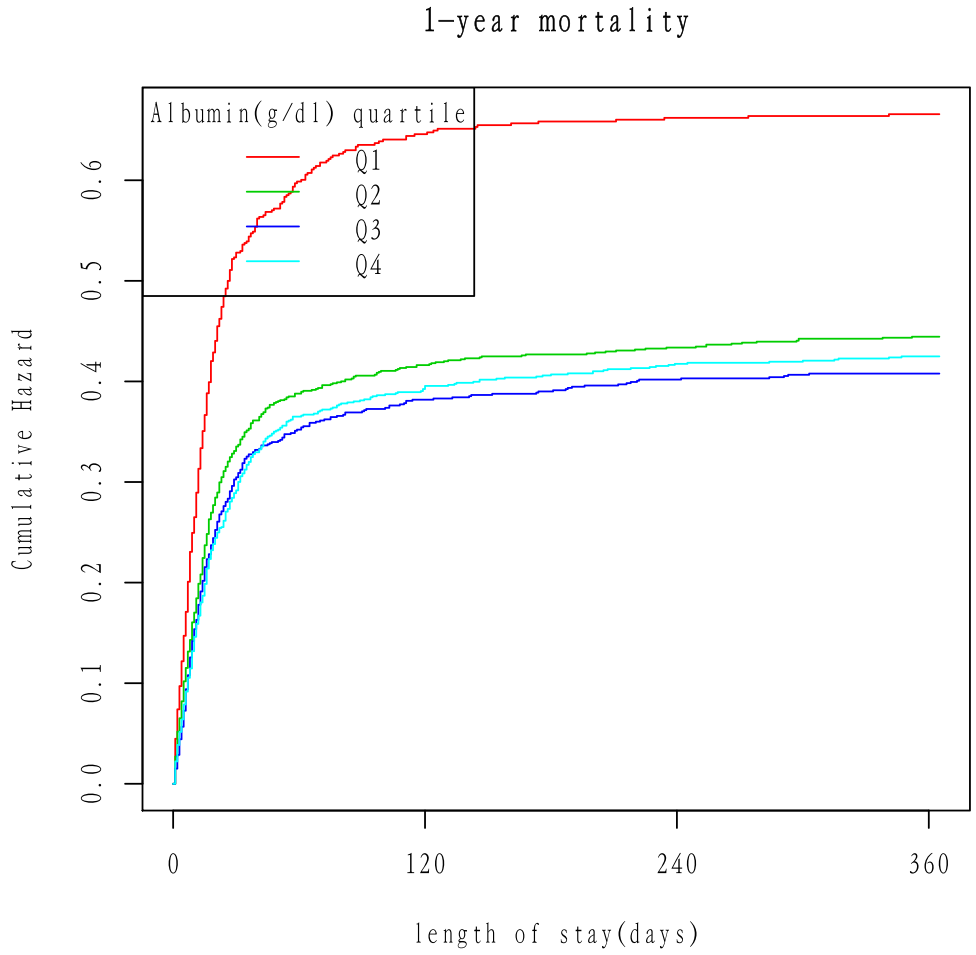

Figure 3 Kaplan–Meier analysis for cumulative hazard of 1-year in sepsis based on quartiles of albumin level (Q1-Q4).

Discussion

In the present study, several main points were concluded. First, albumin level was associated with short-term and long-term outcomes in sepsis. The non-linear relationships between albumin and clinical outcomes were found. Second, when albumin level ≤2.6g/dL, with each 1g/dL increment in albumin level, the risk of mortality in 28-day, 60-day, 180-day and 1-year decreased by 59%, 62%, 65% and 62%, respectively. To the best of our knowledge, this was the first study to explore the relationship between albumin level and outcomes in sepsis in MIMIC-IV.

In adults, serum albumin was conducive to delicately regulating osmotic pressure and vessel permeability as well as carrying exogenous and endogenous compounds for contributing to physiological functions.[16] Albumin supplementation has been broadly utilized in various severe conditions including shock, trauma and sepsis.[17] In addition, albumin level has been applied as an indicator for sensitively and effectively reflecting the condition of nutrition, organ function and physical activity.[18]

