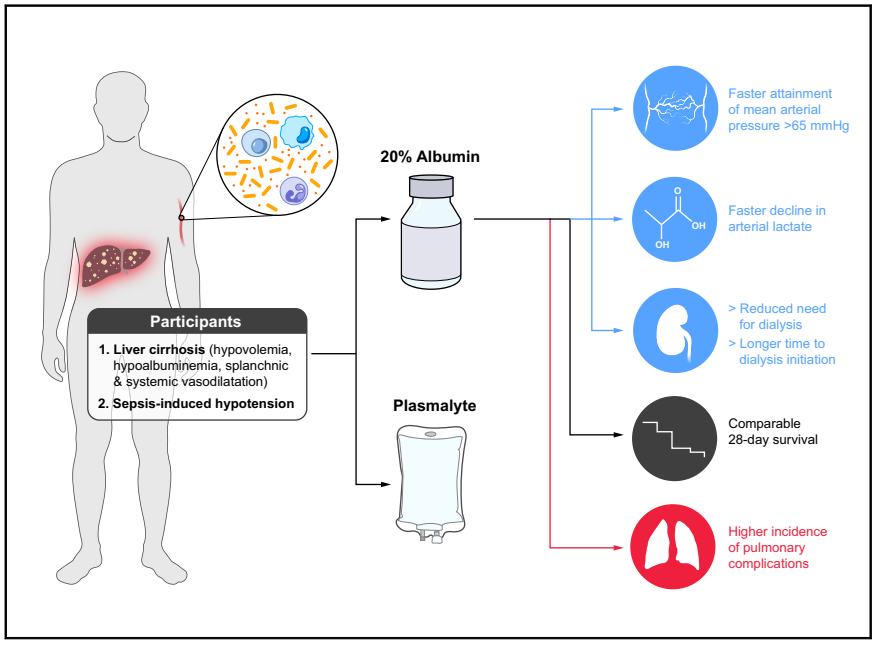
Research Article
Cirrhosis and Liver Failure

JOURNAL
OF HEPATOLOGY

# A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]

## Graphical abstract




## Highlights

- 20% albumin is superior to plasmalyte in reversing sepsis-induced hypotension in critically ill patients with cirrhosis.
- 20% albumin does not provide survival benefit over plasmalyte.
- 20% albumin causes more pulmonary complications than plasmalyte.
- Patients with pneumonia, higher arterial lactate and SOFA score are at higher risk of pulmonary complications after 20% albumin.
- Plasmalyte is a safer fluid for resuscitation of critically ill patients with cirrhosis, pneumonia and lower serum bicarbonate.

## Authors

Rakhi Maiwall, Abhinav Kumar, Samba Siva Rao Pasupuleti, …, Amrish Sahney, Lalita Gouri Mitra, Shiv Kumar Sarin

## Correspondence

sksarin@ilbs.in, shivsarin@gmail.com (S.K. Sarin).

## Lay summary

The current randomized-controlled trial performed in critically ill patients with cirrhosis and sepsis-induced hypotension highlights that 20% albumin restores arterial pressure more quickly but causes more pulmonary complications than plasmalyte. The impact on renal functions was also modest. These effects did not result in improvement in survival at 28 days. Plasmalyte is safer and well-tolerated and can be considered for volume resuscitation in patients with cirrhosis and sepsis-induced hypotension.

https://doi.org/10.1016/j.jhep.2022.03.043
 J. Hepatol. 2022, 77, 670–682

Research Article
Cirrhosis and Liver Failure

JOURNAL OF HEPATOLOGY

# A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]

Rakhi Maiwall[1,#], Abhinav Kumar[1,#], Samba Siva Rao Pasupuleti[2], Ashini Kumar Hidam[5], Harshvardhan Tevethia[1], Guresh Kumar[3], Amrish Sahney[1], Lalita Gouri Mitra[4], Shiv Kumar Sarin[1,*]

[1]*Department of Hepatology, Mizoram University (A Central University), Pachhunga University College Campus, Aizawl, India;* [2]*Department of Statistics, Mizoram University (A Central University), Pachhunga University College Campus, Aizawl, India;* [3]*Department of Biostatistics, Mizoram University (A Central University), Pachhunga University College Campus, Aizawl, India;* [4]*Department of Critical Care and Anaesthesia, Institute of Liver and Biliary Sciences, New Delhi, India;* [5]*Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi, India*

**Background & Aims:** The choice of resuscitation fluid in patients with cirrhosis and sepsis-induced hypotension is unclear. 5% albumin was superior to normal saline in the FRISC study. We compared the efficacy and safety of 20% albumin, which has greater oncotic properties, to plasmalyte in reversing sepsis-induced hypotension.

