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Original Article

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Association between Albumin Administration and Pulmonary Complications in Patients with Septic Shock: An Analysis Using the MIMIC-IV Database

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ABSTRACT

Background: Albumin administration in patients with septic shock has shown potential benefits, but its association with the development of pulmonary complications remains unclear. We aimed to evaluate the impact of albumin administration on acute respiratory distress syndrome development in patients with septic shock.

Materials and Methods: We analyzed clinical data from the Medical Information Mart for Intensive Care IV database and included adult patients with septic shock. Propensity score matching was used to balance the covariates between the albumin and non-albumin groups. The primary outcome was the development of moderate-to-severe acute respiratory distress syndrome within 7 days. Survival analysis using the log-rank test compared acute respiratory distress syndrome development rates between the groups. Subgroup analysis was used to evaluate the effect of albumin administration on the primary outcome in various subgroups.

Results: Among the 2,132 eligible patients, 1,572 (73.7%) did not receive albumin, whereas 560 (26.3%) received albumin. After propensity score matching, the primary outcome was not significantly different between the two groups (17.5% in the albumin group *vs.* 16.3% in the non-albumin group; *P*=0.708). The Kaplan–Meier curve demonstrated no difference in the primary outcome between the groups. Subgroup analysis showed no significant association between albumin administration and increased acute respiratory distress syndrome development rate across various subgroups.

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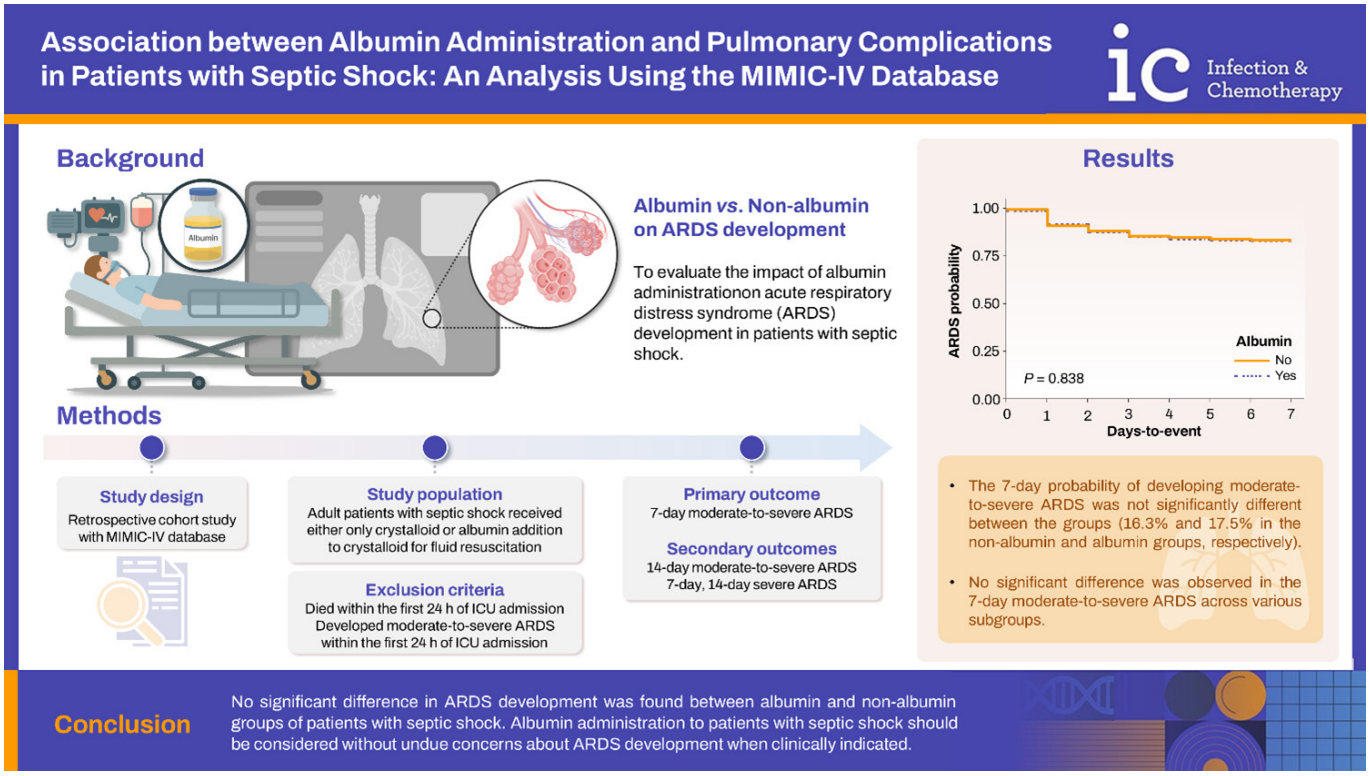
Conclusion: No significant difference in acute respiratory distress syndrome development was found between albumin and non-albumin groups of patients with septic shock. Albumin administration in patients with septic shock should be considered when clinically indicated, without undue concerns about acute respiratory distress syndrome development.

