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ORIGINAL RESEARCH

Impact of Early Administration of Albumin on Mortality Among Severe COVID-19 Patients, China

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Purpose: Hypoalbuminemia is commonly observed in patients with severe Coronavirus Disease 2019 (COVID-19) and is independently associated with adverse outcomes. However, the efficacy of albumin administration on the clinical prognosis of these patients remains uncertain.

Patients and Methods: This multicenter retrospective study enrolled 458 patients with severe COVID-19 in four medical centers from December 1, 2022, to June 1, 2024. Clinical features and laboratory variables were collected through electronic medical records. The cohorts were divided into two groups: albumin administration and non-albumin administration. Propensity score matching (PSM) was used for minimizing confounding effect. Statistical analyses were conducted to assess the relationship between early albumin administration and 28-day mortality.

Results: Four hundred and fifty-eight severe COVID-19 cases were included in the study, of which 167 (36.5%) received early albumin administration, while 291 (63.5%) did not. Among these patients, 140 experienced in-hospital mortality and 318 survived. Compared to survivors, non-survivors exhibited significantly lower serum albumin levels (29.1g/L vs.33.8g/L, $p < 0.05$). In comparison to patients with admission albumin levels ≥30 g/L, those with albumin levels <30 g/L had a significantly higher in-hospital mortality (48.4% vs 21.1%, $p < 0.001$). Prior to PSM, the albumin administration group demonstrated significantly higher 28-day and in-hospital cumulative survival rates compared to the non-albumin group (both $p < 0.001$). However, no significant differences were observed between the two groups following PSM ($p = 0.21$ and $p = 0.41$, respectively).

Conclusion: Hypoalbuminemia was correlated with adverse outcomes in severe COVID-19 patients. However, early albumin administration did not reduce 28-day mortality and in-hospital mortality in these patients, and more relative RCTs were required for validation.

Keywords: COVID-19, SARS-CoV-2, hypoalbuminemia, albumin, administrations, mortality

Introduction

The COVID-19 pandemic has posed unprecedented challenges to the global medical system. Severe cases often develop into acute respiratory distress syndrome (ARDS), multiple organ failure and death. In critically ill patients, serum albumin concentrations are significantly lower than in non-critically ill patients, and hypoalbuminemia is closely associated with adverse clinical outcomes, including an increased risk of mortality.[1–3]

Serum albumin is the most abundant protein in human plasma, accounting for approximately 50% to 60% of total plasma proteins. It possesses multiple physiological functions, maintaining colloid osmotic pressure while also exhibiting

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anti-inflammatory, antioxidant, and anticoagulant properties.[4–6] These functions could be crucial for alleviating the common high inflammatory and hypercoagulable states in patients with severe COVID-19,[2] thereby prompting interest in albumin administration as a therapeutic strategy for COVID-19.

Severe COVID-19 patients experience inflammatory stress, which results in reduced albumin synthesis, increased capillary leakage, and metabolic abnormalities, ultimately leading to abnormal distribution and heightened loss of albumin. Recent investigations have reported an incidence of hypoalbuminemia of approximately 50% in critical COVID-19 patients,[7–9] and it has been associated with disease severity and poor prognosis.[10–15] During the COVID-19 pandemic, studies from China and Italy have shown that albumin infusion significantly reduced the 28-day mortality and improved organ function in COVID-19 patients with hypoalbuminemia.[2,3] However, particularly in severe COVID-19 patients, the use of albumin remains controversial. Notably, there is currently a lack of sufficient research on the correlation between the timing of albumin administration and clinical outcomes in critically ill patients.

In order to investigate the effects of early albumin administration in severe COVID-19 patients, we performed this retrospective multicentre cohort study to analyze the association of albumin administration within the first 7 days on admission with 28-day mortality. We hope to provide evidence-based medical data for optimizing the treatment strategy for severe patients with COVID-19.

Materials and Methods

Study Design and Participants

The multicentre cohort study enrolled patients who were hospitalized from December 1, 2022, to June 1, 2024, in four medical centers, including Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan Infectious Diseases Hospital, Shandong Provincial Chest Hospital, and Binzhou Medical University Hospital. This study was approved by the ethics committee of all participating institutions and complied with the ethical principles outlined in the Declaration of Helsinki.

The diagnosis of COVID-19 was made based on the National Health Commission of China guidance.[16] The presence of SARS-CoV-2 in respiratory specimens was confirmed through real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assays conducted in accordance with the previously described protocol.[17] We enrolled adult patients who had fulfilled confirmed diagnosis of severe COVID-19 at admission. Patients with COVID-19 were considered to have severe illness if they met at least one of following criteria:[18] respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 $\leq$ 93% on room air, or oxygen index < 300 mmHg.

The exclusion criteria were: (I) who were under 18 years old, (II) pregnant patients, (III) non-severe COVID-19 cases, (IV) who were complicated with chronic kidney disease, chronic liver disease, tumors, rheumatism, or other autoimmune disease.