**Methods:** Critically ill patients with cirrhosis underwent open-label randomization to receive either 20% albumin (0.5-1.0 g/kg over 3 hours; n = 50) or plasmalyte (30 ml/kg over 3 hours, n = 50). The primary endpoint of the study was the attainment of mean arterial pressure (MAP) above 65 mmHg at 3 hours.

**Results:** Baseline characteristics were comparable in albumin and plasmalyte groups; arterial lactate (6.16±3.18 mmol/L *vs.* 6.38± 4.77 mmol/L; $p$ = 0.78), MAP (51.4±6.52 mmHg *vs.* 49.9± 4.45 mmHg; $p$ = 0.17) and SOFA score (10.8±2.96 *vs.* 11.1±4.2; $p$ = 0.68), respectively. Most patients were alcoholics (39%) and had pneumonia (40%). In the intention-to-treat analysis, albumin was superior to plasmalyte in achieving the primary endpoint (62% *vs.* 22%; $p$ <0.001). A faster decline in arterial lactate ($p$ = 0.03), a reduced need for dialysis (48% *vs.* 62%; $p$ = 0.16), and a longer time to initiation of dialysis (in hours) (68.13±47.79 *vs.* 99.7± 63.4; $p$ = 0.06) were seen with albumin. However, the 28-day mortality rate was not different (58% *vs.* 62%, $p$ = 0.57) and treatment had to be discontinued in 11 (22%) patients in the albumin group due to adverse effects compared to no discontinuations in the plasmalyte group.

**Conclusion:** In patients with cirrhosis and sepsis-induced hypotension, 20% albumin leads to a faster improvement in hemodynamics and lactate clearance than plasmalyte, while 28-day survival was similar. However, patients on 20% albumin need to be closely monitored as it was more often associated with pulmonary complications.

**Clinical trial registration:** NCT02721238.

**Lay summary:** The current randomized-controlled trial performed in critically ill patients with cirrhosis and sepsis-induced hypotension highlights that 20% albumin restores arterial pressure more quickly but causes more pulmonary complications than plasmalyte. The impact on renal functions was also modest. These effects did not result in improvement in survival at 28 days. Plasmalyte is safer and well-tolerated and can be considered for volume resuscitation in patients with cirrhosis and sepsis-induced hypotension.



## Introduction

Sepsis is an inflammatory response to severe infection characterized by hypovolemia and vasodilation.[1] It is characterized by organ dysfunction secondary to a dysregulated immune response of the host to the microbial pathogen. Prompt identification, early institution of appropriate antibiotics, and fluid resuscitation can improve patient outcomes.[1] Hypoperfusion is a hallmark in patients with sepsis-induced hypotension seen secondary to the increase in oxygen demand and decrease in oxygen delivery to the peripheral tissues causing organ dysfunction.[2] Early and appropriate fluid resuscitation is crucial for improving patient outcomes in sepsis. Patients with cirrhosis and sepsis are a distinct group.[1] The hemodynamic alterations are more profound in patients with cirrhosis with sepsis compared to those without cirrhosis. The choice of fluid, *i.e.* crystalloid *vs.* colloid and balanced *vs.* non-balanced, is controversial.[3] Patients with advanced cirrhosis have effective hypovolemia, hypoalbuminemia, and splanchnic and systemic vasodilatation. These hemodynamic alterations get exacerbated with sepsis.[1,3] Patients with cirrhosis, in addition, have impaired responsiveness to endogenous and exogenous vasoconstrictors. The resultant arterial pooling of blood increases blood volume in the splanchnic circulation. Reduced central blood volume is responsible for a decreased preload and less than expected cardiac output, which compromises renal perfusion and causes sodium and water retention.[3,4] A proportion of these patients

