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Research Article
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Early albumin infusion and mortality in elderly patients with sepsis based on analysis of the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database

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Abstract: As the impact of early albumin infusion on the prognosis of elderly individuals diagnosed with sepsis remains uncertain, this study aimed to investigate this effect in elderly patients with sepsis in the intensive care unit (ICU). We identified the information of elderly patients with sepsis requiring ICU admission from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database. They were divided into hypoalbuminemia group and control group, and the primary outcome was 90-d mortality. A multivariate logistic regression model and a multivariate Cox proportional-hazards model were used to analyze the correlation between hypoalbuminemia and patient prognosis. Kaplan-Meier survival curve and log-rank test were performed to analyze the survival outcomes. Propensity score matching (PSM) was implemented to determine the precise effect of early albumin infusion on the prognosis of elderly ICU patients with sepsis, and subgroups of patients were identified to explore the factors influencing the relationship. Early hypoalbuminemia was strongly associated with an increased risk of adverse clinical outcomes in elderly patients with sepsis in the ICU. In-hospital mortality (28.6% vs. 19.1%, $P<0.001$) and 90-d mortality (48.8% vs. 33.4%, $P<0.001$) were both significantly higher in the early hypoalbuminemia group than in the control group. PSM analysis showed that early albumin infusion was associated with lower in-hospital mortality and 90-d mortality in elderly patients with sepsis combined with hypoalbuminemia in the ICU. Early infusion of albumin could improve patient prognosis and reduce in-hospital mortality and 90-d mortality.

Key words: Sepsis; Albumin; Hypoalbuminemia; Mortality; Propensity score matching (PSM)

1 Introduction

Sepsis is a severe condition characterized by impaired organ function resulting from the disruption of the body's immune response to infection (Singer et al., 2016). Despite the rapid development of diagnostic and therapeutic tools in the field of critical care medicine, sepsis has always been the leading cause of death in patients in the intensive care unit (ICU) (Tidswell et al., 2021). Global statistics indicate that there are approximately 48.9 million sepsis cases annually, with the number of sepsis-related fatalities reaching up to 11 million, representing 19.7% of all deaths (Seymour et al., 2019; Fleischmann-Struzek et al., 2020). Moreover, more than 70 billion US dollars are spent directly on sepsis-related medical expenses every year worldwide, imposing a heavy economic burden on society and families (Cheng et al., 2017). Therefore, how to prevent sepsis at an early stage and provide effective therapeutic measures in a timely manner are major clinical challenges in the international field of critical care medicine.

Acute and severe disorders such as sepsis frequently exhibit hypoalbuminemia, which is mostly attributed to the extravasation of protein-rich fluids resulting from factors such as capillary failure (Hu et al., 2021). Serum albumin levels serve as an indicator of the extent of inflammation in the bodies of people who are acutely unwell (Soeters et al., 2019). A meta-analysis showed that for every 10 g/L decrease in the serum albumin concentration in hospitalized patients, their ICU stay was prolonged by about 30% and their

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morbidity and mortality were increased by 137% (Vincent et al., 2003). Several previous studies have shown that lower serum albumin levels are a risk factor for increased septic mortality (Arnau-Barrés et al., 2019; Kendall et al., 2019). Therefore, how to manage hypoalbuminemia in ICU septic patients is an important question.

Fluid therapy has been recognized as a cornerstone in the management of septic patients requiring emergency treatment and is strongly associated with prognosis (Angus and van der Poll, 2013; Sivayoham et al., 2020). Fluid therapy plays a crucial role in the restoration and preservation of tissue perfusion, which is a vital factor in enhancing the prognosis of individuals afflicted with sepsis (Caironi et al., 2014). Albumin, as a major blood product, has been widely used for fluid resuscitation in hypoalbuminemia patients with both acute and critical illness (Lewis et al., 2018; Ramadori, 2021). Due to its large molecular weight, albumin can theoretically remain in the intravascular space for a longer period of time and effectively maintain hemodynamic stability (Bunn and Trivedi, 2012). Albumin possesses a variety of biological functions, including immunomodulation, organ protection, anti-inflammatory and antioxidant properties, regulation of coagulation, and maintenance of vascular endothelial integrity (Nicholson et al., 2000; Vincent et al., 2014; Joannidis et al., 2022). The use of albumin for initial resuscitation and subsequent intravascular volume replacement has been widely used in fluid therapy for septic patients and is recommended by the Surviving Sepsis Campaign guidelines (Dellinger et al., 2004). Albumin infusion has demonstrated good safety, while it did not decrease fatality rates in sepsis patients (Caironi et al., 2014). Hence, the administration of albumin infusions to septic patients continues to be a subject of controversy. Furthermore, the optimal time for administering an albumin infusion to patients with sepsis remains to be explored.

In heterogeneous diseases such as sepsis, the need for albumin infusion and its benefits vary widely from patient to patient. In recent years, the increasing trend of population aging has made the elderly a substantial category that cannot be ignored. In fact, sepsis is common in elderly patients; according to statistics, more than 50% of septic patients in the United States are over 65 years of age (Mayr et al., 2010). As individuals age, there is a notable decline in the capacity of organ reserves and the equilibrium of water and electrolytes. Furthermore, the functionality of immune-related organs decreases, and vulnerability to infections increases in elderly individuals (El-Sharkawy et al., 2014; Stanojcic et al., 2016). For the above reasons, the clinical therapy of elderly septic patients is characterized by high morbidity and mortality rates, great difficulty in treatment, and high medical costs. However, no studies currently exist on the effects of early albumin infusion therapy for elderly septic patients in the ICU.