Data Collection and Study Outcomes

Data extraction was conducted by a trained team of physicians utilizing a standardized form to gather information from electronic medical records regarding demographic characteristics, underlying medical conditions and outcomes, as well as laboratory tests and treatments. The dosage, administration regimen, and duration of albumin therapy, as well as the drugs used simultaneously, were all recorded in detail. All recorded data underwent double verification by trained physicians, with any discrepancies adjudicated by a third researcher. As of June 1, 2024, all included patients had either been discharged or deceased.

The primary outcomes were defined as all-cause mortality at 28 days following hospital admission and discharge. Secondary outcomes included in-hospital mortality and length of stay.

Intervention

All enrolled patients were treated according to the Chinese national guidelines for the diagnosis and treatment of COVID-19, including antiviral therapy, low-dose corticosteroids, and anticoagulation, etc. The intervention of interest for this cohort study was administration of 20% human serum albumin (Specifications: 20%, 50 mL/bottle (10 g/bottle);

Shandong Taibang Biological Products Co., Ltd). To evaluate the impact of early albumin administration on patient outcomes, we categorized patients into two groups: those who received albumin administration within 7 days of admission and those who did not.

Statistical Analysis

The Kolmogorov–Smirnov test or Shapiro–Wilk test was used to test the normality for continuous variables. Continuous variables with normal distribution were expressed as mean ± SD and compared using unpaired, 2-tailed Student's *t* test. Continuous variables with skewed distribution were presented as median (inter-quartile range) and compared with Mann–Whitney *U*-test. Categorical variables were summarized as numbers (percentages) and compared by Pearson's chi-square test and Fisher's exact test. Kaplan–Meier estimator was constructed to estimate the survival curves over 28-day period and Log rank test was used to compare the survival probability between albumin administration group and non-albumin administration group. To explore the risk factors associated with 28-day mortality, univariate analysis and multivariable logistic regression model were constructed to estimate the OR and 95% confidence interval (95% CI). The variables in the multivariable logistic regression model were as follows: Lymphocyte count, age, gender, leukocyte, platelet, comorbidity, APACHE II score, serum creatinine, total bilirubin (TBIL), albumin and D-dimer on hospital admission and corticosteroid treatment initiation, respectively, all of which were selected based on existing literatures,[19] and significance of the P value in the univariate analysis according to the data in this study.

To evaluate the impact of albumin therapy on mortality, we performed propensity score matching (PSM) to minimize the bias introduced by confounding variables. The propensity score (PS) for each patient was calculated using a logistic regression model that incorporated the same variables utilized in the prior logistic regression model. In both unweighted and pseudo-population cohorts, the standardized mean difference (SMD) was computed. A 1:1 neighbor matching algorithm was applied using a caliper width of 0.2. After PSM, the standardized mean difference (SMD) and p-value were used to assess the balance of essential characteristics between the two groups. An SMD of >10% suggested an imbalance between the groups. The variables that had >5% of values missing were excluded. Numerical missing data was imputed by median and categorical data was imputed by the category with the most frequency. A two-tailed P value of 0.05 or less was considered statistically significant. The variables that had >5% of values missing were excluded. Simple data imputation was done for missing data <5%, using the median for skewed distribution data, or the mode for dichotomous data. Statistical analysis was conducted using SPSS software, version 22.0 (SPSS Inc. Chicago, Illinois, United States), SAS9.4, and R 3.6.2 (R Foundation for Statistical Computing).

Results

Baseline Characteristics and Laboratory Findings of All Patients

A total of 4308 confirmed COVID-19 patients who were admitted to four designated hospitals from December 1, 2022, to June 1, 2024, were screened. Ultimately, a total of 458 severe COVID-19 cases were included in the study (Figure 1), among which 167 (36.5%) received early albumin administration (20% human albumin), while 291 (63.5%) did not. The baseline characteristics and laboratory results of severe COVID-19 patients were presented in Table 1. Among the 458 recruited patients, 140 experienced in-hospital mortality, while 318 survived. The median age of the cohort was 65 years (IQR 56–73), with 267 participants (58.3%) identified as male, and no statistically significant differences were observed between non-survivors and survivors (both $p > 0.05$). Among these patients, comorbidities were observed in nearly half (47.6%), with hypertension (35.8%) being the most common comorbidity, followed by diabetes (16.2%). A significantly higher proportion of non-survivors exhibited these conditions ($p < 0.001$). Additionally, APACHE II score differed significantly between the two groups ($p < 0.001$).