Keywords: septic shock; dialysis; lactate; AKI; ACLF; critically ill.
*Received 6 September 2021; received in revised form 12 March 2022; accepted 15 March 2022; available online 20 April 2022*
* Corresponding author. Address: Department of Hepatology, Institute of Liver and Biliary Sciences, D1 Vasant Kunj, New Delhi 110070, India; Tel.: +91-11-46300000.
*E-mail addresses:* sksarin@ilbs.in, shivsarin@gmail.com (S.K. Sarin).
[#] Co-first authors with equal contribution.
https://doi.org/10.1016/j.jhep.2022.03.043

also have cirrhotic cardiomyopathy. Albumin is recommended for most indications in patients with advanced cirrhosis. However, the data in the context of sepsis-induced hypotension is sparse.[5,6]

A dynamic equilibrium between the interstitium and lymphatics maintains the intravascular concentration of human serum albumin.[7] Albumin expands the intravascular volume and strengthens the colloid osmotic pressure. It has an additional immunomodulatory action.[7]

Albumin has been shown to improve cardiocirculatory function and reduce proinflammatory cytokine levels in cirrhosis and sepsis.[8] 4% and 5% albumin are isotonic and have been evaluated for fluid resuscitation.[5,9] However, these albumin preparations have a higher concentration of sodium and chloride, and therefore, there are risks of hyperchloremic acidosis when used in large amounts.[10] In a large cohort of 304 patients with sepsis-induced hypotension, we have recently reported the superiority of 5% albumin compared to normal saline in fluid resuscitation.[9] In the Albumin Italian Outcome Sepsis (ALBIOS) study, 20% albumin has been evaluated for volume resuscitation.[11] It has a lower sodium concentration and is supposed to be more balanced. We have reported that increased chloride concentrations lead to worse acute kidney injury (AKI) outcomes in critically ill patients with cirrhosis.[12] Plasmalyte is a family of balanced crystalloid solutions with multiple formulations available worldwide. The advantages of plasmalyte include volume and electrolyte deficit correction while addressing acidosis.[13] It shares the same problems as most other crystalloids fluids, *i.e.* fluid overload, lung edema, and worsening of the intracranial pressure. However, no studies have evaluated its benefits in the context of critically ill patients with cirrhosis. We hypothesized that 20% albumin would be superior to plasmalyte in fluid resuscitation in patients with cirrhosis and sepsis-induced hypotension. We aimed to study the efficacy of 20% albumin *vs.* plasmalyte in reversing sepsis-induced hypotension in critically ill patients with cirrhosis.

## Patients and methods

### Study design

We designed an open-label randomized-controlled trial (RCT) conducted at the emergency department and liver intensive care unit of the Institute of Liver and Biliary Sciences, New Delhi, from December 2016 to November 2018. We registered the study protocol with ClinicalTrial.gov (identifier: NCT02721238). The institutional ethics board approved the study protocol and informed consent documentation and written informed consent by the patient's legally authorized representative/family member was taken. All authors had access to the study data and reviewed and approved the final manuscript.

### Participants

Patients with cirrhosis aged more than 18 years with sepsis-induced hypotension were screened and randomized to receive either 20% human albumin or plasmalyte. Sepsis-induced hypotension was defined as mean arterial pressure (MAP) of less than 65 with suspected (as per history or physical examination) or documented evidence of infection.[9] The diagnosis of cirrhosis was considered based on a combination of clinical, biochemical imaging (ultrasonography, computed tomography, or magnetic resonance imaging) and endoscopic findings or liver biopsy results (when available). The documentation of positive cultures was not the criteria for enrolling patients.

We excluded patients with other causes of hypotension and patients who had already received 2 L of fluid within the first 12 hours of presentation. We excluded patients with structural heart disease, and those on vasopressors or inotropes, maintenance hemodialysis, or those requiring an emergency surgical intervention. We excluded patients with known chronic obstructive lung disease, congestive heart failure, other causes of hypotension, serum albumin below 1.5 g/dl, pregnant or lactating women, and patients with a previous adverse reaction to human albumin.