In sepsis, patients were more likely to have lower levels of serum albumin, which were closely associated with poor prognosis.[19–21] One prospective cohort study demonstrated that albumin level was an important predictor for 28-day mortality in sepsis, and 29.2g/L was the best threshold value with good sensitivity and specificity.[22] In sepsis with acute kidney injury, the albumin level was an independent indicator for both 28-day and 90-day mortality (HR = 0.75, 95% CI: 0.62–0.90 and HR = 0.73, 95% CI: 0.63–0.86, respectively) based on a retrospective study.[23] In elderly sepsis patients, albumin level <2.6 g/dL was a prognostic factor with 30-day mortality even after adjusting for age, gender, and comorbidities.[24] Moreover, in septic and septic shock patients admitted in emergency department, the initial albumin level was identified to be the largest contributor to clinical outcomes.[25] One recent retrospective study with 725 sepsis

patients showed that a lower level of serum albumin with <2.5 g/dL was linked with 1-year mortality,[26] which was partly similar with our research, but many more patients were included in our study.

Our research revealed that decreased levels of albumin were significantly associated with poor prognosis in sepsis. Some potential mechanisms could explain this phenomenon. First, sepsis causes systemic inflammatory factors increasing significantly, which could impair the function of vascular endothelium and increase the permeability of capillary vessels. Then, albumin may leak into the outside of vessels, resulting in a decrease in the level of plasma albumin, which significantly increases the risk of poor outcomes.[27] In addition, increased levels of cytokines may influence the gene expression and catabolism of albumin, and also lower the concentration of plasma albumin.[28] Second, physiologically, albumin is synthesized in the liver and liver function may be impaired in sepsis, leading to the synthesis deficiency of albumin.[29] Third, inflammation damages the renal function, lead to proteinuria by upregulating glomerular infiltration and cause the leakage of albumin.[30] Moreover, in sepsis, gastrointestinal function is usually injured partly, which affects the absorption of nutrients and causes malnutrition status.[31] All in all, the level of serum albumin in sepsis might be an indicator of inflammatory response, capillary leakage and organ dysfunction, which are associated with the prognostic role of plasma albumin in septic patients.

The present study has many strengths. First, the inclusion criterion is based on the definition of sepsis 3.0, which is more in line with the latest definition of sepsis. The MIMIC-IV database is a large public database, which spans more than one decade. It has a large sample size and is representative of the US population. Second, this study adjusted for more than thirty variables to exclude the potential effects of confounding factors as many as possible. Third, the relationship between albumin level and clinical outcomes was non-linear, and 2.6g/dL was the inflection point. When albumin level ≤2.6g/dL, the lower the albumin level, the higher the risk of mortality. With each 1g/dL increment in albumin level, the risk of mortality in 28-day, 60-day, 180-day and 1-year decreased by 59%, 62%, 65% and 62%, respectively. Therefore, albumin supplementation might be beneficial for septic patients with serum albumin<2.6g/dL. Fourth, albumin, as a single and easily available index, is convenient for physicians to implement in clinical practice. Our study might help physicians to evaluate the prognosis in sepsis and make individualized plans for patients.

However, some limitations in our study could not be avoided. First, it was a retrospective study based on public database in US Selection bias may exist and the application of our results could be limited in other countries and populations. Second, due to lack of some data, subclinical diseases such as subclinical nonalcoholic fatty liver disease which could confound our results were not included. However, we have comprehensively adjusted the potential confounders including different organ function variables. Third, hypoalbuminemia can be caused by various conditions, including hepatic cirrhosis,[32] heart failure,[33] malignant cancer,[34] and malnutrition,[35] which were considered as risk factors for the poor prognosis. Although we enrolled the variables including morbidities and lab findings as many as possible for analysis, not all the factors could be included due to the lack of some data in MIMIC-IV. Fourth, our research did not investigate the association between albumin infusion as a therapeutic intervention and patient's outcomes. Further studies of randomized controlled trials need to be conducted to validate our conclusions and further recommendations can be performed based on clinical utility of these findings.

Conclusion

Albumin level was associated with short-term and long-term outcomes in sepsis. The non-linear negative relationships between albumin and clinical outcomes were confirmed. Albumin supplementation might be beneficial for septic patients with serum albumin<2.6g/dL.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; WBC, white blood cells; PLT, platelet; RDW, RBC distribution width; RBC, RBCs; PT, prothrombin time; TT, thrombin time; AG, anion gap; INR, international normalized ratio; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; LOS, length of stay; ICU, intensive care unit; IQR, interquartile ranges; MICU, medical intensive care unit;

HR, hazard ratios; MIMIC-IV, Medical Information Mart for Intensive Care IV; SQL, structure query language; OR, odds ratio; CI, confidential interval.