The median serum albumin concentration on admission was 32.1 g/L across all patients. In comparison to survivors of severe COVID-19, non-survivors exhibited significantly lower lymphocyte counts (0.60 vs.1.06), serum albumin levels (29.1 vs 33.8) and platelet counts (168 vs.218, all $p < 0.05$). Distribution of serum albumin concentration on admission is seen in Figure 2. Thirty-two cases (7.0%) manifested albumin levels lower than 25 g/L and 127 cases (27.7%) ranged between 25 and 29.9 g/L, while the in-hospital mortality rates were 59.4% and 45.7%, respectively. Compared to patients

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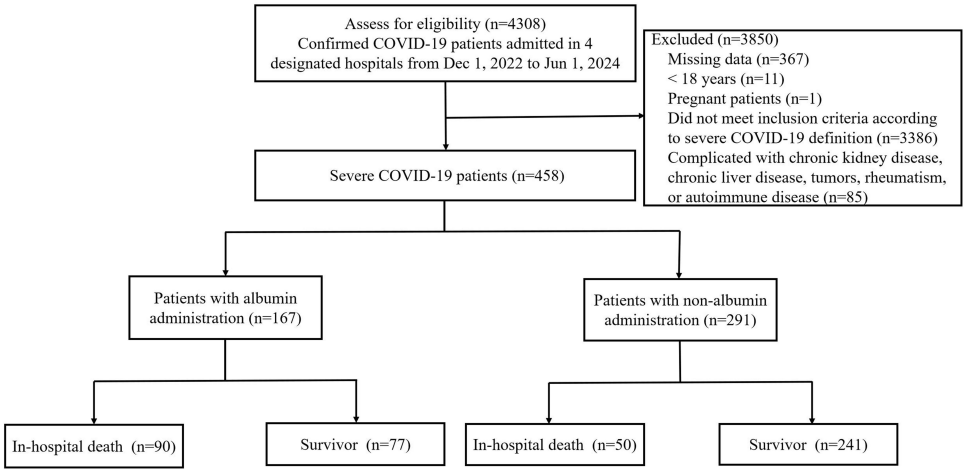

Figure 1 Patient recruitment flow chart.

with albumin levels ≥30g/L on admission, the in-hospital mortality rate of severe COVID-19 patients with albumin level <30g/L was significantly higher (48.4% vs 21.1%, $p < 0.001$).

Characteristics and Clinical Outcomes With and Without Albumin Administration

The 20% of human serum albumin was utilized for administration therapy. The median time from admission to the initiation of albumin therapy was 3.0 days (IQR 2–6 days), the median days of albumin administration was 4.0 days (IQR 2–6 days), and the median total dose of albumin during hospitalization was 80 g (IQR 40–160g). Table 2 presents a comprehensive comparison of the clinical characteristics and outcomes of severe COVID-19 patients who received albumin administration versus those who did not during the first 7 days after admission. Compared to the non-albumin therapy cohort, patients receiving albumin administration were older (67 [59, 76] vs 63 [55, 72], $p < 0.001$) and exhibited a higher male proportion (65.87% vs 53.95%, $p = 0.014$), as well as an increased prevalence of hypertension (44.31% vs 30.93%, $p = 0.004$). The Charlson Comorbidity Index (CCI) showed significant differences between the two groups ($p = 0.040$). Additionally, the albumin administration group demonstrated elevated Acute Physiology and Chronic Health Evaluation II (APACHE II) scores within the first 24 hours post-admission compared to their non-albumin counterparts ($p < 0.001$).

In comparison to severe COVID-19 patients who did not receive albumin administration, those receiving such treatment demonstrated significantly elevated levels of leukocytes, serum creatinine, total bilirubin (TBIL), and

Table 1 Baseline Characteristics and Laboratory Results of Severe COVID-19 Patients

Characteristic	Overall (n=458)	Non-survivor (N=140)	Survivor (N=318)	*p* value
Age (yr)	65 (56, 73)	67 (58, 74)	64 (56, 72)	0.085
Gender				
Male, n (%)	267 (58.3)	91 (65.0%)	176 (55.3%)	0.054
Female, n (%)	191 (41.7)	49 (35.0%)	142 (44.7%)	
Comorbidities, n (%)	218 (47.6)	83 (59.3%)	135 (42.5%)	0.001
Hypertension, n (%)	164 (35.8)	67 (47.9%)	97 (30.5%)	<0.001
Diabetes, n (%)	74 (16.2)	34 (24.3%)	40 (12.6%)	0.002
Coronary artery disease, n (%)	38 (8.3)	10 (7.1%)	28 (8.8%)	0.552
Chronic lung disease, n (%)	7 (1.5)	3 (2.1%)	4 (1.3%)	0.766
Stroke/TIA, n (%)	24 (5.2)	10 (7.1%)	14 (4.4%)	0.325
Tuberculosis, n (%)	6 (1.3)	3 (2.1%)	3 (0.9%)	0.552

(*Continued*)

Table 1 (Continued).

