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Early albumin infusion and mortality in elderly patients with sepsis based on analysis of 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 (MIMIC-IV) database. They were divided into hypoalbuminaemia group and control group, and the primary outcome was 90-day mortality. A multivariate logistic regression model and a multivariate Cox proportional-hazards model were used to analyze the correlation between hypoalbuminaemia and the prognosis. Kaplan-Meier survival curve and log-rank test were performed to analyze the survival outcome. 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-day mortality (48.8% vs. 33.4%, $P < 0.001$) were both significantly higher in the early hypoalbuminemia group than the control group. PSM analysis showed that early albumin infusion was associated with lower in-hospital mortality and 90-day mortality in elderly patients with sepsis combined with hypoalbuminemia in the ICU. Early infusion of albumin could improve prognosis and reduce in-hospital mortality and 90-day mortality rates.

Key words: Sepsis; Albumin; Hypoalbuminemia; Mortality; Propensity score matching

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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 of patients in intensive care units (ICUs) (Tidswell et al., 2021). Global statistics indicate that there are around 48.9 million sepsis cases annually, with sepsis-related fatalities reaching up to 11 million, representing 19.7% of all deaths (Seymour et al., 2019; Fleischmann-Struzek et al., 2020). What is more, more than 70 billion US dollars are spent directly on sepsis-related medical expenses every year worldwide, posing a heavy economic burden for 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.

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Acute and severe disorders such as sepsis frequently exhibit hypoalbuminemia, 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 serum albumin in hospitalized patients, their ICU stay was prolonged by about 30% and their 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 (Kendall et al., 2019; Arnau-Barrés 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 et al., 2013; Sivayoham et al., 2020). Fluid therapy plays a crucial role in the restoration and preservation of tissue perfusion, 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 in both acute and critical illness (Lewis et al., 2018; Ramadori et al., 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 et al., 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 (Vincent et al., 2014; Joannidis et al., 2022; Nicholson et al., 2000). 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 of administering 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 becomes diminished and there is elevated vulnerability to infections in the elderly (El-Sharkawy et al., 2014; Stanojcic et al., 2016). Due to 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 (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 Data and methods

2.1 Study design

We conducted a retrospective cohort study utilizing MIMIC-IV, a prominent database in the United States (Johnson et al., 2023). This database is recognized for its comprehensiveness and high data quality, and includes patient admissions to the ICUs at Beth Israel Deaconess Medical Center from 2008 to 2019. One of the

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researchers, Jinmin Chen, completed the requisite training and obtained certification (No. 12473022) to access and use the MIMIC-IV database. Since the research had no impact on clinical care and all patient information were de-identified, the individual consent requirement could be waived.

2.2 Selection of participants

Patients in the MIMIC-IV who met the criteria for sepsis were considered eligible candidates for participation in the study. The presence of sepsis was determined based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria (Singer et al., 2016). Briefly, sepsis was diagnosed in individuals with proven or suspected infection and an acute change in Sequential Organ Failure Assessment (SOFA) total score of $\geqslant$ 2 points. The MIMIC-IV recognizes infection based on the International Classification of Diseases, 9th Edition (ICD-9) code. This study included data from the initial hospital/ICU admission (if a patient has been admitted many times). We excluded patients less than 65 years of age, patients who spent less than 24 hours in the ICU, and emergency patients. The patient enrollment process is depicted in Figure 1.

2.3 Variable extraction

After bridging the PostgreSQL software to Navicat Premium software (version 15.0), clinical information on the study population was extracted using SQL based on the inclusion and exclusion criteria. General clinical information about the study population at the time of ICU admission was collected, including age, gender, weight, insurance type, SOFA score, and simplified acute physiology score (SAPS) II. Interventions received by the study population within 24 hrs of ICU admission were extracted, including albumin therapy, mechanical ventilation, vasoactive drugs, extracorporeal membrane oxygenation (ECMO), and continuous renal replacement therapy (CRRT). Data on the underlying comorbidites in the study population was also gathered, including sepsis, hypertension, diabetes mellitus, myocardial infarction (MI), congestive heart failure (CHF), cerebrovascular disease, chronic obstructive pulmonary disease (COPD), liver disease, renal disease, and malignant tumors. Vital signs of the study population at the time of admission to the ICU were collected, including heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), temperature, and pulse oxygen saturation (SpO2). Moreover, laboratory parameters, including serum albumin, white blood cell (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), were extracted from the study population during the first 24 hours from ICU admission.