Keywords: Serum albumin; Respiratory distress syndrome; Shock, septic; Intensive care units

GRAPHICAL ABSTRACT



INTRODUCTION

Sepsis is a life-threatening condition characterized by organ dysfunction caused by a dysregulated host response to infection. Septic shock represents a severe subset of sepsis, marked by profound circulatory, cellular, and metabolic abnormalities that significantly increase the risk of mortality [1]. Sepsis and septic shock pose critical global health challenges, contributing to millions of deaths each year [2, 3].

Fluid resuscitation is a cornerstone of managing sepsis and septic shock owing to its beneficial effects on reducing lactate levels, reversing hypoxemia, and addressing shock [4, 5]. With regards to the ongoing debate over whether crystalloid or albumin administration is the optimal approach to fluid resuscitation [6], evidence suggests that using albumin provides benefits in conditions such as septic shock. The Albumin Italian Outcome Sepsis (ALBIOS) study and Saline versus Albumin Fluid Evaluation (SAFE) trial reported reduced mortality among albumin-treated patients compared with that of crystalloid-treated patients in subgroups with septic shock and severe sepsis, respectively [7, 8]. The Fluid Resuscitation in Sepsis-Induced Hypotension among Patients with Cirrhosis (FRISC) study reported that treatment with 5% albumin compared with saline treatment resulted in hypotension reversal and 1-week survival improvement in patients with cirrhosis and sepsis-induced hypotension [9].

Acute respiratory distress syndrome (ARDS) is a frequent complication of sepsis-induced acute circulatory failure [10]. While some studies have reported improved partial pressure of arterial oxygen to the fractional concentration of inspired oxygen ratio with albumin use, others have highlighted the risk of fluid overload during resuscitation, potentially exacerbating pulmonary edema and increasing ARDS risk [11-13]. Wiedermann recently raised concerns about the potential for albumin treatment to contribute to increased pulmonary edema in patients with sepsis, emphasizing the need for further investigation [14]. However, to our knowledge, no study has specifically focused on the correlation between albumin administration and ARDS development in patients with sepsis or septic shock. In this study, we investigated the relationship between albumin administration and ARDS development in patients with septic shock.

MATERIALS AND METHODS

1. Study design

This retrospective cohort study utilized data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database version 2.2 [15, 16]. The MIMIC-IV database is a publicly accessible, de-identified electronic health record database containing comprehensive clinical information on patients admitted to the intensive care unit (ICU) at the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, between 2008 and 2019. Access to the database required completing an online training course on human research and signing a data-use agreement.

2. Ethics statement

The Institutional Review Board of the BIDMC approved the study and waived the requirement for informed consent (approval number: 2001P001699).

3. Study population

We included patients aged ≥18 years who met the Sepsis-3 diagnostic criteria for septic shock. The criteria define sepsis by a sequential organ failure assessment (SOFA) score ≥2 points due to infection and septic shock as requirement of vasopressor administration and a serum lactate level ≥2 mmol/L [1]. The diagnosis was based on the time of ICU admission. Patients were categorized into those who only received crystalloid solutions for fluid resuscitation (non-albumin group) and those who received albumin in addition to crystalloid during the first 24 h of ICU admission (albumin group). The exclusion criteria were death and occurrence of moderate-to-severe ARDS within the first 24 h of ICU admission, considering these ARDS cases are independent of albumin administration.

4. Variables and outcome measures

The following variables were extracted using a structured query language on the BigQuery platform: demographics (age, sex, and race), comorbidities, SOFA score, laboratory findings, vasopressor administration, mechanical ventilation, renal replacement therapy, chest radiography findings, and cardiac rhythm. The Charlson comorbidity index was calculated using coding algorithms with the International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) and ICD-10 codes [17]. These variables were extracted based on the criteria used during ICU admission. The most abnormal values of laboratory investigations on the first day of the ICU stay were considered. The SOFA score was calculated using the most abnormal values on the first day of the ICU stay.