Characteristic	Overall (n=458)	Non-survivor (N=140)	Survivor (N=318)	*p* value
CCI	0 (0, 1)	1 (0, 2)	0 (0, 1)	<0.001
APACHE II score	15 (12, 17)	23 (18, 26)	12 (9, 13)	<0.001
Laboratory values				
Leukocyte ($\times 10^9$ /L)	6.80 (5.00, 9.99)	9.08 (6.61, 13.87)	6.20 (4.80, 8.65)	<0.001
Lymphocyte ($\times 10^9$ /L)	0.94 (0.59, 1.35)	0.60 (0.44, 0.82)	1.06 (0.72, 1.48)	<0.001
Platelet ($\times 10^9$ /L)	205 (146, 261)	168 (122, 225)	218 (162, 273)	<0.001
Serum creatinine (μmol/L)	69.9 (57.4, 84.5)	76.9 (65.1, 96.1)	67.6 (56.3, 81.8)	<0.001
ALT (U/L)	27 (18, 46)	34 (22, 55)	25 (17, 41)	0.001
TBIL (U/L)	11.20 (8.60, 16.38)	14.30 (10.35, 21.18)	10.15 (8.08, 13.93)	<0.001
Serum albumin (g/L)	32.1 (28.6, 35.7)	29.1 (26.7, 31.6)	33.8 (29.8, 37.2)	<0.001
Serum albumin <30g/L, n (%)	159 (34.7)	77 (55.0%)	82 (25.8%)	<0.001
D-dimer (μg/mL)	1.18 (0.55, 3.30)	3.78 (1.04, 16.35)	0.93 (0.45, 1.96)	<0.001
Drugs treatment				
Albumin administration, n (%)	167 (36.5)	90 (64.3)	77 (24.2)	<0.001
Corticosteroid Therapy, n (%)	216 (47.2)	102 (72.9)	114 (35.8)	<0.001
Antiviral treatment, n (%)	458 (100)	140 (100)	318 (100)	-
Anticoagulant therapy, n (%)	332 (72.5)	92 (65.7)	240 (75.5)	0.031
Hospital length of stay (d)	16 (11, 23)	11 (7, 19)	18 (13, 25)	<0.001

Note: Data are median (IQR) unless specified otherwise.
Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; TIA, Transient ischemic attack; CCI, Charlson Comorbidity Index; APACHE, Acute Physiology and Chronic Health Evaluation; ALT, alanine amino transferase; TBIL, total bilirubin. p< 0.05 means had significantly different.

D-dimer (all $p < 0.05$), while lymphocyte counts and platelet levels were notably diminished (both $p < 0.05$). Furthermore, the serum albumin concentration in patients receiving administration was significantly lower than that in non-albumin individuals (29.1 g/L vs 34.2 g/L, $p < 0.001$). The 28-day mortality (50.9% vs 16.2%) and in-hospital mortality (53.9% vs 17.2%) were significantly higher among severe COVID-19 patients with albumin administration compared to those without it (both $p < 0.001$). However, no statistically significant difference was noted regarding the length of hospital stay between the two groups.

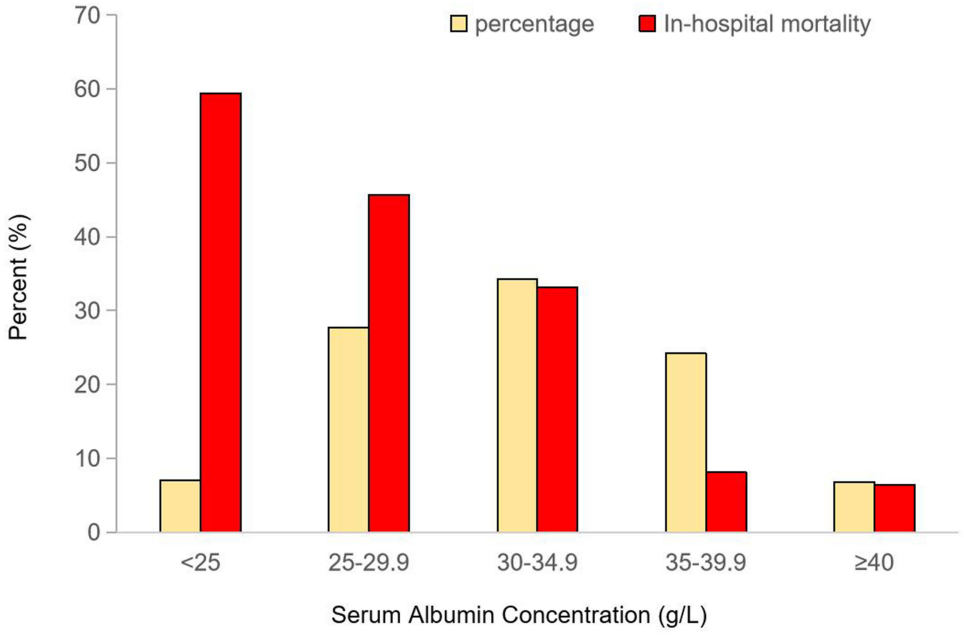

Figure 2 Distribution of serum albumin concentration on admission.