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2.4 Outcomes

The primary outcome of this study was 90-day mortality, and the secondary outcomes were in-hospital mortality and length of ICU stay. Survival information was provided by the US Social Security Administration, which is accurate and reliable. Hypoalbuminaemia was defined as a serum albumin level $\leqslant$ 30 g/L (Finfer et al., 2004).

2.5 Statistical analyses

The median (interquartile range) [M (Q1, Q3)] describes continuous variables that do not conform to normal distribution, and the frequency (percentage) [n (%)] describes categorical variables. The Mann-Whitney U test was used to compare continuous variables between groups, and the chi-squared or Fisher's test was used to compare categorical variables between groups. Multifactorial logistic regression models and multifactorial Cox proportional-hazards models were used to explore the independent risk factors for in-hospital mortality as well as 90-day mortality in the selected patients. Kaplan-Meier survival curves and log-rank tests were used to compare survival between the two groups. The variance inflation factor (VIF) was employed to assess the covariance between variables. The VIFs of the indicators in this study were all below 10, indicating that their multicollinearity could be ignored. Based on the non-parsimonious multivariate logistic regression model, PSM was performed using 1:1 greedy nearest neighbor matching with a caliper value of 0.2 (Kane et al., 2020; Ryan

et al., 2021). Standardized mean difference (SMD) was mainly used to measure the heterogeneity of variables between groups as a way to assess the effect of PSM, with SMD < 0.1 indicating that the groups were well-balanced (Austin et al., 2009). To determine the stability of the results, the multifactorial Cox proportional-hazards model was used for subgroup analysis.

The data of this study was analyzed by R software (version 4.0). All hypothesis tests were two-tailed, and $P < 0.05$ was considered a statistically significant difference.

3 Results

3.1 Study population

The ICU admission records of 20,082 elderly septic patients meeting Sepsis 3.0 diagnostic criteria were screened from MIMIC-IV 2.0. After excluding 1,709 cases without ICU admission and multiple ICU admissions, 2,039 cases due to length of ICU stay ⩽ 24 hrs, 7,224 cases of non-emergent ICU admissions, and 4,547 cases with missing clinical data, 4,563 patients who satisfied the inclusion criteria were incorporated into the analysis (Figure 1). The study population comprised 2,467 male patients (54.1%) with a median age of 77.73 years (70.76-84.76). The median SOFA score was 3, with a range of 2.00 to 4.00. The median minimum serum albumin level within 24 hours of ICU admission was 31.00 (26.00-35.00) g/L.