### Randomization and interventions

One hundred patients with sepsis-induced hypotension were enrolled and randomized in the trial. Group A patients received 20% albumin 0.5-1.0 g/kg over the first 3 hours (n = 50). Group B patients (n = 50) received 30 ml/kg of PlasmaLyte-148 solution over 3 hours. Plasmalyte is a product of Baxter and an isotonic solution. One liter has an ionic concentration of 140 mEq sodium, 5 mEq of potassium, 3 mEq of magnesium with a low chloride level of 98 mEq, 27 mEq acetate, and 23 mEq gluconate; it is physiologically balanced at a pH of 7.4; it is iso-osmolar, with an osmolarity of 294 mOsmol/L.[13] We continued the same fluid in each arm for the next 24 hours. At admission, all patients underwent a detailed history, physical examination, and baseline investigations to identify the cause of sepsis. The clinical trial coordinator performed block randomization with a block size of 10 with 5 blocks. We performed allocation concealment by sequentially numbered opaque sealed envelopes. The clinical trial coordinator provided the envelopes.

### Primary and secondary outcomes

The primary outcome was to compare the efficacy of using 20% human albumin *vs.* plasmalyte for fluid resuscitation to attain MAP above 65 mmHg at 3 hours after the intervention. The secondary outcomes were to study the effects of fluid resuscitation on lactate clearance, renal replacement therapy (RRT) requirement, duration of ICU stay, time spent on mechanical ventilation, and 28-day mortality.

### Monitoring and study definitions

We monitored the MAP hourly until the reversal of shock. We defined the reversal of shock as a sustained increase in MAP above 65 mmHg without the use of vasopressors. Patients who did not attain MAP >65 mmHg after the 3 hours (or earlier as required) were initiated on vasopressors. Norepinephrine was commenced at a rate of 7.5 μg/min and gradually increased to a maximum dose of 60 μg/min. The patients unable to maintain a MAP of more than 65 mmHg despite the highest amount of the single vasopressor were assigned to salvage therapy. The salvage therapy included a combination of norepinephrine with another vasopressor (either terlipressin or vasopressin) and low dose hydrocortisone. We continued the same fluid in each group for 24 hours. In maintenance doses, we continued 20% albumin in group A and plasmalyte in group B. We recorded the cumulative fluid administered in both groups. We administered the antibiotics on an empirical basis per our institute's microbiological epidemiology. We revised the antibiotics if necessary, based on culture positivity. We considered enteral or parenteral nutrition depending upon tolerance. We

provided anti-coma measures for hepatic encephalopathy and RRT for standard renal indications. These included metabolic acidosis, fluid overload, hyperkalemia, and advanced uremia. We performed prolonged (over 8-10 hours) sustained low-efficiency dialysis (SLED). SLED was delivered using the dialysis machines (Fresenius, 4008S, Dialyser F6 HPS). SLED sessions were targeted to 8-10 hours in duration with blood and dialysate flows of 150-200 ml/min and 300 ml/min, respectively. The minimum frequency of SLED treatments was 3 times per week. We performed continuous RRT (CRRT) for renal indications in hemodynamically unstable patients. CRRT was administered by the nephrologists as continuous venovenous hemodiafiltration using Prisma and Prismaflex (Gambro) devices, with blood flows ranging from 150–180 ml/hour and target effluent rates of 20–25 ml/kg/hour. We did not use anticoagulation during dialysis.

We recorded the time to initiation of RRT for both groups. We measured arterial lactate at 0 hours, and 3, 6, 12, 24 and 48 hours post-intervention, lactate clearance were calculated as ([lactate initial – lactate delayed]/[lactate initial] x 100%).

### Sample-size calculation

In the diseased state, such as seen with severe sepsis, it has been suggested that the plasma volume increment that is seen with 20% human albumin is close to 5 times the plasmalyte administration in equivalence of 30 ml/kg. Also, albumin stays in the intravascular compartment for 2-3 hours after bolus administration in contrast to crystalloids that are immediately taken up into the extravascular compartment. Hence, we designed the current trial as a superiority trial to evaluate the efficacy of 20% albumin compared to plasmalyte solution with respect to improvement in sepsis-induced hypotension. In the absence of preliminary data on plasmalyte, we assumed a 60% efficacy with plasmalyte and 85% with 20% human albumin, with an alpha of 5%, and power of 90%; we needed to enroll 90 cases with 45 cases in each arm. However, with 10% attrition rates, we decided to enroll 50 patients in each group.