To address the above shortcomings, this research examines the impact of hypoalbuminemia on the prognosis of elderly septic patients in the ICU by screening these patients in the Medical Information Mart for Intensive Care-IV (MIMIC-IV). Furthermore, by employing propensity score matching (PSM), we intend to investigate the correlation between early albumin infusion and the prognosis of elderly septic patients who present with hypoalbuminemia in the ICU. The ultimate objective is to offer precise, scientifically based recommendations for the clinical management of albumin therapy in these patients.

2 Results

2.1 Study population

The ICU admission records of 20 082 elderly septic patients meeting the Sepsis 3.0 diagnostic criteria were screened from MIMIC-IV 2.0. Among them, 1709 cases were excluded because of the absence of ICU admission or multiple ICU admissions, 2039 cases were excluded as the length of ICU stay was ⩽24 h, 7224 cases of non-emergent ICU admissions were excluded, and 4547 cases with missing clinical data were excluded. Finally, 4563 cases who satisfied the inclusion criteria were included in the analysis (Fig. 1). The study population comprised 2467 male patients (54.1%) with a median age of 77.73 years (interquartile range: 70.76–84.76 years). The median Sequential Organ Failure Assessment (SOFA) score was 3.00, with a range of 2.00 to 4.00. The median minimum serum albumin level within 24 h of ICU admission was 31.00 g/L (interquartile range: 26.00–35.00 g/L).

2.2 Comparison of general clinical information between the hypoalbuminemia and control groups

This study identified elderly patients with sepsis and divided them into hypoalbuminemia group (n=

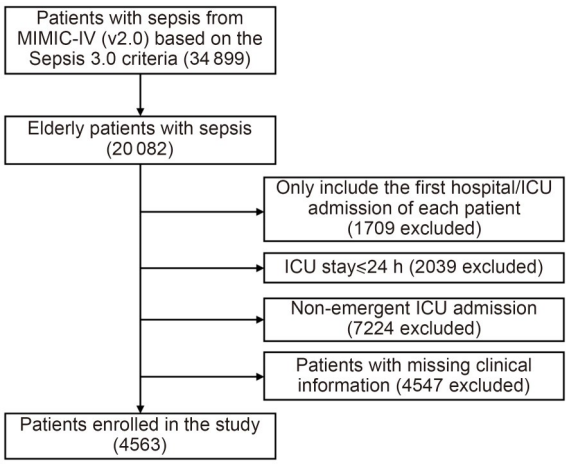

Fig. 1 Screening chart for inclusion in the study population. ICU: intensive care unit; MIMIC: Medical Information Mart for Intensive Care.

2160) and control group (n=2403). In both groups, patients were significantly different in terms of weight, SOFA, simplified acute physiology score (SAPS) II, use of mechanical ventilation, use of vasoactive drugs, use of continuous renal replacement therapy (CRRT), underlying diseases (hypertension, congestive heart failure (CHF), cerebrovascular diseases, chronic obstructive pulmonary disease (COPD), liver disease, and malignancy), vital signs (heart rate (HR), mean arterial pressure (MAP), temperature, pulse oxygen saturation (SpO_2)), white blood cells (WBC), hematocrit (HCT), hemoglobin (HGB), platelet (PLT), international normalized ratio (INR), sodium, potassium, calcium, bicarbonate, anion gap (AG), blood glucose (Glu), total bilirubin, creatinine (Cr), and blood urea nitrogen (BUN) (all P<0.05; Table 1).

2.3 Comparison of clinical outcomes between patients in the hypoalbuminemia and control groups

Among the 4563 elderly septic patients in the ICU included in this study, 1078 (23.6%) died in hospital and 1856 (40.7%) died within 90 d. Hypoalbuminemia was strongly associated with an increased risk of adverse clinical outcomes in elderly ICU septic patients, with patients in the early hypoalbuminemia group having significantly higher in-hospital mortality (28.6% vs. 19.1%, P<0.001) and 28-d mortality (48.8% vs. 33.4%, P<0.001) compared to the control group. However, no significant difference was found in the length of ICU stay between the two groups, as shown in Table 2.

2.4 Comparison of general clinical data of hypoalbuminemia patients before PSM

By utilizing PSM analysis, the prognostic significance of early albumin infusion therapy in elderly septic patients in the ICU with concomitant hypoalbuminemia was further investigated. The patients were categorized based on whether or not they underwent albumin infusion within the initial 24 h of ICU admission. A total of 1252 patients (58.0%) were assigned to the early albumin infusion group, while 908 patients were assigned to the control group. The general clinical data of the patients in the two groups were compared prior to PSM (Table 3).