Albumin administration was defined as albumin use for fluid resuscitation within the first 24 h of ICU admission. Considering the various percentages of albumin solutions used in previous studies, we included both 5% and 20% albumin solutions, and their usage was quantified by bottle count. The acute kidney injury (AKI) stage was classified using the Kidney Disease: Improving Global Outcomes criteria [18]. Pleural effusion and pulmonary edema were identified on chest radiographs. The variables were determined based on the most abnormal values on the first day of the ICU stay.

The primary outcome measure was 7-day moderate-to-severe ARDS. ARDS was defined by acute hypoxemia with a partial pressure of arterial oxygen to the fractional concentration of inspired oxygen ratio ≤300 for mild ARDS, ≤200 for moderate ARDS, and ≤100 for severe ARDS [10]. Secondary outcomes included moderate-to-severe ARDS at 14 days and severe ARDS at both 7 and 14 days. Out-of-hospital mortality was obtained from state death records [16]. The state and hospital dates of death records were retrieved from the MIMIC-IV database two years after the last patient was discharged. The structured query language code used for data extraction is available on GitHub (https://github.com/MIT-LCP/mimic-iv).

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5. Statistical analysis

Propensity score matching (PSM) was performed to balance the differences caused by covariates and potential confounders between the two groups [19]. Logistic regression was used to estimate propensity scores, with albumin administration as the dependent variable and covariates and potential confounders (including demographics, admission unit, comorbidities, severity index, net fluid balance, and radiologic findings) as independent variables. The caliper width was set to 0.2 of the standard deviation of the logit of the propensity score, which has been reported to minimize mean square error, eliminate 98% of the bias in the initial estimates, and result in optimal confidence intervals (CIs) [20]. After PSM, covariate balance was assessed using propensity score distributions and standardized mean differences (SMDs). Covariates with an SMD <0.1 indicated adequate balance [21]. The statistical power of the primary outcome analysis post-PSM was 94.1% for an effect size of 0.1 at a significance level of 0.05.

Baseline characteristics of continuous variables were compared using a two-tailed Student's *t* test or Mann–Whitney *U* test. The Shapiro–Wilk test was used to assess normality. Continuous variables are presented as mean ± standard deviation for normally distributed data or as median (interquartile range [IQR]) for non-normally distributed data. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, as appropriate. Survival analysis was performed using the log-rank test to compare 7-day moderate-to-severe ARDS development between the non-albumin and albumin groups and to compare the effect of different bottle counts of albumin administration within the albumin group. Subgroup analysis was used to evaluate the effect of albumin administration on 7-day moderate-to-severe ARDS development in various subgroups. A Cox regression model with mortality as a competing risk was used to calculate the hazard ratio (HR) between various subgroups, including age, sex, chronic liver disease, chronic kidney disease, congestive heart failure, ventilator use, lactate levels, AKI stage, and atrial fibrillation. Albumin administration was the only independent variable in the Cox regression model, as covariates were balanced after PSM [21]. Multivariable logistic regression analysis was conducted to identify independent associations between albumin administration and ARDS development. Confounders with *P*-values <0.05 in the univariable analysis were included in the multivariable logistic regression model. Differences were considered statistically significant at $P<0.05$. All statistical analyses were conducted using R (version 4.2.2, The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Patient characteristics

Of 5,120 patients diagnosed with septic shock (**Fig. 1**), 170 died within the first 24 h, and 2,818 experienced moderate-to-severe ARDS within the first 24 h. Finally, 2,132 patients (1,572 [73.7%] in the non-albumin group and 560 [26.3%] in the albumin group) were included in the analysis.

The median age was 71 years (IQR, 59–81 years) in the non-albumin group and 67 years (IQR, 58–76 years) in the albumin group (**Supplementary Table 1**). The proportion of male patients was 56.7% in the non-albumin group and 60.2% in the albumin group. The Charlson comorbidity index was higher in the non-albumin group (median 7.0, IQR, 5.0–9.0 *vs.* 6.0, IQR, 4.0–8.0). Overall, the two groups showed significant differences in most baseline characteristics, including demographics, admission unit, comorbidities, severity index, and radiologic findings. The albumin group had a higher degree of severity.