Data Sharing Statement

The data that support the findings of this study are available from the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC).

Ethics Approval and Consent to Participate

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. MIMIC-IV was an anonymized public database. To apply for access to the database, we passed the Protecting Human Research Participants exam (No.32900964). The project was approved by the institutional review boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) and was given a waiver of informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Arroyo V, Garcia-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol*. 2014;61(2):396–407. doi:10.1016/j.jhep.2014.04.012
2. Hu T, Zhang Z, Jiang Y. Albumin corrected anion gap for predicting in-hospital mortality among intensive care patients with sepsis: a retrospective propensity score matching analysis. *Clin Chim Acta*. 2021;521:272–277. doi:10.1016/j.cca.2021.07.021
3. Artigas A, Wernerman J, Arroyo V, Vincent JL, Levy M. Role of albumin in diseases associated with severe systemic inflammation: pathophysiologic and clinical evidence in sepsis and in decompensated cirrhosis. *J Crit Care*. 2016;33:62–70. doi:10.1016/j.jcrc.2015.12.019
4. Onal C, Gultekin M, Yavas G, et al. The impact of serum albumin-to-alkaline phosphatase ratio in cervical cancer patients treated with definitive chemoradiotherapy. *J Obstet Gynaecol*. 2022;42:1–7.
5. Wong Y, Loo J. Albumin therapy for hepatic encephalopathy: current evidence and controversies. *Metab Brain Dis*. 2022. doi:10.1007/s11011-022-01002-8
6. Ding N, Guo C, Song K, et al. Nomogram for the prediction of in-hospital incidence of acute respiratory distress syndrome in patients with acute pancreatitis. *Am J Med Sci*. 2022;363(4):322–332. doi:10.1016/j.amjms.2021.08.009
7. Shin J, Hwang SY, Jo IJ, et al. Prognostic value of the lactate/albumin ratio for predicting 28-day mortality in critically ill sepsis patients. *Shock*. 2018;50(5):545–550. doi:10.1097/SHK.0000000000001128
8. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. *Crit Care*. 2020;24(1):255. doi:10.1186/s13054-020-02995-3
9. Ronit A, Kirkegaard-Klitbo DM, Dohlmann TL, et al. Plasma albumin and incident cardiovascular disease: results from the CGPS and an updated meta-analysis. *Arterioscler Thromb Vasc Biol*. 2020;40(2):473–482. doi:10.1161/ATVBAHA.119.313681
10. Omiya K, Sato H, Sato T, et al. Albumin and fibrinogen kinetics in sepsis: a prospective observational study. *Crit Care*. 2021;25(1):436. doi:10.1186/s13054-021-03860-7
11. Kendall H, Abreu E, Cheng AL. Serum albumin trend is a predictor of mortality in ICU patients with sepsis. *Biol Res Nurs*. 2019;21(3):237–244. doi:10.1177/1099800419827600
12. Johnson A, Pollard T, Shen L, et al. MIMIC-III, a freely accessible critical care database. *Sci Data*. 2016;3:160035. doi:10.1038/sdata.2016.35