2.5 Comparison of clinical outcomes between patients in the early albumin infusion and control groups before PSM

Before PSM, patients in the early albumin infusion group had a lower in-hospital mortality rate (26.0% vs. 32.2%, P=0.002) compared to the control group. However, there was no statistically significant difference between the two groups in the length of ICU stay or 90-d mortality (Table 4). The results of the Kaplan-Meier survival curve analysis showed no statistically significant difference in the 90-d mortality rate of patients in the early albumin infusion group compared to the control group before PSM (P=0.080).

2.6 Comparison of general clinical data after PSM in hypoalbuminemia patients

Table 5 presents a comparison of the general clinical data of the two patient groups subsequent to PSM. The comparable nature of the general clinical data between the two patient groups is indicated by the improved balance of the matched general clinical data (standardized mean difference (SMD)<0.1; Fig. 2).

2.7 Comparison of clinical outcomes between patients in the early albumin infusion and control groups after PSM

After PSM, patients in the early albumin infusion group had lower in-hospital mortality (10.4% vs. 31.6%, P<0.001) and 90-d mortality (38.3% vs. 49.9%, P<0.001) compared to the control group. However, when comparing the length of ICU stay, there was no significant difference between the two groups (Table 6).

Table 1 Demographic information and basic clinical characteristics of elderly septic patients in the hypoalbuminemia and control groups

Variables	Hypoalbuminemia group (*n*=2160)	Control group (*n*=2403)	*P*
Age (years)	77.72 (70.64–84.69)	77.81 (70.89–84.88)	0.553
Male	1164 (53.9)	1303 (54.2)	0.844
Weight (kg)	73.60 (62.00–86.90)	76.00 (63.80–90.50)	<0.001
Insurance	1547 (71.6)	1700 (70.7)	0.536
SOFA	3.00 (2.00–5.00)	3.00 (2.00–4.00)	<0.001
SAPS II	47.00 (39.00–57.00)	42.00 (35.00–51.00)	<0.001
Mechanical ventilation	927 (42.9)	933 (38.8)	0.005
Vasoactive drugs	1277 (59.1)	1037 (43.2)	<0.001
ECMO	4 (0.18)	1 (0.05)	0.196
CRRT	144 (6.7)	120 (5.0)	0.019
Hypertension	871 (40.3)	1066 (44.4)	0.006
Diabetes	290 (13.4)	319 (13.3)	0.916
MI	458 (21.2)	523 (21.8)	0.671
CHF	824 (38.1)	1099 (45.7)	<0.001
Cerebrovascular diseases	267 (12.4)	521 (21.7)	<0.001
COPD	623 (28.8)	788 (32.8)	0.004
Liver disease	171 (7.9)	95 (4.0)	<0.001
Kidney disease	746 (34.5)	813 (33.8)	0.639
Malignant tumors	468 (21.7)	327 (13.6)	<0.001
HR (beats/min)	87.32 (75.30–99.57)	82.89 (72.04–95.14)	<0.001
RR (times/min)	20.00 (17.32–23.16)	19.64 (17.36–22.52)	0.070
MAP (mmHg)	71.48 (66.24–77.35)	75.13 (68.96–82.46)	<0.001
Body temperature (℃)	36.76 (36.48–37.06)	36.86 (36.60–37.17)	<0.001
SpO_2 (%)	97.36 (95.81–98.67)	97.04 (95.54–98.46)	<0.001
WBC ($\times10^9$ L^{-1})	14.70 (9.70–20.90)	13.00 (9.40–18.15)	<0.001
HCT (%)	27.30 (23.70–31.53)	31.50 (27.05–35.50)	<0.001
HGB (g/dL)	8.80 (7.50–10.30)	10.30 (8.80–11.60)	<0.001
PLT ($\times10^9$ L^{-1})	166.00 (102.00–252.30)	173.00 (125.00–234.50)	0.008
INR	1.50 (1.30–2.00)	1.30 (1.10–1.80)	<0.001
Sodium (mmol/L)	140.00 (137.00–143.00)	140.00 (138.00–143.00)	0.044
Potassium (mmol/L)	4.60 (4.10–5.20)	4.60 (4.20–5.30)	0.031
Calcium (mg/dL)	8.30 (7.80–8.70)	8.80 (8.30–9.30)	<0.001
Bicarbonate (mmol/L)	19.00 (16.00–23.00)	21.00 (18.00–24.00)	<0.001
AG (mmHg)	17.00 (14.00–21.00)	18.00 (15.00–21.00)	<0.001
Glu (mg/L)	134.40 (107.40–172.80)	139.40 (113.00–176.60)	<0.001
Total bilirubin (μmol/L)	28.00 (16.00–68.25)	24.00 (15.00–46.00)	<0.001
Cr (mg/dL)	1.60 (1.00–2.50)	1.40 (1.00–2.20)	0.001
BUN (mg/dL)	36.00 (23.00–54.00)	31.00 (21.00–49.00)	<0.001

Data were presented as number (percentage) or mean (interquartile range). SOFA: sequential organ failure assessment; SAPS: simplified acute physiology score; ECMO: extracorporeal membrane pulmonary oxygenation; CRRT: continuous renal replacement therapy; MI: myocardial infarction; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; HR: heart rate; RR: respiratory rate; MAP: mean arterial pressure; SpO_2: pulse oxygen saturation; WBC: white blood cells; HCT: hematocrit; HGB: hemoglobin; PLT: platelet; INR: international normalized ratio; AG: anion gap; Glu: blood glucose; Cr: creatinine; BUN: blood urea nitrogen. 1 mmHg=0.133 kPa.