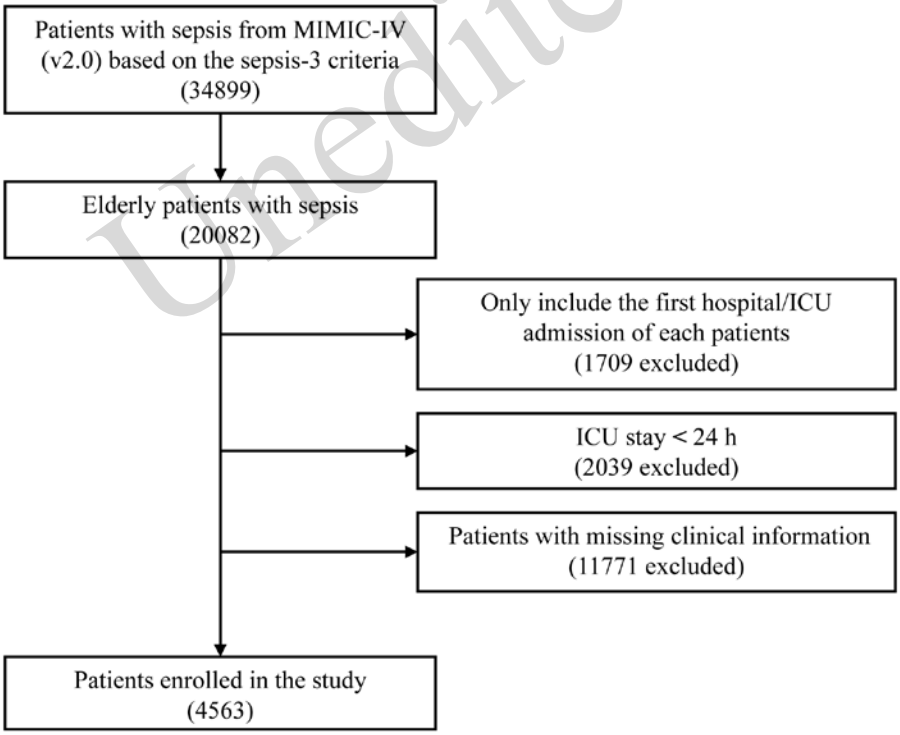

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Fig. 1 Screening chart for inclusion in the study population. ICU, intensive care unit, MIMIC, Medical Information Mart for Intensive Care.

3.2 Comparison of general clinical information between the hypoalbuminemia group and the control group

This study identified elderly patients with sepsis and divided them into hypoalbuminaemia group (n = 2,160) and control group (n = 2,403). In both groups, patients were statistically different in terms of weight, SOFA, SAPS II, use of mechanical ventilation, use of vasoactive drugs, use of CRRT, underlying diseases

(hypertension, CHF, cerebrovascular disease, COPD, liver disease, malignancy), vital signs (HR, MAP, temperature, SpO_2), WBC, HCT, HGB, PLT, INR, sodium, potassium, calcium, AG, Glu, total bilirubin, Cr, and BUN ($P < 0.05$, Table 1).

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

Variables	Hypoalbuminaemia group (n = 2,160)	Control group (n = 2,403)	*P*
Age, years	77.72 (70.64-84.69)	77.81 (70.89-84.88)	0.553
Male, n (%)	1,164 (53.9)	1,303 (54.2)	0.844
Weight, kg	73.60 (62.00-86.90)	76.00 (63.80-90.50)	< 0.001
Insurance, n (%)	1,547 (71.6)	1,700 (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, n (%)	927 (42.9)	933 (38.8)	0.005
Vasoactive drugs, n (%)	1,277 (59.1)	1,037 (43.2)	< 0.001
ECMO, n (%)	4 (0.2)	1 (0.0)	0.196
CRRT, n (%)	144 (6.7)	120 (5.0)	0.019
Hypertension, n (%)	871 (40.3)	1066 (44.4)	0.006
Diabetes, n (%)	290 (13.4)	319 (13.3)	0.916
MI, n (%)	458 (21.2)	523 (21.8)	0.671
CHF, n (%)	824 (38.1)	1099 (45.7)	< 0.001
Cerebrovascular diseases, n (%)	267 (12.4)	521 (21.7)	< 0.001
COPD, n (%)	623 (28.8)	788 (32.8)	0.004
Liver disease, n (%)	171 (7.9)	95 (4.0)	< 0.001
Kidney disease, n (%)	746 (34.5)	813 (33.8)	0.639
Malignant tumors, n (%)	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, Beats/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, $\times 10^9$ /L	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, $\times 10^9$ /L	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

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; HB, hemoglobin; PLT, platelet; INR, international normalized ratio; AG, anion gap; Glu, blood glucose; Cr, creatinine; BUN, blood urea nitrogen.

3.3 Comparison of clinical outcomes between patients in the hypoalbuminemia group and the control group

Among the 4,563 elderly septic patients in the ICU included in this study, 1,078 (23.6%) died in hospital and 1,856 (40.7%) died within 90 days. 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-day mortality (48.8% vs.