### Statistical methods

We analyzed the continuous variables using independent sample Student's *t* test or Mann-Whitney *U* test, depending upon whether normality assumptions hold or not. We analyzed the categorical variables using Fischer's Exact-test or the Chi-square test. We applied repeated measure analysis to see the change over the period using two-way ANOVA followed by *post hoc* comparison by the Bonferroni method. As a part of using repeated measures ANOVA, Mauchly's test of sphericity was used to test the validity of sphericity assumption, *i.e.* whether variances of the differences between all combinations of related groups or levels are the same or not. If the assumption of sphericity was violated then we used multivariate ANOVA-related results from SPSS output or we used within-subject effects table results from our SPSS output. We performed the paired comparison of categorical variables by the McNemar test and intention-to-treat analysis, and per-protocol analysis. We used the log-rank test to compare the Kaplan-Meier survival curves. All tests were 2-tailed, and $p$ <0.05 was considered significant. We performed the statistical analysis using the statistical package for social sciences (IBM corp Ltd. Armonk, NY version 22.0), and SAS university edition.

## Results

From October 2016 to January 2018, 319 patients with hypotension were screened from the emergency department, of whom 100 patients were randomized to either 20% albumin or plasmalyte (Fig. 1). The baseline characteristics of the patients randomized into 2 groups were comparable (Table 1).

The most common infection was pneumonia. Of all patients, 58% had culture-positive infections, and 16% had infections at more than 1 site. These infections were due to gram-negative bacteria in 89.3%, and gram-positive infections in 7.1% The organisms included Enterobacteriaceae, *i.e. Escherichia coli* in 6 (10%); *Klebsiella pneumonia* in 25 (43%); *Acinetobacter baumannii* in 12 (21%); *Pseudomonas aeruginosa* in 3 (5%), *Stenotrophomonas maltophila* in 1 (2 %). The gram-positive organisms included vancomycin-resistant enterococcus in 2 (3%), methicillin-resistant *Staphylococcus aureus* in 1 (2%) and *Streptococcus pneumoniae* in 1 (2%). We observed fungal infections in 6 (3.6%) patients.

The mean baseline arterial lactate (6.16 ± 3.18 mmol/L *vs.* 6.38 ± 4.77 mmol/L; $p$ = 0.78), MAP (51.4 ± 6.52 mmHg *vs.* 49.88 ± 4.45 mmHg; $p$ = 0.78) and sequential organ failure assessment (SOFA) scores (10.8 ± 2.96 *vs.* 11.10±4.21; $p$ = 0.68) were comparable in albumin *vs.* plasmalyte groups, respectively. The most common etiology of cirrhosis was alcohol in 39%, and the commonest type of sepsis was pneumonia in 40%.

### Primary outcome

The reversal of hypotension without initiation of vasopressors was significantly different in the albumin compared to the plasmalyte group at 3 hours (31 [62%] *vs.* 11 [22%]; $p$ <0.001) and 6 hours (33 [66%] *vs.* 14 [28%]; $p$ <0.001). However, the reversal in shock was similar at 48 hours (40 [80%] *vs.* 36 [72%]; $p$ = 0.35). The MAP was maintained in both groups by use of vasopressors. The dose of norepinephrine was significantly higher in the plasmalyte compared to the albumin group at 3 hours ($p$ <0.001), 6 hours ($p$ = 0.004), and 12 hours ($p$ = 0.046). The dose was similar in both the groups at 24 hours ($p$ = 0.44) and 48 hours ($p$ = 0.36). The dose of vasopressin or terlipressin modified as norepinephrine equivalents was not different between the groups (Tables 2, 3).

### Secondary outcomes

*Arterial lactate and lactate clearance*

The arterial lactate level decreased significantly faster in the albumin group than in the plasmalyte group. At enrolment, the arterial lactate was higher in both groups. We observed a significant decrease in lactate levels in both groups with treatment. However, the decline was significantly different and more rapid in the albumin compared to the plasmalyte group ($p$ = 0.027). Arterial lactate levels were significantly different between the 2 groups at each time point (Tables 2, 3 and Fig. 2).