Table 2 Characteristics of the clinical outcomes of elderly septic patients in the hypoalbuminemia and control groups

Outcomes	Hypoalbuminemia group (*n*=2160)	Control group (*n*=2403)	*P*
Length of ICU stay (d)	3.24 (1.98–6.40)	3.16 (1.89–6.06)	0.153
Hospitalized mortality	618 (28.6)	460 (19.1)	<0.001
90-d mortality	1054 (48.8)	802 (33.4)	<0.001

Data were presented as number (percentage) or mean (interquartile range). ICU: intensive care unit.

Table 3 Comparison of demographic information and basic clinical characteristics before PSM

Variables	Early albumin infusion group (*n*=1252)	Control group (*n*=908)	SMD
Age (years)	77.50 (70.77–84.66)	77.93 (70.42–84.72)	0.005
Male	679 (54.2)	485 (53.4)	0.016
Weight (kg)	73.78 (62.20–87.00)	73.30 (61.58–86.50)	0.016
Insurance	906 (72.4)	641 (70.6)	0.039
SOFA	3.00 (2.00–5.00)	3.000 (2.00–5.00)	0.001
SAPS II	46.00 (38.75–56.00)	48.00 (39.75–58.00)	0.109
Mechanical ventilation	515 (41.1)	412 (45.4)	0.086
Vasoactive drugs	906 (72.4)	641 (70.6)	0.036
ECMO	2 (0.2)	2 (0.2)	0.014
CRRT	82 (6.5)	62 (6.8)	0.011
Hypertension	496 (39.6)	375 (41.3)	0.034
Diabetes	177 (14.1)	113 (12.4)	0.050
MI	258 (20.6)	200 (22.0)	0.035
CHF	471 (37.6)	353 (38.9)	0.026
Cerebrovascular diseases	159 (12.7)	108 (11.9)	0.025
COPD	356 (28.4)	267 (29.4)	0.021
Liver disease	100 (8.0)	71 (7.8)	0.006
Kidney disease	435 (34.7)	311 (34.3)	0.010
Malignant tumors	263 (21.0)	205 (22.6)	0.038
HR (beats/min)	87.33 (75.75–99.45)	87.30 (74.55–99.66)	0.005
RR (times/min)	19.82 (17.17–22.91)	20.31 (17.63–23.48)	0.141
MAP (mmHg)	71.48 (66.33–77.64)	71.54 (66.12–76.97)	0.015
Body temperature (℃)	36.74 (36.47–37.04)	36.78 (36.49–37.08)	0.027
SpO_2 (%)	97.29 (95.82–98.67)	97.46 (95.80–98.67)	0.004
WBC ($\times10^9$ L^{-1})	14.60 (9.68–20.50)	14.90 (9.70–21.50)	0.114
HCT (%)	27.50 (23.78–31.70)	27.10 (23.60–31.30)	0.047
HGB (g/dL)	8.80 (7.50–10.40)	8.70 (7.58–10.10)	0.047
PLT ($\times10^9$ L^{-1})	167.00 (104.00–252.00)	163.00 (100.00–253.00)	0.006
INR	1.50 (1.30–2.00)	1.50 (1.30–2.00)	0.027
Sodium (mmol/L)	140.00 (137.00–143.00)	140.00 (137.00–143.00)	0.019
Potassium (mmol/L)	4.60 (4.10–5.20)	4.50 (4.10–5.20)	0.009
Calcium (mg/dL)	8.20 (7.70–8.70)	8.30 (7.80–8.80)	0.057
Bicarbonate (mmol/L)	20.00 (16.00–23.00)	19.00 (16.00–23.00)	0.058
AG (mmHg)	17.00 (14.00–20.00)	17.00 (14.00–21.00)	0.092
Glu (mg/L)	134.60 (107.70–171.80)	134.30 (107.00–172.80)	0.047
Total bilirubin (mg/dL)	0.70 (0.40–1.70)	0.70 (0.40–1.60)	0.040
Cr (ng/dL)	1.60 (1.00–2.43)	1.60 (1.00–2.60)	0.036
BUN (mg/dL)	36.00 (23.00–54.00)	35.00 (24.00–55.00)	0.030

Data were presented as number (percentage) or mean (interquartile range). PSM: propensity score matching; SMD: standardized mean difference; SOFA: sequential organ failure assessment; SAPS: simplified acute physiology score; ECMO: extracorporeal membrane pulmonary oxygenation; CRRT: continuous renal replacement therapy; MI: myocardial infarction; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; HR: heart rate; RR: respiratory rate; MAP: mean arterial pressure; SpO_2: pulse oxygen saturation; WBC: white blood cells; HCT: hematocrit; HGB: hemoglobin; PLT: platelet; INR: international normalized ratio; AG: anion gap; Glu: blood glucose; Cr: creatinine; BUN: blood urea nitrogen. 1 mmHg=0.133 kPa.