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Table 2 Characteristics and Clinical Outcomes of Severe COVID-19 Patients With Albumin Administration and Non-Albumin Administration Within the First 7 days After Admission

Characteristic	Albumin Administration (N=167)	Non-albumin Administration (N=291)	*p* value
Age (yr)	67 (59, 76)	63 (55, 72)	<0.001
Gender			
Male, n (%)	110 (65.9)	157 (54.0)	0.014
Female, n (%)	57 (34.13)	134 (46.05)	
Comorbidities, n (%)	88 (52.69)	130 (44.67)	0.098
Hypertension, n (%)	74 (44.31)	90 (30.93)	0.004
Diabetes, n (%)	31 (18.56)	43 (14.78)	0.289
Coronary artery disease, n (%)	13 (7.78)	25 (8.59)	0.763
Chronic lung disease, n (%)	3 (1.80)	4 (1.37)	1.000
Stroke/TIA, n (%)	12 (7.19)	12 (4.12)	0.157
Tuberculosis, n (%)	1 (0.599)	5 (1.718)	0.557
CCI	1 (0, 1)	0 (0, 1)	0.040
APACHE II score	18 (15, 20)	16 (14, 18)	<0.001
Laboratory values			
Leukocyte ($\times 10^9$ /L)	8.73 (6.18, 12.55)	6.10 (4.80, 8.65)	<0.001
Lymphocyte ($\times 10^9$ /L)	0.68 (0.50, 1.06)	1.05 (0.69, 1.50)	<0.001
Platelet ($\times 10^9$ /L)	194 (132, 243)	208 (158, 272)	0.002
Serum creatinine (μmol/L)	73.6 (61.3, 88.5)	68.1 (56.7, 83.0)	0.006
ALT (U/L)	32 (18, 48)	26 (18, 44)	0.133
TBIL (U/L)	12.00 (9.20, 17.65)	10.90 (8.25, 15.30)	0.011
Serum albumin (g/L)	29.1 (26.9, 31.4)	34.2 (30.7, 37.6)	<0.001
Serum albumin <30g/L, n (%)	97 (58.1)	62 (21.3)	<0.001
D-dimer (μg/mL)	2.58 (1.02, 7.11)	0.91 (0.43, 1.85)	<0.001
Outcomes			
28-day mortality (n, %)	85 (50.9)	47 (16.2)	<0.001
In-hospital mortality (n, %)	90 (53.9)	50 (17.2)	<0.001
Hospital length of stay (d)	16 (10, 24)	17 (11, 23)	0.711

Notes: Data are median (IQR) unless specified otherwise.
Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; TIA, Transient ischemic attack; CCI, Charlson Comorbidity Index; APACHE, Acute Physiology and Chronic Health Evaluation; ALT, alanine amino transferase; TBIL, total bilirubin. p< 0.05 means had significantly different.

Early Albumin Administration and Clinical Outcomes After PSM

We performed a propensity score matching (PSM) analysis to equilibrate the covariates. A total of 110 patients receiving albumin administration were matched with 110 patients not receiving such treatment in a 1:1 ratio. Following the matching process, baseline characteristics used for calculating the propensity score were well balanced between the two groups (SMD < 0.1, seen in Table 3 and Figure 3). After PSM, the comparison between the group receiving albumin administration and the group without it within the first 7 days of admission revealed no statistically significant difference in 28-day mortality (p = 0.072). Additionally, there were no differences observed for secondary outcomes (p > 0.05).

Survival Analysis of Albumin Administration Before and After PSM

Prior to propensity score matching, the albumin administration group exhibited significantly higher 28-day and in-hospital cumulative survival rates compared to the non-albumin group (both p < 0.001, Log rank test; Figure 4A). However, following propensity score matching, no significant differences were observed between the two groups regarding their 28-day and in-hospital cumulative survival rates (p = 0.21 and p = 0.41, respectively, Log rank test; Figure 4B).

Table 3 Characteristics and Clinical Outcomes of Severe COVID-19 Patients With Albumin Administration and Non- Albumin Administration Within the First 7 days of Admission After Propensity-Score Matching