*28-day mortality*

The mortality in both groups was not significantly different. A total of 31 (62%) patients in the plasmalyte group died while a similar proportion of patients, 29 (58%), died in the albumin group. The difference in mortality was insignificant at 28 days (log-rank; $p$ = 0.57) (Fig. 3). The early deaths on day 7 were also not significantly different between the 2 groups (albumin *vs.* plasmalyte): 19 (38%) *vs.* 14 (28%) ($p$ = 0.29). When we analyzed

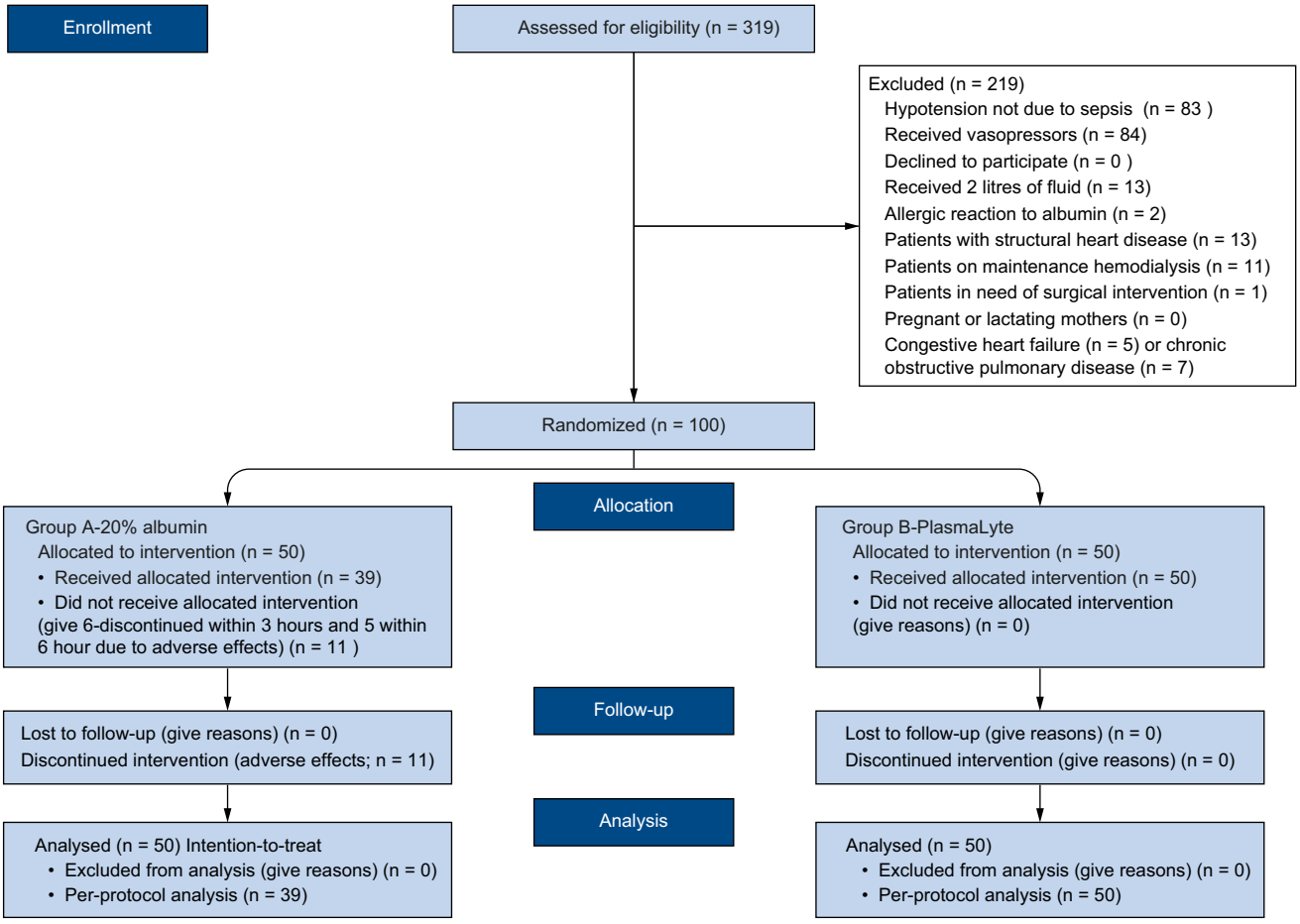



**Fig. 1. Consort diagram.**

the cause of death, the proportion of deaths due to multi-organ failure and septic shock were the same between the albumin and plasmalyte groups (0.52 *vs.* 0.48; $p = 0.69$) and (0.06 *vs.* 0.14; $p = 0.18$), respectively.