After PSM, no significant differences were found between the groups regarding demographics, comorbidities, severity indices, or radiologic findings (**Table 1**).

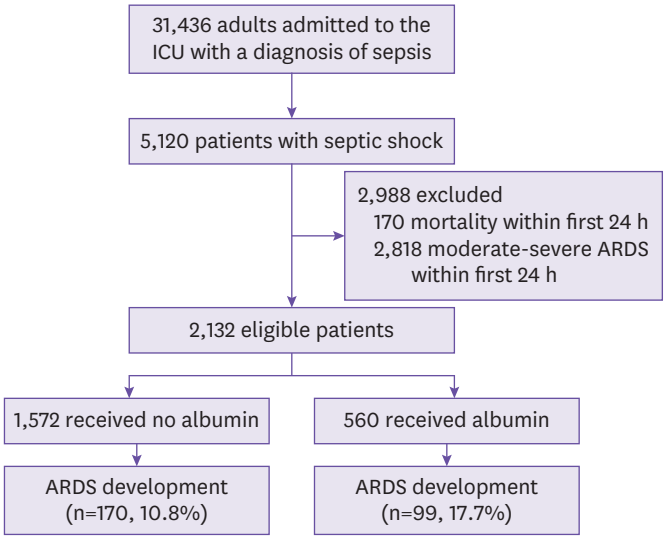

Figure 1. Flowchart of participant enrollment.
ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

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Table 1. Baseline characteristics of patients with septic shock after propensity score matching

Characteristics	Albumin (−) (n=405)	Albumin (+) (n=405)	SMD	*P*-value
Age (years)	68.0 (56.0, 77.0)	67.0 (58.0, 75.0)	0.015	0.887
Male sex	246 (60.7)	239 (59.0)	0.035	0.667
Race				
White	274 (67.7)	273 (67.4)	0.050	>0.999
Black	45 (11.1)	38 (9.4)	0.057	0.487
Others	37 (9.1)	41 (10.1)	0.033	0.721
Unknown	49 (12.1)	53 (13.1)	0.030	0.751
ED admission	356 (87.9)	332 (82.0)	0.166	0.024[a]
MICU	81 (20.0)	78 (19.3)	0.019	0.860
MICU-SICU	50 (12.3)	46 (11.4)	0.031	0.744
SICU	75 (18.5)	66 (16.3)	0.059	0.458
TSICU	86 (21.2)	72 (17.8)	0.087	0.249
CVICU	108 (26.7)	136 (33.6)	0.151	0.039[a]
Comorbidities				
Diabetes mellitus	115 (28.4)	118 (29.1)	0.016	0.877
Congestive heart failure	130 (32.1)	132 (32.6)	0.011	0.940
Myocardial infarction	65 (16.0)	72 (17.8)	0.046	0.574
Chronic renal disease	98 (24.2)	96 (23.7)	0.012	0.934
Mild liver disease	121 (29.9)	120 (29.6)	0.050	>0.999
Severe liver disease	82 (20.2)	78 (19.3)	0.025	0.791
COPD	78 (19.3)	86 (21.2)	0.049	0.540
Cancer	80 (19.8)	68 (16.8)	0.077	0.317
CCI	6.0 (4.0, 8.0)	6.0 (4.0, 8.0)	0.033	0.737
SOFA score	9.0 (7.0, 12.0)	9.0 (7.0, 12.0)	0.021	0.664
Ventilator care	221 (54.6)	233 (57.5)	0.060	0.436
RRT	39 (9.6)	38 (9.4)	0.080	>0.999
AKI stage			0.054	0.898
0	93 (23.0)	100 (24.7)		
1	63 (15.6)	66 (16.3)		
2	119 (29.4)	117 (28.9)		
3	130 (32.1)	122 (30.1)		
Norepinephrine use	398 (98.3)	393 (97.0)	0.082	0.353
Vasopressin use	105 (25.9)	104 (25.7)	0.060	>0.999
Epinephrine use	44 (10.9)	62 (15.3)	0.132	0.077
Albumin (mg/dL)	2.60 (2.20, 3.20)	2.60 (2.20, 3.0)	0.102	0.204
Lactate (mmol/L)	3.80 (2.80, 6.0)	3.90 (2.80, 5.5)	0.060	0.783
P/F ratio	247.5 (206.0, 323.4)	250.0 (210.0, 295.8)	0.029	0.754
Atrial fibrillation	76 (18.8)	79 (19.5)	0.019	0.858
Radiologic findings				
Pneumonia	9 (2.2)	7 (1.7)	0.035	0.801
Pleural effusion	42 (10.4)	41 (10.1)	0.080	>0.999
Edema	27 (6.7)	26 (6.4)	0.010	>0.999
Net fluid balance	3,008.7 (1,250.8–5,362.2)	3,191.7 (1,460.4–5,175.9)	0.024	0.493
28-day mortality	161 (39.8)	110 (27.2)	0.269	<0.001[b]