Characteristic	Overall (n=220)	Albumin Administration (N=110)	Non-albumin Administration (N=110)	*p* value	SMD
Age (yr)	66 (56, 75)	66 (57, 77)	65 (56, 75)	0.523	0.075
Male, n (%)	141 (64.1)	68 (61.8)	73 (66.4)	0.574	0.095
CCI	1 (0, 1)	1 (0, 1)	1 (0, 1)	0.853	0.040
APACHE II score	17 (14, 19)	17 (14, 19)	17 (14, 18)	0.455	0.093
Serum albumin <30g/L, n (%)	104 (47.3)	54 (49.1)	50 (45.5)	0.685	0.073
Laboratory values					
Leukocyte ($\times 10^9$ /L)	7.80 (5.19, 10.51)	7.75 (5.39, 10.50)	7.81 (5.11, 10.47)	0.697	0.034
Lymphocyte ($\times 10^9$ /L)	0.75 (0.55, 1.13)	0.78 (0.54, 1.16)	0.75 (0.55, 1.07)	0.794	0.015
Platelet ($\times 10^9$ /L)	206 (145, 254)	210 (151, 254)	194 (144, 255)	0.400	0.023
Serum creatinine (μmol/L)	72.8 (57.4, 89.4)	72.8 (58.6, 84.6)	72.5 (54.7, 92.0)	0.907	0.072
ALT (U/L)	28 (18, 49)	30 (17, 46)	28 (19, 53)	0.806	0.012
TBIL (U/L)	11.95 (9.00, 17.20)	11.55 (9.12, 16.47)	12.30 (9.00, 18.35)	0.314	0.026
Serum Albumin (g/L)	30.3 (27.7, 32.7)	30.1 (27.9, 32.7)	30.6 (27.5, 32.7)	0.708	0.014
D-dimer (μg/mL)	1.48 (0.72, 4.28)	1.75 (0.80, 5.00)	1.29 (0.65, 3.28)	0.121	0.068
Clinical outcomes					
28-day mortality, n (%)	86 (39.1)	50 (45.5)	36 (32.7)	0.072	0.263
In-hospital mortality, n (%)	90 (40.9)	51 (46.4)	39 (35.5)	0.131	0.223
Hospital length of stay (d)	16 (11, 25)	18 (11, 25)	15 (10, 24)	0.558	0.059

Note: Values are median (IQR) unless stated otherwise.
Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; SMD, standard mean difference; CCI, Charlson Comorbidity Index; APACHE, Acute Physiology and Chronic Health Evaluation; ALT, alanine amino transferase; TBIL, total bilirubin. p< 0.05 means had significantly different.

Discussion

This multicenter retrospective cohort study indicated that hypoalbuminemia in severe patients with COVID-19 was significantly associated with poor prognosis. However, early albumin administration did not reduce the 28-day mortality and in-hospital mortality among these patients.

Serum albumin serves as the principal protein responsible for maintaining plasma colloid osmotic pressure and acts as an acute phase reactant with notable anti-inflammatory and antioxidative properties. Hypoalbuminemia is commonly observed in critical illness, serving as an indicator of malnutrition, hepatic and renal dysfunction, as well as poor prognosis. It is associated with increased mortality among seriously ill patients across various chronic and acute diseases.[6,20,21] In patients experiencing severe infections (such as ARDS, sepsis, or viral infections), albumin levels decrease rapidly within a short timeframe during the early acute inflammatory phase, with the extent of this decline correlating directly to disease severity. Similarly, several studies have indicated that low serum albumin levels on admission are quite prevalent in the early stages of COVID-19.[3,11,22–24]

In our study, the prevalence of hypoalbuminemia was approximately 67.7%, which was higher than that reported in other studies.[8,9] This might be attributed to the fact that all patients included in our cohort were critically ill and presented with more severe conditions. This was consistent with other studies showing that low albumin levels were more pronounced in severe cases with COVID-19.[16,25] Hypoalbuminemia in patients with SARS-CoV-2 infection may be associated with multiple mechanisms, such as transcapillary leakage, and the direct cytopathic effect of SARS-CoV-2, etc.[14] Reduction in colloid pressure from hypoalbuminemia might contribute to the deterioration of pulmonary edema in severe patients with COVID-19.[26,27] Whether severe COVID-19 caused hypoalbuminemia or vice versa is unknown.

Hypoalbuminemia has been associated with disease severity and poor outcomes, including sepsis and cirrhosis.[10–14,28] Huang et al confirmed that hypoalbuminemia was an independent predictor of mortality in COVID-19 patients.[22] Additionally, a retrospective study demonstrated that higher albumin levels on admission were associated with better prognosis in COVID-19 patients.[29] Our study found that the mortality of severe COVID-19 patients was significantly correlate with low albumin levels at hospital admission, which aligned with findings from other studies.[8,30,31]