Table 4 Characterization of clinical outcomes before PSM

Outcomes	Early albumin infusion group (*n*=1252)	Control group (*n*=908)	*P*
Length of ICU stay (d)	3.12 (1.96–6.11)	3.37 (2.01–6.66)	0.393
Hospitalized mortality	326 (26.0)	292 (32.2)	0.002
90-d mortality	595 (47.5)	459 (50.6)	0.178

Data were presented as number (percentage) or mean (interquartile range). PSM: propensity score matching; ICU: intensive care unit.

Table 5 Comparison of demographic information and basic clinical characteristics after PSM

Variables	Early albumin infusion group (*n*=884)	Control group (*n*=884)	SMD
Age (years)	76.64 (70.44–84.04)	77.95 (70.41–84.72)	0.057
Male	486 (55.0)	472 (53.4)	0.032
Weight (kg)	73.73 (62.00–86.50)	73.45 (61.98–86.83)	0.023
Insurance	255 (28.8)	257 (29.1)	0.005
SOFA	3.00 (2.00–5.00)	3.00 (2.00–5.00)	0.019
SAPS II	46.00 (38.00–56.00)	47.00 (39.00–57.00)	0.072
Mechanical ventilation	378 (42.8)	397 (44.9)	0.043
Vasoactive drugs	502 (56.8)	530 (60.0)	0.064
ECMO	2 (0.2)	2 (0.2)	<0.001
CRRT	49 (5.5)	59 (6.7)	0.047
Hypertension	379 (42.9)	367 (41.5)	0.027
Diabetes	112 (12.7)	111 (12.6)	0.003
MI	186 (21.0)	193 (21.8)	0.019
CHF	333 (37.7)	342 (38.7)	0.021
Cerebrovascular diseases	99 (11.2)	107 (12.1)	0.028
COPD	251 (28.4)	259 (29.3)	0.020
Liver disease	73 (8.3)	69 (7.8)	0.017
Kidney disease	296 (33.5)	304 (34.4)	0.019
Malignant tumors	199 (22.5)	194 (21.9)	0.014
HR (beats/min)	87.04 (75.35–99.14)	87.30 (74.55–99.41)	0.013
RR (times/min)	20.08 (17.32–23.40)	20.19 (17.54–23.30)	0.035
MAP (mmHg)	71.37 (66.48–77.62)	71.66 (66.28–76.97)	0.004
Body temperature (°C)	36.75 (36.49–37.06)	36.78 (36.49–37.08)	0.030
SpO_2 (%)	97.40 (95.96–98.74)	97.47 (95.80–98.67)	0.044
WBC ($\times10^9$ L^{-1})	15.00 (9.90–21.83)	14.60 (9.60–21.13)	0.018
HCT (%)	26.90 (23.10–31.00)	27.10 (23.50–31.33)	0.055
HGB (g/dL)	8.70 (7.40–10.10)	8.80 (7.58–10.10)	0.041
PLT ($\times10^9$ L^{-1})	166.50 (104.00–254.30)	164.50 (101.00–254.00)	0.004
INR	1.50 (1.30–1.93)	1.50 (1.28–2.00)	0.003
Sodium (mmol/L)	140.00 (136.00–143.00)	140.00 (137.00–143.00)	0.029
Potassium (mmol/L)	4.50 (4.10–5.20)	4.50 (4.10–5.20)	0.042
Calcium (mg/dL)	8.20 (7.70–8.70)	8.30 (7.80–8.80)	0.043
Bicarbonate (mmol/L)	19.00 (16.00–23.00)	19.00 (16.00–23.00)	0.019
AG (mmHg)	17.00 (14.00–20.00)	17.00 (14.00–21.00)	0.055
Glu (mg/L)	136.60 (107.90–176.30)	133.80 (107.00–171.60)	0.025
Total bilirubin (μmol/L)	0.70 (0.40–1.70)	0.70 (0.40–1.60)	0.002
Cr (mg/dL)	1.55 (1.00–2.40)	1.60 (1.00–2.50)	0.017
BUN (mg/dL)	36.00 (22.00–53.00)	35.00 (24.00–54.00)	0.046

Data were presented as number (percentage) or mean (interquartile range). PSM: propensity score matching; SOFA: sequential organ failure assessment; SAPS: simplified acute physiology score; ECMO: extracorporeal membrane pulmonary oxygenation; CRRT: continuous renal replacement therapy; MI: myocardial infarction; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; HR: heart rate; RR: respiratory rate; MAP: mean arterial pressure; SpO_2: pulse oxygen saturation; WBC: white blood cells; HCT: hematocrit; HGB: hemoglobin; PLT: platelet; INR: international normalized ratio; AG: anion gap; Glu: blood glucose; Cr: creatinine; BUN: blood urea nitrogen. 1 mmHg= 0.133 kPa.