Data are presented as number (%) or median (interquartile range).
[a]*P*<0.05, [b]*P*<0.001.
SMD, standardized mean difference; ED, emergency department; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma SICU; CVICU, cardiac vascular intensive care unit; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; RRT, renal replacement therapy; AKI, acute kidney injury; P/F, partial pressure of arterial oxygen to fractional concentration of inspired oxygen.

The balance of covariates before and after PSM was evaluated using the propensity score distribution and SMDs (**Supplementary Fig. 1**). Covariates were well balanced after PSM; however, emergency department admission was less frequent (SMD=0.166, *P*=0.024), and admission to the cardiovascular ICU was more frequent (SMD=0.151, *P*=0.039) in the albumin group than in the non-albumin group. Furthermore, the 28-day mortality was significantly lower in the albumin group (SMD=0.269, *P* <0.001). However, most of the covariates fell within the optimal SMD range and were well-matched (**Supplementary Fig. 1**).

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2. Fluid administration

The mean net fluid balance during the first 7 days following ICU admission was calculated for both groups, with day 0 representing the initial 24 h post-admission, day 1 indicating 24–48 h, and subsequent days following this pattern (**Supplementary Fig. 2**). The mean net fluid balance was comparable on day 0 between the albumin group (input=6,440.4 mL, output=2,847.6 mL, net fluid balance=3592.8 mL) and non-albumin group (input=5,571.4 mL, output=2068.3 mL, net fluid balance=3,503.1 mL) (*P*=0.732). Over subsequent days, the net fluid balance became lower in the albumin group. Significant differences were observed on days 2 and 3. In the albumin group, the mean input of crystalloid solution before albumin administration was 2,310.8 mL (IQR, 586.9–3113.9).

3. Outcomes

After PSM, the 7-day probability of developing moderate-to-severe ARDS was 16.3% and 17.5% in the non-albumin and albumin groups, respectively (*P*=0.708), showing no significant difference (**Table 2**). Kaplan–Meier analysis also found no significant difference in the 7-day moderate-to-severe ARDS probability between the groups (log-rank test: *P*=0.838; **Fig. 2**). Furthermore, Kaplan–Meier analysis suggested no significant difference in the 7-day moderate-to-severe ARDS probability between patients who were administered varying amounts of albumin within the albumin group (log-rank test: *P*=0.391; **Supplementary Fig. 3**).

No significant differences were observed in secondary outcomes. The 14-day moderate-to-severe ARDS probabilities were 17.3% and 17.8% in the non-albumin and albumin groups, respectively. For severe ARDS, the 7-day probabilities were 5.2% in the non-albumin group and 4.0% in the albumin group, while the 14-day probabilities were 5.7% and 4.4%, respectively (**Table 2**).

Before PSM, the 7-day probability of developing moderate-to-severe ARDS was higher in the albumin group (17.7%) than in the non-albumin group (10.8%; *P* <0.001); at 14 days, the probabilities were 17.9% and 11.7%, respectively (*P* <0.001). Regarding severe ARDS, the 7-day probabilities were 3.4% and 3.1% in the albumin and non-albumin groups, respectively, and the 14-day probabilities were 4.1% and 3.4%, respectively (**Supplementary Table 2**).