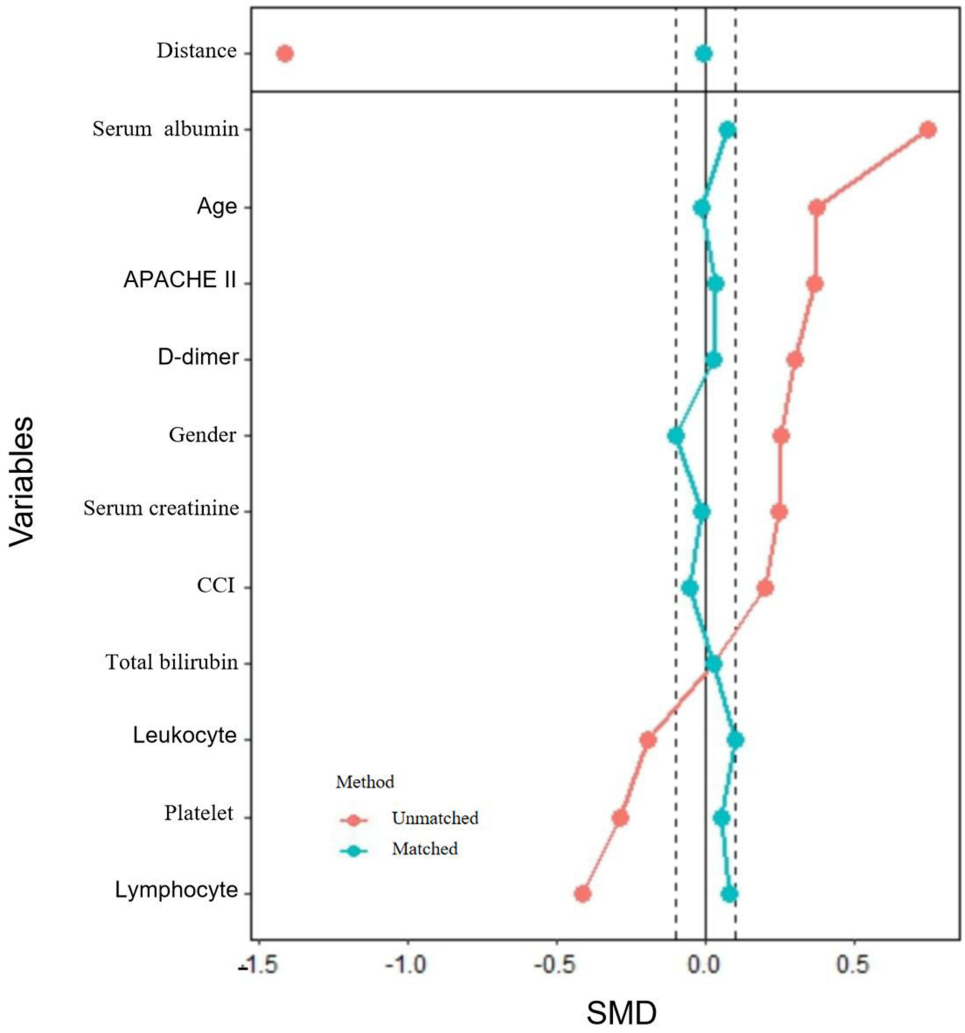

Figure 3 Summaries of the balance of variables before and after propensity score matching.
Abbreviations: SMD, standard mean difference; APACHE, Acute Physiology and Chronic Health Evaluation; CCI, Charlson Comorbidity Index.

Human serum albumin was a critical therapeutic used in the treatment of hypoproteinemia,[32] which was widely used for fluid resuscitation in sepsis and critical illnesses. Previous studies showed that albumin treatment could improve oxygenation and reduce lung injury in ARDS,[33,34] as well as improve the prognosis of other chronic diseases including liver cirrhosis.[35] However, previous studies regarding the correction of albumin in severe sepsis had shown no significant benefit in mortality.[36,37] At present, clinical trials of albumin therapy on the prognosis of severe diseases still have shown inconsistent results.[14,38,39]

A recent study demonstrated that albumin binds to SARS-CoV-2 virions and this process might inhibit the formation of the endothelial glycocalyx by inhibition of albumin transport-binding sites. These authors suggested that albumin therapy should be tested as a matter of urgency in patients presenting with COVID-19 disease.[40] Unfortunately, albumin administration at admission showed no significant improvement in mortality at either 28-day or in-hospital for severe COVID-19 patients in our study, which was not consistent with other researches. A preliminary report conducted on COVID-19 patients[2] showed a significant difference in the number of deaths in albumin-treated group compared with the control group. Recently, Zhang et al[3] demonstrated that the albumin infusion group exhibited significantly longer survival times and shorter hospital stays compared to the control group in COVID-19 ICU patients. Albumin infusion could enhance plasma volume expansion and exhibit significant anti-inflammatory, antioxidative, antiplatelet, and anticoagulant effects.[41] Nevertheless, the sample sizes in these studies were relatively small. Moreover, the cohort receiving albumin administration demonstrated a more severe progression of illness within our study population. Additionally, the dosage of albumin administered in our study was lower (mean daily dose: 20g) compared to the higher dosages utilized in other studies. Ultimately, uncertainties surrounding the timing and frequency of albumin administration