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33.4%, $P < 0.001$) than controls. However, no statistical difference was found in the length of ICU stay between the two groups, as shown in Table 2.

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

Outcomes	Hypoalbuminaemia group (n = 2,160)	Control group (n = 2,403)	*P*
Length of ICU stay, d	3.24 (1.98-6.40)	3.16 (1.89-6.06)	0.153
Hospitalized mortality, n (%)	618 (28.6)	460 (19.1)	< 0.001
90-day mortality, n (%)	1,054 (48.8)	802 (33.4)	< 0.001

ICU, Intensive Care Unit.

3.4 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 twenty-four hours of ICU admission. A total of 1,252 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 (see Table 3).

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

Variables	Early albumin infusion group (n = 1,252)	Control group (n = 908)	SMD
Age, years	77.50 (70.77-84.66)	77.93 (70.42-84.72)	0.005
Male, n (%)	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, n (%)	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, n (%)	515 (41.1)	412 (45.4)	0.086
Vasoactive drugs, n (%)	906 (72.4)	641 (70.6)	0.036
ECMO, n (%)	2 (0.2)	2 (0.2)	0.014
CRRT, n (%)	82 (6.5)	62 (6.8)	0.011
Hypertension, n (%)	496 (39.6)	375 (41.3)	0.034
Diabetes, n (%)	177 (14.1)	113 (12.4)	0.050
MI, n (%)	258 (20.6)	200 (22.0)	0.035
CHF, n (%)	471 (37.6)	353 (38.9)	0.026
Cerebrovascular diseases, n (%)	159 (12.7)	108 (11.9)	0.025
COPD, n (%)	356 (28.4)	267 (29.4)	0.021
Liver disease, n (%)	100 (8.0)	71 (7.8)	0.006
Kidney disease, n (%)	435 (34.7)	311 (34.3)	0.010
Malignant tumors, n (%)	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, Beats/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, $\times 10^9$ /L	14.60 (9.675-20.50)	14.90 (9.700-21.50)	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, $\times 10^9$ /L	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

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BUN, mg/dL	36.00 (23.00-54.00)	35.00 (24.00-55.00)	0.030

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; HB, hemoglobin; PLT, platelets; INR, international normalized ratio; AG, anion gap; Glu, blood glucose; Cr, creatinine; BUN, blood urea nitrogen.

3.5 Comparison of clinical outcomes between patients in the early albumin infusion group and the control group 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 and 90-day mortality (Table 4). The results of the Kaplan-Meier survival curve analysis showed no statistically significant difference in the 90-day mortality rate of patients in the early albumin infusion group compared to the control group before PSM (P = 0.080).

Table 4 Characterisation of clinical outcomes before PSM

Outcomes	Early albumin infusion group (n = 1,252)	Control group (n = 908)	P
Length of ICU stay, d	3.12 (1.96-6.11)	3.37 (2.008-6.66)	0.393
Hospitalized mortality, n (%)	326 (26.0)	292 (32.2)	0.002
90-day mortality, n (%)	595 (47.5)	459 (50.6)	0.178

PSM, propensity score matching; ICU, intensive care unit.

3.6 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 (SMD < 0.1, Figure 2).

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, n (%)	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, n (%)	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, n (%)	378 (42.8)	397 (44.9)	0.043
Vasoactive drugs, n (%)	502 (56.8)	530 (60.0)	0.064
ECMO, n (%)	2 (0.2)	2 (0.2)	< 0.001
CRRT, n (%)	49 (5.5)	59 (6.7)	0.047
Hypertension, n (%)	379 (42.9)	367 (41.5)	0.027
Diabetes, n (%)	112 (12.7)	111 (12.6)	0.003
MI, n (%)	186 (21.0)	193 (21.8)	0.019
CHF, n (%)	333 (37.7)	342 (38.7)	0.021
Cerebrovascular diseases, n (%)	99 (11.2)	107 (12.1)	0.028
COPD, n (%)	251 (28.4)	259 (29.3)	0.020
Liver disease, n (%)	73 (8.3)	69 (7.8)	0.017
Kidney disease, n (%)	296 (33.5)	304 (34.4)	0.019
Malignant tumors, n (%)	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, Beats/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, ^{o}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, $\times 10^9$ /L	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, $\times 10^9$ /L	166.50 (104.00-254.30)	164.50 (101.00-254.00)	0.004