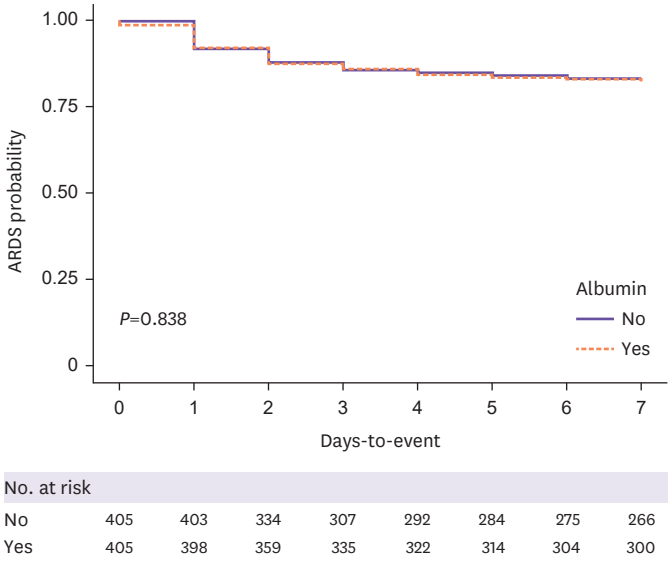

Figure 2. Kaplan–Meier survival curves on ARDS probability in patients with septic shock. Albumin- and non-albumin-treated patients were compared using log-rank tests.
ARDS, acute respiratory distress syndrome.

4. Subgroup analysis

Competing risk analysis showed no significant ARDS development in the albumin group (HR, 1.08; 95% CI, 0.78–1.50; *P*=0.630). Consistent with the overall patient results, no significant difference was observed in the 7-day moderate-to-severe ARDS across subgroups based on age, sex, chronic liver disease, chronic kidney disease, ventilator use, lactate levels, AKI stage, or atrial fibrillation (**Fig. 3**).

Table 2. Clinical outcomes of patients with septic shock after propensity score matching

Clinical outcomes	Albumin (−) (n=405)	Albumin (+) (n=405)	SMD	*P*-value
Primary outcome				
7-day moderate-to-severe ARDS	66 (16.3)	71 (17.5)	0.033	0.708
Secondary outcomes				
14-day moderate-to-severe ARDS	70 (17.3)	72 (17.8)	0.013	0.926
7-day severe ARDS	21 (5.2)	16 (4.0)	0.059	0.501
14-day severe ARDS	23 (5.7)	18 (4.4)	0.056	0.521

Data are presented as number (%) or median (interquartile range).
SMD, standardized mean difference; ARDS, acute respiratory distress syndrome.

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Subgroups	No. of patients	No albumin	Albumin	HR (95% CI)	*P*-value
Overall	810	66 (16.3)	71 (17.5)	1.08 (0.78–1.50)	0.630
Age					
≥65	468	27 (11.6)	39 (16.6)	1.47 (0.91–2.37)	0.120
<65	342	39 (22.7)	32 (18.8)	0.81 (0.51–1.28)	0.370
Sex					
Male	485	41 (16.7)	41 (17.2)	1.03 (0.67–1.56)	0.910
Female	325	25 (15.7)	30 (18.1)	1.18 (0.70–1.98)	0.540
Chronic liver disease	257	32 (23.9)	19 (15.4)	0.63 (0.36–1.09)	0.098
Chronic kidney disease	194	13 (13.3)	21 (21.9)	1.72 (0.87–3.37)	0.120
Congestive heart failure	262	15 (11.5)	24 (18.2)	1.61 (0.86–3.04)	0.140
Ventilator care					
Yes	454	48 (21.7)	52 (22.3)	1.03 (0.71–1.51)	0.870
No	356	18 (9.8)	19 (11.0)	1.14 (0.60–2.15)	0.690
Lactate					
>4 mmol/L	392	37 (19.2)	51 (25.6)	1.37 (0.91–2.06)	0.130
2–4 mmol/L	418	29 (13.7)	20 (9.7)	0.70 (0.40–1.23)	0.210
AKI stage 2–3	488	43 (17.3)	51 (21.3)	1.26 (0.85–1.87)	0.260
AF	155	10 (13.2)	17 (21.5)	1.66 (0.77–3.59)	0.190