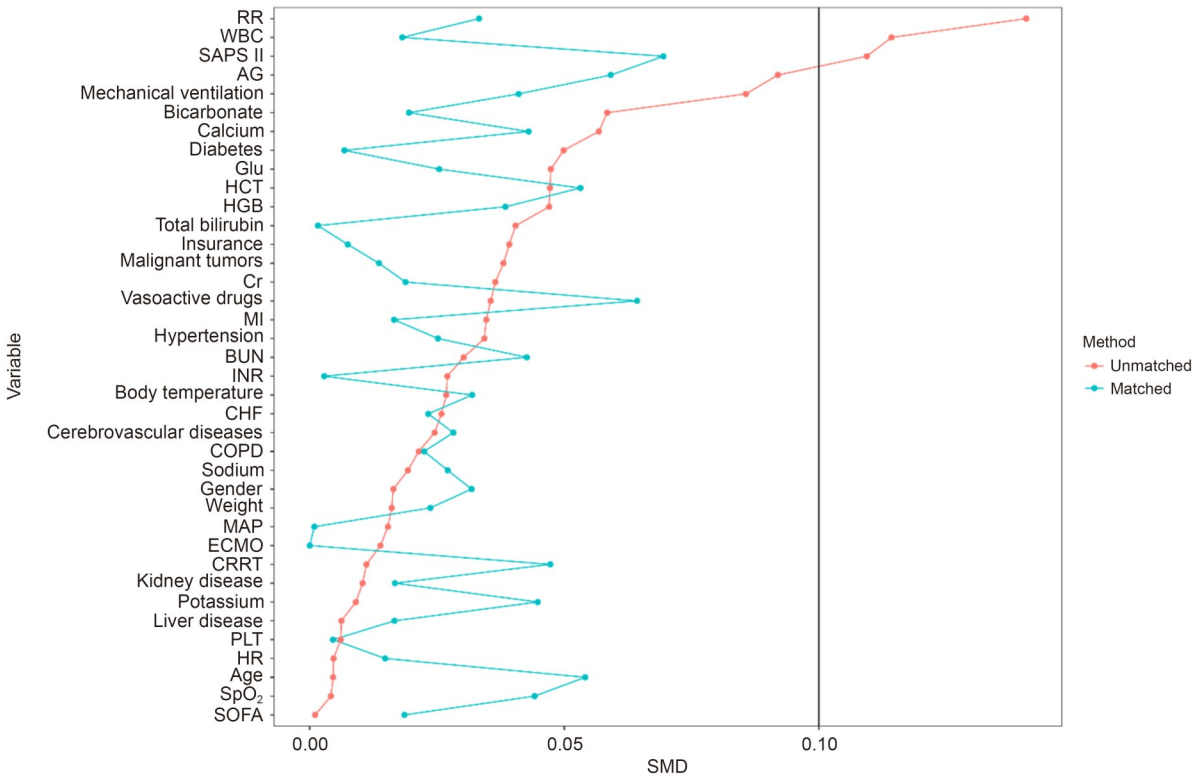

Fig. 2 Comparison of standardized mean difference (SMD) of general clinical data of patients before and after propensity score matching (PSM). RR: respiratory rate; WBC: white blood cells; SAPS: simplified acute physiology score; AG: anion gap; Glu: blood glucose; HCT: hematocrit; HGB: hemoglobin; Cr: creatinine; MI: myocardial infarction; BUN: blood urea nitrogen; INR: international normalized ratio; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; MAP: mean arterial pressure; ECMO: extracorporeal membrane pulmonary oxygenation; CRRT: continuous renal replacement therapy; PLT: platelet; HR: heart rate; SpO_2: pulse oxygen saturation; SOFA: sequential organ failure assessment.

Table 6 Characterization of clinical outcomes after PSM

Outcomes	Early albumin infusion group (*n*=884)	Control group (*n*=884)	*P*
Length of ICU stay (d)	3.11 (1.96–6.05)	3.39 (2.00–6.69)	0.272
Hospitalized mortality	92 (10.4)	279 (31.6)	<0.001
90-d mortality	339 (38.3)	441 (49.9)	<0.001

Data were presented as number (percentage) or mean (interquartile range). PSM: propensity score matching; ICU: intensive care unit.

The results of the logistic regression model showed that early albumin infusion was associated with a lower in-hospital mortality rate (odds ratio=0.25, 95% confidence interval (CI) 0.19–0.32, P<0.001) in elderly patients with sepsis combined with hypoalbuminemia in the ICU. The results of the Cox proportional-hazards model showed that early albumin infusion was associated with a lower 90-d mortality rate (hazard ratio=0.66, 95% CI 0.57–0.76, P<0.001) in elderly patients with sepsis combined with hypoalbuminemia in the ICU. The results of the Kaplan-Meier survival curve analysis revealed that the early albumin infusion group had a lower 90-d mortality than the control group did (P<0.001; Fig. 3).

2.8 Subgroup analyses

To further investigate the stability of the results across different populations, subgroup analyses were performed after stratifying the study population of patients by gender, SOFA score, and comorbidities, and similar results persisted across subgroups (P<0.05). In addition, there was no interaction effect between early albumin infusion and the different gender, SOFA score, or comorbidities subgroups (P for interaction

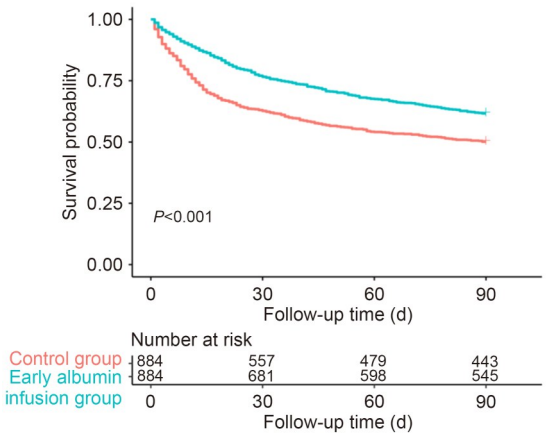

Fig. 3 Kaplan-Meier survival plot after propensity score matching (PSM).