*Renal replacement therapy*

Even though patients in the plasmalyte group more frequently required dialysis compared to those in the albumin group, this was not significantly different (62% *vs.* 48%, respectively; $p = 0.16$). Dialysis was initiated earlier in the plasmalyte group than the albumin group ($p = 0.06$) (Table 3). Most patients underwent SLED, 53 (96.3%), while only 2 (3.7%) patients in the albumin group underwent CRRT.

*Mechanical ventilation, length of the hospital, and ICU stay*

By day 1 after study initiation, 18 (36%) *vs.* 23 (46%) patients ($p = 0.31$) required mechanical ventilation in the plasmacyte *vs.* albumin groups, respectively, of whom 4 patients in the albumin group *vs.* none in the plasmalyte group required non-invasive ventilation. Finally, 26 (42%) *vs.* 30 (60%) patients in the plasmalyte *vs.* albumin groups needed mechanical ventilation, respectively ($p = 0.42$). The ICU and hospital stay durations were not different between the 2 groups.

*Adverse effects*

The most feared side effect of albumin transfusion in patients with septic shock is the risk of volume overload. We observed a significant decline in the partial pressure of oxygen and fraction of inspired oxygen ($PaO_2/FiO_2$) ratio in the albumin group compared to the plasmalyte group (Table 3). The increase in the central venous pressure and inferior vena cava (IVC) diameter was also higher in the albumin compared to plasmalyte group. We had to discontinue albumin in a total of 11 (22%) patients. Six (55%) patients developed adverse effects at 3 hours while 5 (45%) patients did at 6 hours. We noted a concomitant increase in the partial pressure of carbon dioxide levels in albumin group (Table 3). The main side effects of albumin were pulmonary edema in 6 (12%) patients, 1 patient had an allergic reaction with rashes and bronchospasm, 6 (12%) patients had bronchospasm and wheeze, and rebound hypertension in 2 (4%) patients. At the same time, the plasmalyte was safer with few adverse effects. There were no protocol violations in the plasmalyte group even though some patients experienced a decline in pulmonary