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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)	8.300 (7.800-8.800)	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

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; HB, hemoglobin; PLT, platelets; INR, international normalized ratio; AG, anion gap; Glu, blood glucose; Cr, creatinine; BUN, blood urea nitrogen.

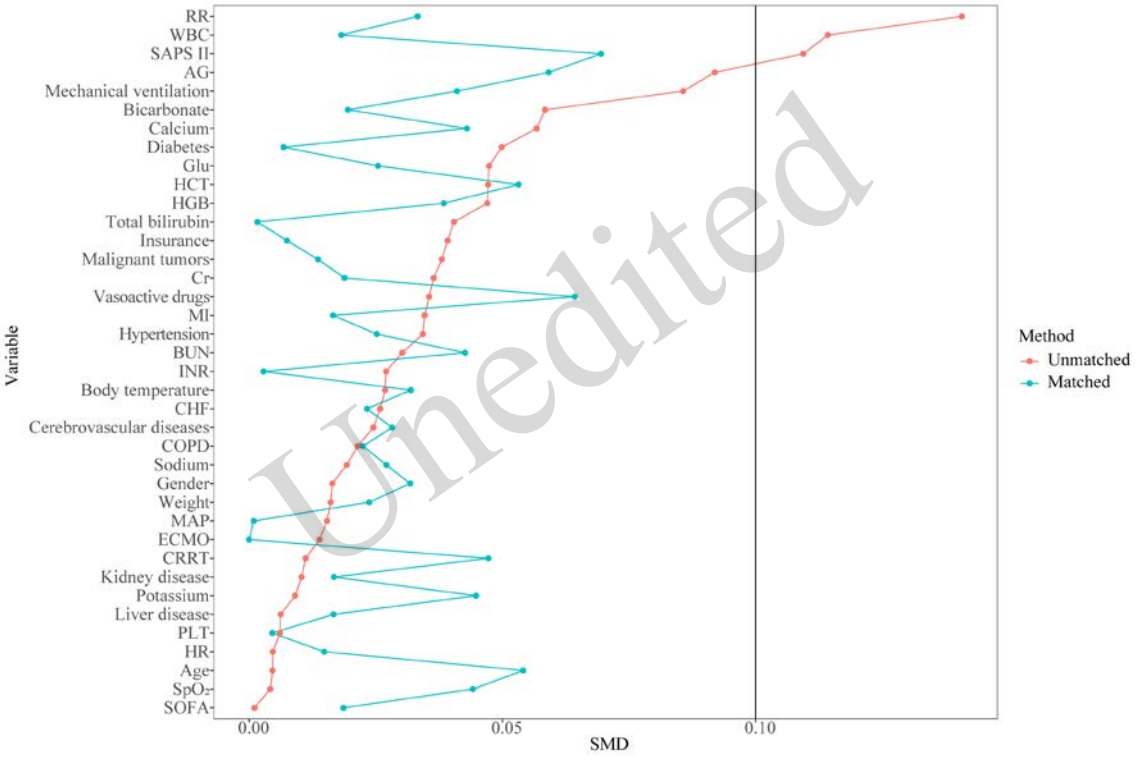

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Fig. 2 Comparison of SMD of general clinical data of patients before and after PSM. SMD, standardized mean difference; PSM, propensity score matching; SOFA, sequential organ failure assessment; SAPS, simplified acute physiology score; ECMO, extracorporeal 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; HB, hemoglobin; PLT, platelets; INR, international normalized ratio; AG, anion gap; Glu, blood glucose; Cr, creatinine; BUN, blood urea nitrogen.