>0.05; Table 7), suggesting a lack of statistically significant difference in the effect of early albumin infusion on 90-d mortality in elderly septic patients in the ICU across these subgroups.

3 Discussion

The data source for the study population was the large critical care medicine database MIMIC-IV 2.0. In addition to examining the correlation between clinical outcomes and hypoalbuminemia in elderly septic patients in the ICU within 24 h of admission, we investigated the impact of early albumin infusion on clinical prognosis. Early hypoalbuminemia was positively correlated with unfavorable clinical outcomes among these patients, and it was identified as an independent risk factor for 90-d mortality among this patient population. In order to ascertain the impact of early albumin infusion on the prognosis of elderly septic patients with combined hypoalbuminemia in the ICU, patients were categorized based on whether or not they underwent early albumin infusion. To ensure comparability among groups and mitigate the influence of heterogeneous confounding variables, PSM was applied to each group. According to the final results, in elderly ICU patients with sepsis combined with hypoalbuminemia, early albumin infusion was associated with a reduced risk of in-hospital mortality and 90-d mortality. Furthermore, subgroup analyses revealed that the correlation between early albumin infusion and 90-d mortality persisted as a significant finding across subgroups categorized by gender, SOFA score, and comorbidities.

Table 7 Subgroup analyses

Subgroup	Hazard ratio (95% CI)	P^*	P for interaction**
Gender			0.786
Male	0.69 (0.62–0.76)	<0.001	
Female	0.60 (0.53–0.69)	<0.001	
SOFA score			0.251
<5	0.71 (0.63–0.80)	<0.001	
≥5	0.66 (0.56–0.75)	<0.001	
Hypertension			0.376
Yes	0.73 (0.58–0.92)	0.008	
No	0.62 (0.52–0.74)	<0.001	
Diabetes			0.487
Yes	0.72 (0.60–0.91)	<0.001	
No	0.65 (0.56–0.76)	<0.001	
MI			0.265
Yes	0.62 (0.46–0.82)	<0.001	
No	0.68 (0.58–0.80)	<0.001	
CHF			0.477
Yes	0.63 (0.51–0.78)	<0.001	
No	0.69 (0.57–0.83)	<0.001	
Cerebrovascular diseases			0.129
Yes	0.66 (0.53–0.78)	<0.001	
No	0.63 (0.54–0.74)	<0.001	
COPD			0.267
Yes	0.62 (0.47–0.82)	<0.001	
No	0.67 (0.57–0.80)	<0.001	
Liver disease			0.210
Yes	0.61 (0.53–0.70)	<0.001	
No	0.64 (0.55–0.74)	<0.001	
Kidney disease			0.301
Yes	0.71 (0.56–0.90)	0.005	
No	0.64 (0.54–0.76)	<0.001	
Malignant tumors			0.578
Yes	0.72 (0.59–0.89)	<0.001	
No	0.63 (0.53–0.74)	<0.001	

* Represents the P for comparing different subgroups, testing the significance of differences between the groups. ** Represents the P for the interaction effect between subgroups, testing whether there is a significant interaction between the groups. CI: confidence interval; SOFA: sequential organ failure assessment; MI: myocardial infarction; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease.

Albumin is the most prevalent protein in the plasma and is synthesized primarily by the liver, and its half-life is approximately 21 d (Fanali et al., 2012; Vincent et al., 2014). In the current study, 47.34% of septic patients were found to have hypoalbuminemia

(≤30 g/L) within 24 h of ICU admission. Combined hypoalbuminemia in patients with sepsis may be related to the following factors: (1) the release of a large number of inflammatory mediators in the early response to infection in patients with sepsis leads to a decrease in the ability of the liver to synthesize albumin and a decrease in albumin production; (2) albumin degradation is increased resulting from fasting and the highly catabolic state of sepsis; and (3) under the infection-related stress, damage to the endothelium occurs, leading to an increase in the vascular permeability and subsequent leakage of albumin into the interstitium (Dubois et al., 2006; Schuetz et al., 2010; Gatta et al., 2012; Montealegre and Lyons, 2021). Prior research has established that hypoalbuminemia significantly correlates with an unfavorable prognosis among sepsis patients (Jones et al., 2008; Gaieski et al., 2010; Yamaguchi et al., 2018; Furukawa et al., 2019). On the one hand, hypoalbuminemia can result in a reduction in the osmolality of plasma colloids, which in turn diminishes the effective volume of blood in circulation. This can lead to microcirculatory dysfunction and insufficient perfusion of critical tissues, thereby heightening the risk of an unfavorable prognosis. On the other hand, a deficiency in serum albumin concentration can obstruct the synthesis of antibody-associated enzymes, which subsequently compromises the immune system and undermines the body's ability to fight infection (Giles and Czuprynski, 2003). For the early assessment of sepsis, the rapid SOFA scoring and screening of patients with suspected sepsis can be expected to lead to an earlier start of treatment (Seymour et al., 2016). If the initial simple admission data (e.g., serum albumin level) can be used to predict the severity and outcome of sepsis after rapid SOFA assessment, physicians can plan timelier treatment for patients in the high mortality group in conjunction with a variety of interventions.