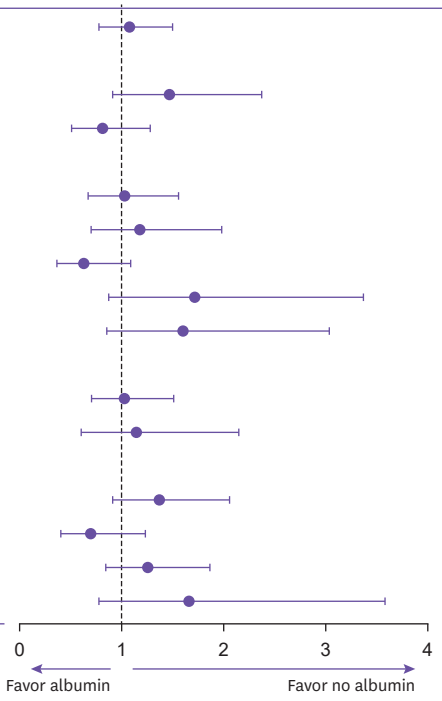

Figure 3. Forest plot of subgroup analysis comparing the effect of albumin administration on acute respiratory distress syndrome development (ARDS). Competing risk analysis was performed with mortality as the competing risk. The 7-day moderate-to-severe ARDS development of each group is presented as number (%).
The AKI stage was determined according to the Kidney Disease: Improving Global Outcomes classification [18].
HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury; AF, atrial fibrillation.

5. Risk factors for ARDS development

We performed a multivariable logistic regression adjusted for age, history of diabetes, variables of disease severity, lactate level, and net fluid balance (**Supplementary Table 3**) and found no significant association between albumin administration and ARDS development in patients with septic shock (odds ratio, 1.17; 95% CI,-0.75–1.82; *P*=0.482). Independent risk factors for ARDS development included higher SOFA scores, ventilator use, lower partial pressure of arterial oxygen to the fractional concentration of inspired oxygen ratios, and greater net fluid balance.

DISCUSSION

In this study, we evaluated ARDS development in patients with septic shock following albumin administration and found no significant difference in ARDS development between the albumin and non-albumin groups after matching baseline characteristics and degree of severity. These findings suggest that clinicians may consider albumin administration to patients with septic shock when clinically indicated, without undue concerns about ARDS development.

Previous studies have extensively debated the efficacy of albumin administration in patients with sepsis or septic shock [7, 8, 22]. The SAFE trial, a multicenter randomized controlled trial (RCT) involving >7,000 patients, reported no significant differences in mortality, organ failure, ICU stay duration, or days on mechanical ventilation between the albumin- and saline-treated groups [7]. The ALBIOS study, a multicenter, open-label randomized trial involving 1,818 patients with severe sepsis across more than 100 ICUs, found that the administration of 5% albumin resulted in higher mean arterial pressure and lower net fluid balance but did not significantly affect the 28- or 90-day mortality compared with crystalloid administration [8]. Owing to the high cost and lack of proven benefits of albumin, albumin use in sepsis management is currently considered as second line of therapy after crystalloids. According to the 2021 Sepsis International Guidelines, albumin administration is recommended to patients who remain hypotensive despite adequate fluid resuscitation with crystalloid solutions [22]. However, several reports

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have continued to suggest evidence that albumin provides benefits in severe conditions such as septic shock.

In the ALBIOS study, a post hoc analysis of 1,121 patients with septic shock showed a significantly lower 90-day mortality in the albumin group than in the crystalloid group [8]. In the SAFE trial, subgroup analysis of patients with severe sepsis showed reduced mortality in the albumin group compared with that of the saline group [7]. Similarly, a meta-analysis of 8 RCTs involving 5,124 patients with sepsis and 3,482 patients with septic shock demonstrated that albumin administration significantly reduced 90-day mortality compared with crystalloid administration [23]. The FRISC study, a single-center open-label RCT targeting patients with cirrhosis and sepsis-induced hypotension, reported that treatment with 5% albumin resulted in hypotension reversal and 1-week survival improvement compared with saline treatment [9]. The Albumin for Liver Cirrhosis in Patients with Sepsis-Induced Hypotension (ALPS) trial observed a faster hemodynamic recovery and decline in arterial lactate with 20% albumin administration compared with plasmalyte administration [24]. A study using the MIMIC-III database reported that early albumin administration in patients with septic shock with ARDS is associated with reduced 28-day mortality [25]. These studies suggest that albumin administration can be beneficial in severe conditions such as septic shock and underlying liver cirrhosis. Consistent with the results of the previous studies, our findings demonstrated reduced 28-day mortality in the albumin group compared with that of the non-albumin group in patients with septic shock. Although mortality reduction associated with albumin use in patients with sepsis was not the primary focus of this study, the finding is consistent with evidence from previous RCTs, including the ALBIOS and FRISC studies [8, 9]. However, other meta-analyses have reported inconsistent results regarding the survival benefits of using albumin versus crystalloid solutions for fluid resuscitation [26, 27]. Therefore, further studies are needed to clarify the clinical benefits of albumin administration in reducing mortality in patients with sepsis, particularly to identify specific subgroups in whom it may be most effective.