3.7 Comparison of clinical outcomes between patients in the early albumin infusion group and the control group 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-day mortality (38.3% vs. 49.9%, $P < 0.001$) compared with the control group. However, when comparing the length of ICU stay, there was no statistical difference between the two groups (Table 6). The results of the logistic regression model showed that the early albumin infusion group was associated with a lower in-hospital mortality rate (OR 0.25, 95% CI 0.19-0.32, $P < 0.001$) in elderly patients with

sepsis-combined hypoalbuminemia in the ICU. The results of the Cox proportional-hazards model showed that the early albumin infusion group was associated with a lower 90-day mortality rate (HR 0.66, 95% CI 0.57-0.76, $P < 0.001$) in elderly sepsis-combined hypoalbuminemic patients in the ICU. The results of the Kaplan-Meier survival curve analyses revealed that the early albumin infusion group had a lower 90-day mortality than the control group ($P < 0.001$), as shown in Figure 3.

Table 6 Characterisation 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, n (%)	92 (10.4)	279 (31.6)	< 0.001
90-day mortality, n (%)	339 (38.3)	441 (49.9)	< 0.001

PSM, propensity score matching; ICU, intensive care unit.

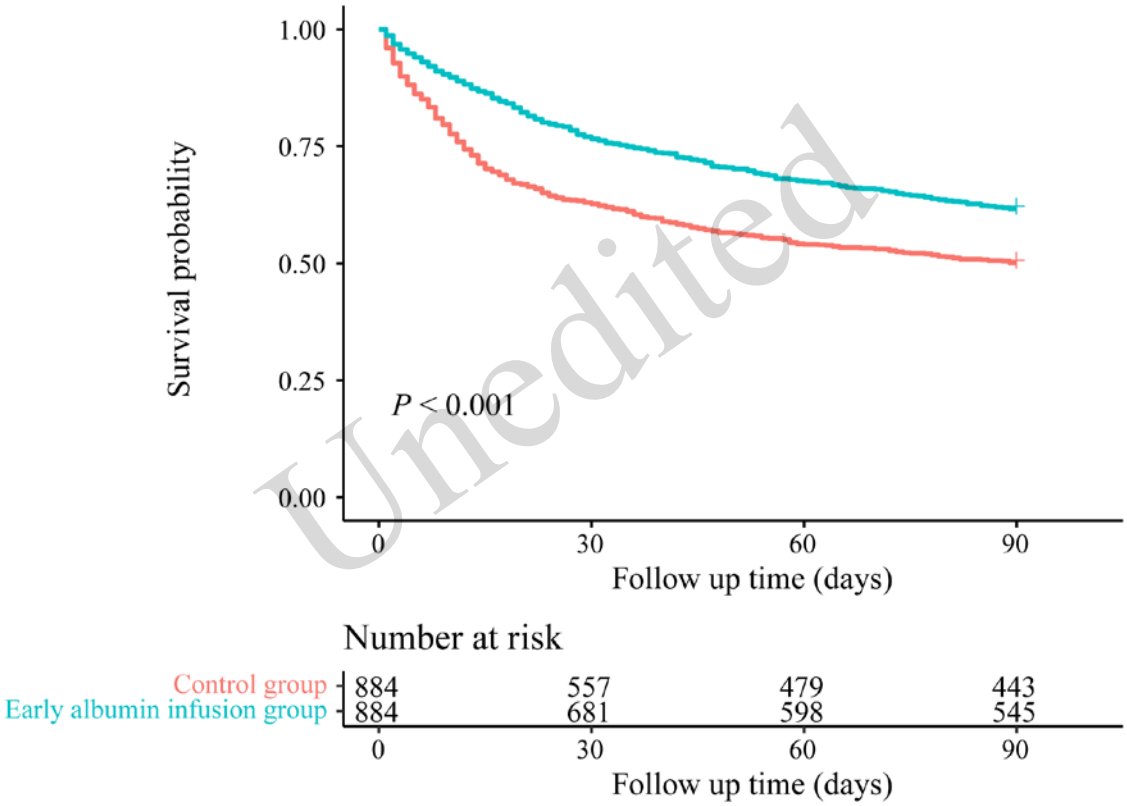

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Fig. 3 Kaplan-Meier survival plot after PSM. PSM, propensity score matching.