Since its application during World War II in 1941, human albumin has become a widely used blood product (Garcia-Martinez et al., 2013). Despite the considerable body of research devoted to albumin infusion in septic patients, the impact of this procedure on the prognosis of individuals in this particular population remains contentious. According to the findings of a randomized controlled trial, human albumin infusion is safe and effective in reversing septic hypotension in patients with cirrhotic sepsis, improving systemic hemodynamics, tissue perfusion, and short-term in-hospital survival (Philips et al., 2021). However, a retrospective study found no statistically significant difference in 28-d mortality between patients in the albumin infusion group and the control group (Hu et al., 2021). These contradictory findings could potentially arise from the adherence to guidelines in clinical practices regarding albumin infusion, particularly with regard to hypoalbuminemia. This factor is already unequally distributed among patients enrolled in the albumin-infused group compared to those in the non-infused group, thereby introducing a significant systematic bias. By matching groups using rigorous PSM and screening a population of elderly ICU patients with sepsis and hypoalbuminemia, we were able to eliminate the potential bias between groups as much as possible, thereby demonstrating the benefit of early albumin infusion. The results of this study showed that early albumin infusion was associated with lower in-hospital (hazard ratio=0.66, 95% CI 0.57–0.76, $P<0.001$) and 90-d mortality (odds ratio=0.25, 95% CI 0.19–0.32, $P<0.001$) in elderly ICU patients with sepsis combined with hypoalbuminemia. This is because albumin infusion increases glial osmotic pressure and reduces leukocyte and platelet permeability and adhesion, thereby limiting edema formation (Milford and Reade, 2019). Albumin plays a critical role in maintaining oncotic pressure and fluid balance, and its infusion in sepsis patients may help restore vascular permeability and reduce interstitial fluid accumulation, improving hemodynamic stability. In the pathophysiology of sepsis, widespread inflammation and endothelial dysfunction contribute to vascular leakage, leading to hypoperfusion and tissue edema. Owing to its large molecular size and ability to bind and carry various molecules, albumin can help stabilize the microcirculation and reduce the impact of endothelial injury. In addition to its effects on fluid balance, albumin has potential antioxidant and anti-inflammatory properties: it can scavenge reactive oxygen species (ROS) and bind pro-inflammatory cytokines, thereby mitigating the systemic inflammatory response. This could be particularly beneficial in sepsis, where excessive inflammation plays a significant role in tissue injury and organ dysfunction. Moreover, albumin may help modulate immune responses by interacting with immune cells and promoting the resolution of inflammation, potentially improving patient outcomes. Hariri et al. (2018) reported that albumin infusion improved endothelial function in patients with

infectious shock or sepsis. Furthermore, critically ill patients who could tolerate enteral nutrition and an increased daily caloric intake exhibited improved tolerance to albumin infusion (Wigmore et al., 2019). Hence, albumin is an advised component of the treatment regimen for sepsis patients whose condition necessitates prompt resolution in conjunction with hypoalbuminemia.

The present study is subject to the following limitations. (1) As a retrospective cohort study, despite the use of the MIMIC-IV database, which offers extensive clinical data and a large sample size, a potential bias still exists. Although PSM helps to reduce initial imbalances between groups, residual confounding remains a potential concern and should be acknowledged. (2) Information pertaining to variables that might indicate the severity of the disease in septic patients, such as high-sensitivity C-reactive protein and lactic acid, is lacking. (3) Complications arising from deficiencies in the study design and data structure have not been addressed; nevertheless, the clinical outcomes examined in this investigation were 90-d mortality and in-hospital mortality, which may provide an indirect indication of the safety and effectiveness of albumin infusion. (4) The findings are based on an observational database, which means that they are suggestive rather than conclusive, and their generalizability remains unverified. To confirm the results and better assess their applicability, prospective randomized controlled trials are needed.

4 Conclusions

In summary, hypoalbuminemia is a risk factor for the poor prognosis of elderly septic patients in the ICU, while early albumin infusion can improve the prognosis and reduce the in-hospital and 90-d mortality. This study provides not only new ideas for elucidating the effect of hypoalbuminemia on the prognosis of elderly septic patients in the ICU but also a scientific basis for identifying the risk of these septic patients based on the assessment of the serum albumin level, with a positive clinical significance for improving the prognosis of critically ill patients.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

Data availability statement

Please refer to the detailed information on the following websites: https://www.physionet.org/content/mimiciv/2.0.

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Author contributions

Jinmin CHEN conceived the idea, performed the data analysis, and wrote and edited the manuscript. Yuanqiang LU contributed to the study design, data analysis, and writing and editing of the manuscript. Both authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Jinmin CHEN and Yuanqiang LU declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by either of the authors.

Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

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Supplementary information

Materials and methods