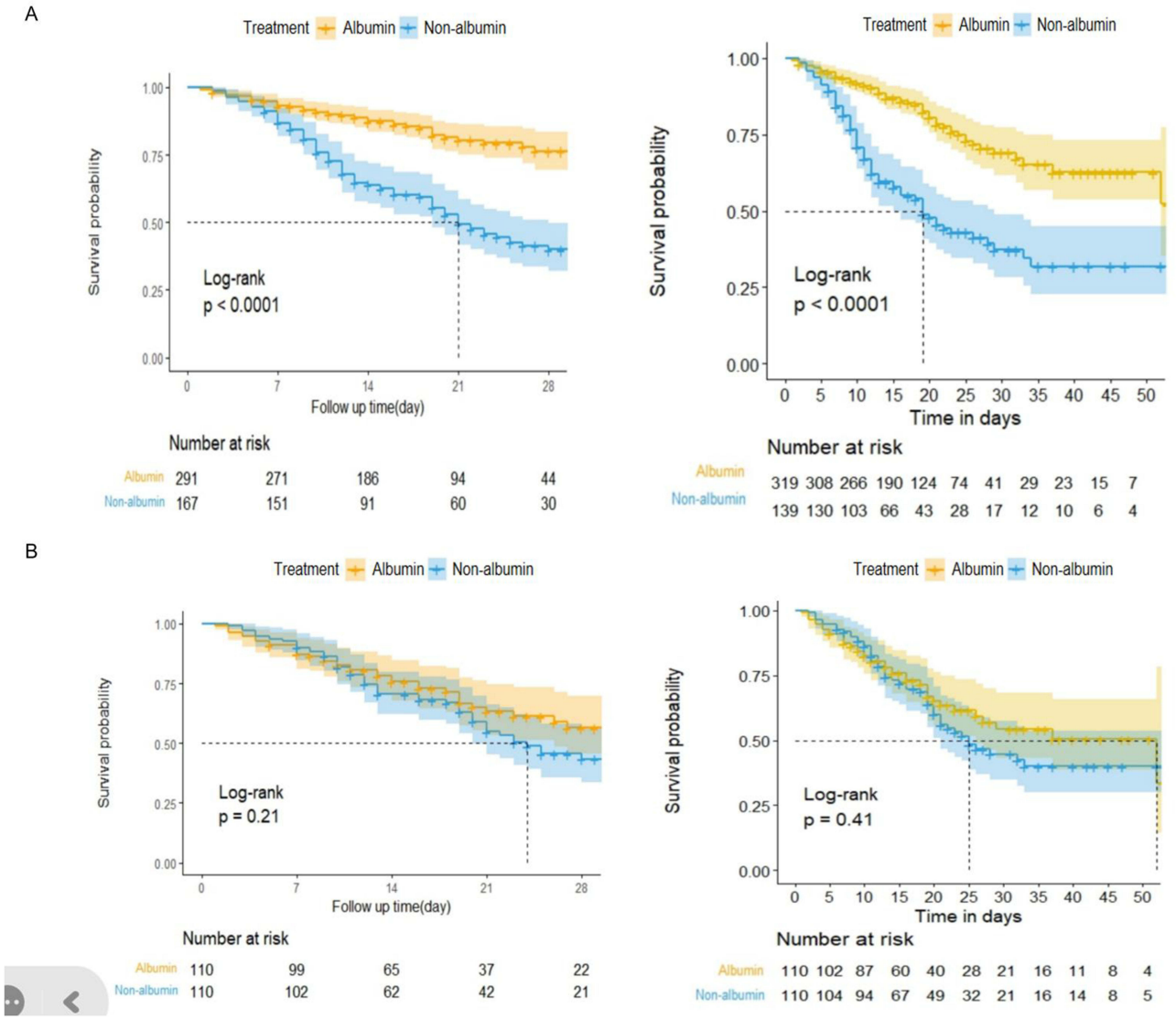

Figure 4 The 28-day and in-hospital survival curves according to albumin administration. Kaplan-Meier survival curves before (**A**) and after propensity-score matching (**B**).

might also impact prognosis. The pathogenesis of COVID-19 was complex, necessitating relevant prospective studies to further assess the beneficial effects of albumin administration.

Limitations

This study had several limitations. First, it was a retrospective multicenter study, and probably had a significant referral bias, recall bias and measurement bias. Besides, as an observational study, its results were subject to unobserved confounding factors. Second, the indices at admission were selected for analysis without dynamic monitoring, and the levels of albumin following administration treatment were not measured. Finally, this study was an exploratory study, and the results might have certain biases, which need to be confirmed by large-scale clinical studies and basic research to explore individualized assessment of risk factors.

Conclusion

In conclusion, hypoalbuminemia was correlated with adverse outcomes in severe COVID-19 patients. However, early albumin administration in the first 7 days at admission did not reduce 28-day mortality and in-hospital mortality in these patients. Further study is warranted to explore the application value of albumin in critically ill COVID-19 patients.

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Data Sharing Statement

All data and materials generated during the current study can be availed by the correspondence author upon reasonable request.

Consent for Participation

The studies involving human participants were reviewed and approved by Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan Infectious Diseases Hospital, Shandong Provincial Chest Hospital, and Binzhou Medical University Hospital. The patients/participants provided their written informed consent to participate in this study.

Consent for Publication

Not applicable because the manuscript lacked the names, identifiers, or images of the patients.

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Disclosure

The authors have declared that they have no conflicts of interest in this work.

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