3.8 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 ($P < 0.001$). In addition, there was no interaction effect between early albumin infusion and the different gender, SOFA score and comorbidities subgroups (P for interaction > 0.05, Table 7), suggesting the lack of statistically significant difference in the effect of early albumin infusion on 90-day mortality in elderly septic patients in the ICU across these subgroups.

Table 7 Subgroup analyses

Subgroup	*HR* (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	

HR, risk ratio; CI, confidence interval; SOFA, sequential organ failure assessment; MI, myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

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4 Discussion

The ICU admission records of 20,082 elderly septic patients meeting Sepsis 3.0 diagnostic criteria were screened from MIMIC-IV 2.0. After excluding 1,709 cases without ICU admission and multiple ICU admissions, 2,039 cases due to length of ICU stay ⩽ 24 hrs, 7,224 cases of non-emergent ICU admissions, and 4,547 cases with missing clinical data, 4The 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 hours 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-day 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, the PSM was applied to each group. According to the final results, in elderly ICU patients with sepsis-combined hypoalbuminemia, early albumin infusion was associated with a reduced risk of in-hospital mortality and 90-day mortality. Furthermore, subgroup analyses revealed that the correlation between early albumin infusion and 90-day mortality persisted as a significant finding across subgroups categorized by gender, SOFA score and comorbidities.

Albumin is the most prevalent protein in the plasma and is primarily synthesized by the liver, and its half-life is approximately 21 days (Vincent et al., 2014; Fanali et al., 2012). In the current study, 47.34% of septic patients were found to have hypoalbuminemia (⩽ 30 g/L) within 24 hours of ICU admission. Combined hypoalbuminemia in patients with sepsis may be related to the following factors: (1) the release of a large

amount of inflammatory mediators in the early response to infection in patients with sepsis leads to a decrease in the liver's ability to synthesize albumin and a decrease in albumin production; (2) increased albumin degradation resulting from fasting and the highly catabolic state of sepsis; (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 (Schuetz et al., 2010; Dubois et al., 2006; Montealegre et al., 2021; Gatta et al., 2012). Prior research has established that hypoalbuminemia significantly correlates with unfavorable prognosis among sepsis patients (Yamaguchi et al., 2018; Gaieski et al., 2010; Jones et al., 2008; Furukawa et al., 2019). On the one hand, hypoalbuminemia can result in a reduction in the osmolality of plasma colloid, which in turn diminishes the effective volume of blood in circulation. This can lead to microcirculatory dysfunction and the 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 the infection (Giles et al., 2003). As 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-day 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 the early albumin infusion group was associated with lower in-hospital (HR 0.66, 95% CI 0.57-0.76, $P < 0.001$) and 90-day mortality (OR 0.25, 95% CI 0.19-0.32, $P < 0.001$) in elderly ICU patients with sepsis-combined hypoalbuminemia. This is because albumin infusion increases glial osmotic pressure and reduces leukocyte and platelet permeability and adhesion, thereby limiting edema formation (Milford et al., 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. The experimental results in Hariri et al.’s (2018) study showed 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

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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-day 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.

5 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-day mortalities. 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 risk identification of these septic based on the assessment of serum albumin level, with a positive clinical significance for improving the prognosis of critically ill patients.

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Data availability statement

Please refer to the detailed information in the following websites (https://www.physionet.org/content/mimiciv/3.1/).

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Author contributions

Jinmin CHEN conceived the idea and performed data analyses, wrote and edited the manuscript. Yuanqiang LU contributed to the study design, data analysis, writing and editing of the manuscript. All 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 conflict of interest.

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

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