Despite these benefits, there are safety concerns with albumin administration, which can trigger pulmonary complications in patients with sepsis [14]. The ALPS study reported treatment discontinuation in 22% of patients in the albumin group owing to the development of pulmonary complications, compared with those in the plasmalyte group [14, 24]. ARDS is a severe pulmonary complication associated with sepsis [10]. Excessive fluid administration during sepsis treatment can exacerbate lung edema, potentially increasing the risk of ARDS [11]. As no study has specifically evaluated the development of ARDS based on albumin-specific outcomes [28], our study focused on the development of ARDS in patients with septic shock treated with albumin. Using PSM, we achieved well-balanced covariates between the albumin and non-albumin groups. Before PSM, the ARDS development rate was higher in the albumin group than in the non-albumin group, which may be attributable to the higher degree of severity observed in the albumin group. After PSM, no significant difference was observed. Day 0 mean net fluid balance was balanced as a covariate, showing comparable amounts in the albumin group and non-albumin group. However, on subsequent days, patients in the albumin group had a significantly lower net fluid balance than those in the non-albumin group, suggesting that albumin administration may mitigate fluid overload and pulmonary edema in ARDS management.

The subgroup analysis revealed no significant differences in ARDS development across the various subgroups. Interestingly, the chronic liver disease subgroup also showed no significant difference in the incidence of ARDS between the two groups. This result contrasts with that of the ALPS study, which reported higher ARDS development rates in the albumin group than in the plasmalyte group in liver cirrhosis patients with sepsis-induced hypotension [24]. This difference may be related to the large number of patients with advanced cirrhosis and pneumonia in the ALPS study compared with the high percentage of patients receiving ventilator care in the non-albumin group (55.1%) in our study. Further research is required to explain these conflicting results.

Our study had some limitations. First, as a single-center retrospective cohort study using data from the MIMIC-IV database, our findings are limited to ICU patients from a predominantly Western population. Second, unmeasured confounders might have influenced the results. No detailed evaluation of the heart function was performed through methods such as echocardiography. Moreover, liver function was not assessed using the Child–Pugh score or other indices [29]. Third, we did not exclude acute hypoxemia due to cardiac dysfunction or fluid overload, which is part of the Berlin definition of ARDS [30]. However, we addressed this limitation by matching relevant variables through PSM, including comorbidities

such as congestive heart failure, chronic kidney disease, and chronic liver disease, net fluid balance, radiologic findings (*e.g.*, pleural effusion, pulmonary edema), and atrial fibrillation. Future research should prioritize large-scale RCTs to investigate the relationship between albumin administration and ARDS development across diverse patient populations.

In conclusion, we found no significant difference in ARDS development between albumin-treated and non-albumin-treated patients with septic shock. Notably, the lower net fluid balance observed in albumin-treated patients compared with that of non-albumin-treated patients over time suggests that albumin administration may be a safe fluid resuscitation strategy in ARDS management by mitigating fluid overload. Albumin administration to patients with septic shock should be considered when clinically indicated, without undue concerns about ARDS development.

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Conflict of Interest
JYC is editorial board of *Infect Chemother*; however, he did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions
Conceptualization: YL, JK. Data curation: YL, JK. Formal analysis: YL, JK. Investigation: YL, JK. Methodology: JK, YL, JHS, JS, JAL, JHK, JYA, SJJ, NSK, JYC, JSY. Supervision: JHK, JYA, SJJ, NSK, JYC, JSY, YL. Visualization: YL, JK. Writing - original draft: JK. Writing - review & editing: JK, YL, JHS, JS, JAL, JHK, JYA, SJJ, NSK, JYC, JSY.

Data sharing statement
The dataset analyzed in this study is available on the MIMIC-IV website (https://physionet.org/content/mimiciv/2.2/).

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Baseline characteristics of patients with septic shock before propensity score matching

Supplementary Table 2
Clinical outcomes of patients with septic shock before propensity score matching

Supplementary Table 3
Multivariate analysis of risk factors for ARDS development in patients with septic shock

Supplementary Figure 1
Covariate balance assessment.

Supplementary Figure 2
Comparison of mean net fluid balance between albumin and non-albumin groups.

Supplementary Figure 3
Kaplan–Meier survival curves on ARDS probability of patients with septic shock. Patients receiving different bottle counts of albumin were compared using log-rank tests.

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