13. Giesa N, Heeren P, Klopfenstein S, et al. MIMIC-IV as a clinical data schema. *Stud Health Technol Inform*. 2022;294:559–560. doi:10.3233/SHTI220522
14. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):e1063–e1143. doi:10.1097/CCM.0000000000005337
15. Ding Q, Su Y, Li C, Ding N. Red cell distribution width and in-hospital mortality in septic shock: a public database research. *Int J Lab Hematol*. 2022;44(5):861–867. doi:10.1111/ijlh.13925
16. Takegawa R, Kabata D, Shimizu K, et al. Serum albumin as a risk factor for death in patients with prolonged sepsis: an observational study. *J Crit Care*. 2019;51:139–144. doi:10.1016/j.jcrc.2019.02.004
17. Vincent J-L, Russell JA, Jacob M, et al. Albumin administration in the acutely ill: what is new and where next?. *Crit Care*. 2014;18(6):1.
18. Tai H, Zhu Z, Mei H, Sun W, Zhang W. Albumin-to-fibrinogen ratio independently predicts 28-day mortality in patients with peritonitis-induced sepsis. *Mediators Inflamm*. 2020;2020:7280708. doi:10.1155/2020/7280708
19. Lu J, Xun Y, Yu X, et al. Albumin-globulin ratio: a novel predictor of sepsis after flexible ureteroscopy in patients with solitary proximal ureteral stones. *Transl Androl Urol*. 2020;9(5):1980–1989. doi:10.21037/tau-20-823
20. Li T, Li X, Liu X, et al. Association of procalcitonin to albumin ratio with the presence and severity of sepsis in neonates. *J Inflamm Res*. 2022;15:2313–2321. doi:10.2147/JIR.S358067
21. Song K, Guo C, Zeng Z, Li C, Ding N. Factors associated with in-hospital mortality in adult sepsis with Escherichia coli infection. *BMC Infect Dis*. 2022;22(1). doi:10.1186/s12879-022-07201-z
22. Yin M, Si L, Qin W, et al. Predictive value of serum albumin level for the prognosis of severe sepsis without exogenous human albumin administration: a prospective cohort study. *J Intensive Care Med*. 2018;33(12):687–694. doi:10.1177/0885066616685300
23. Sheng S, Zhang YH, Ma HK, Huang Y. Albumin levels predict mortality in sepsis patients with acute kidney injury undergoing continuous renal replacement therapy: a secondary analysis based on a retrospective cohort study. *BMC Nephrol*. 2022;23(1):52. doi:10.1186/s12882-021-02629-y
24. Arnau-Barres I, Guerri-Fernandez R, Luque S, Sorli L, Vazquez O, Miralles R. Serum albumin is a strong predictor of sepsis outcome in elderly patients. *Eur J Clin Microbiol Infect Dis*. 2019;38(4):743–746. doi:10.1007/s10096-019-03478-2
25. Seo MH, Choa M, You JS, et al. Hypoalbuminemia, low base excess values, and tachypnea predict 28-day mortality in severe sepsis and septic shock patients in the emergency department. *Yonsei Med J*. 2016;57(6):1361–1369. doi:10.3349/ymj.2016.57.6.1361
26. Lee S, Jo Y, Lee J, et al. Associations of the serum albumin concentration and Sequential Organ Failure Assessment score at discharge with 1-year mortality in sepsis survivors: a retrospective cohort study. *Shock*. 2023. doi:10.1097/SHK.0000000000002083
27. Han T, Cheng T, Liao Y, et al. Analysis of the value of the blood urea nitrogen to albumin ratio as a predictor of mortality in patients with sepsis. *J Inflamm Res*. 2022;15:1227–1235. doi:10.2147/JIR.S356893
28. Kim MH, Ahn JY, Song JE, et al. The C-reactive protein/albumin ratio as an independent predictor of mortality in patients with severe sepsis or septic shock treated with early goal-directed therapy. *PLoS One*. 2015;10(7):e0132109.
29. Yu Y, Wu W, Dong Y, Li J. C-reactive protein-to-albumin ratio predicts sepsis and prognosis in patients with severe burn injury. *Mediators Inflamm*. 2021;2021:6621101. doi:10.1155/2021/6621101
30. Qin Z, Li H, Wang L, et al. Systemic immune-inflammation index is associated with increased urinary albumin excretion: a population-based study. *Front Immunol*. 2022;13:863640. doi:10.3389/fimmu.2022.863640
31. Hsieh M, Liao S, Chia-rong hsieh V, How C. Occurrence and impact of gastrointestinal bleeding and major adverse cardiovascular events during sepsis: a 15-year observational study. *Emerg Med Int*. 2020;2020:9685604. doi:10.1155/2020/9685604
32. Zhang T, Ye B, Shen J. Prognostic value of albumin-related ratios in HBV-associated decompensated cirrhosis. *J Clin Lab Anal*. 2022;36(4):e24338. doi:10.1002/jcla.24338
33. Otaki Y, Shimizu M, Watanabe T, et al. Albumin-to-globulin ratio predicts clinical outcomes of heart failure with preserved ejection fraction in women. *Heart Vessels*. 2022;37(11):1829–1840. doi:10.1007/s00380-022-02087-y
34. Ho S, Liu P, Hsu C, et al. Tumor burden score as a new prognostic surrogate in patients with hepatocellular carcinoma undergoing radiofrequency ablation: role of albumin-bilirubin (ALBI) grade vs easy ALBI grade. *Expert Rev Gastroenterol Hepatol*. 2022;16:1–9.
35. Gonzales G, Njunge J, Gichuki B, et al. The role of albumin and the extracellular matrix on the pathophysiology of oedema formation in severe malnutrition. *EBioMedicine*. 2022;79:103991. doi:10.1016/j.ebiom.2022.103991