**Table 1. Baseline characteristics between 20% albumin and plasmalyte group.**

| Variables | 20% Albumin (n = 50) | Plasmalyte (n = 50) | *p* value |
|---|---|---|---|
| Age (years) | 50.58 ± 9.87 | 47.28 ± 11.29 | 0.12 |
| Male sex | 44 (88) | 44 (88) | 0.10 |
| Etiology of cirrhosis | | | |
| Alcohol | 20 (40) | 19 (38) | 0.62 |
| Non-alcoholic steatohepatitis | 16 (32) | 14 (28) | |
| Hepatitis B | 5 (10) | 6 (12) | |
| Hepatitis C | 7 (14) | 8 (16) | |
| Autoimmune or cholestatic disorders | 1 (2) | 2 (4) | |
| Other etiologies | 1 (2) | 1 (2) | |
| **Physiological parameters** | | | |
| Temperature (Fahrenheit) | 99.67 ± 1.00 | 99.43 ± 0.81 | 0.20 |
| Respiratory rate (per minute) | 23.08±2.43 | 22.62±2.66 | 0.37 |
| Mean arterial pressure (mmHg) | 51.40 ± 6.52 | 49.88 ± 4.45 | 0.17 |
| Fraction of inspired oxygen | 29.82 ± 5.75 | 32.06 ± 9.11 | 0.14 |
| Heart rate (per minute) | 107.52 ±11.00 | 110.56± 12.54 | 0.20 |
| Central venous pressure (cm of $H_2O$) | 9.70 ± 1.11 | 9.90 ± 1.13 | 0.37 |
| Inferior vena cava diameter (mm) | 14.20 ± 1.70 | 13.96 ± 1.23 | 0.42 |
| **Arterial blood gas parameters** | | | |
| pH | 7.36 ± 0.15 | 7.34 ± 0.09 | 0.16 |
| Arterial lactate (mmol/L) | 6.16 ± 3.19 | 6.38 ± 4.77 | 0.78 |
| Serum bicarbonate (mEq/L) | 14.16 ± 3.95 | 15.66 ± 3.91 | 0.06 |
| Partial pressure of oxygen (mmHg) | 94.80 ± 13.65 | 93.88± 19.99 | 0.79 |
| Partial pressure of carbon dioxide (mmHg) | 26.22±3.83 | 26.17±3.81 | 0.95 |
| Central venous oxygen saturation ($ScvO_2$) | 74.36 ± 7.65 | 76.96 ± 4.11 | 0.26 |
| $PaO_2$:$FiO_2$ | 352.3±78.71. | 328.44±157.95 | 0.89 |
| **Biochemical parameters** | | | |
| Hemoglobin (g/dl) | 7.92 ± 1.47 | 8.29 ± 2.14 | 0.32 |
| Platelet count (x$10^9$/lit) | 78.8 ± 48.22 | 91.02 ± 61.28 | 0.27 |
| Serum creatinine (mg/dl) | 2.08 ± 0.93 | 2.49 ± 1.51 | 0.10 |
| International normalized ratio | 2.46± 0.62 | 2.68 ± 0.92 | 0.17 |
| Serum bilirubin (mg/dl) | 9.50 ± 7.57 | 13.02 ± 10.82 | 0.16 |
| Serum albumin (g/dl) | 2.13±0.49 | 2.26±0.49 | 0.18 |
| **Severity scores** | | | |
| SOFA | 10.80 ± 2.96 | 11.10 ± 4.21 | 0.68 |
| MELD | 29.55±7.23 | 31.84±10.67 | 0.21 |
| Child-Pugh class | | | |
| A | 1 (2) | 1 (2) | 0.23 |
| B | 11 (22) | 5 (10) | |
| C | 38 (76) | 44 (88) | |
| Child-Pugh score | 11.06 ±1.94 | 11.44 ±1.85 | 0.32 |
| **Clinical parameters** | | | |
| Glasgow coma score | 10.24 ± 5.57 | 8.66 ± 4.49 | 0.12 |
| Ascites grade at enrolment* | | | |
| 1 | 14 (28) | 17 (34) | 0.16 |
| 2 | 29 (58) | 19 (38) | |
| 3 | 7 (14) | 14 (28) | |
| Refractory ascites | 5 (10) | 11 (22) | 0.10 |
| Cause of sepsis | | | |
| Pneumonia | 19 (38) | 20 (42) | |
| Spontaneous bacterial peritonitis | 11(22) | 12 (24) | |
| Urinary tract infection | 10 (20) | 12 (24) | |
| Spontaneous bacterial empyema | 2 (4) | 1(2) | |
| Cellulitis | 5 (10) | 3(6) | |
| Others | 3 (4) | 2 (4) | |
| Culture-positive infections | 28 (56) | 30 (60) | 0.69 |
| Site of culture-positive infection (n = 58) | | | |
| Urine | 6 (21.4) | 5 (16.7) | 0.31 |
| Broncho-alveolar lavage | 13 (46.4) | 20 (66.7) | |
| Ascitic fluid | 5 (17.9) | 3 (10.0) | |
| Blood | 3 (10.7) | 0 (0) | |
| Pleural fluid | 0 (0) | 1 (3.3) | |
| Skin and soft tissue | 4 (14.3) | 1 (3.3) | |
| Infection at more than 1 site | 7 (25) | 9 (30) | 0.67 |

(*continued on next page*)

**Table 1.** (*continued*)

| Variables | 20% Albumin (n = 50) | Plasmalyte (n = 50) | *p* value |
|---|---|---|---|
| Type of infection | | | |
| Gram-negative | 25 (89.3) | 25 (83.3) | 0.10 |
| Gram-positive | 2 (7.1) | 0 (0) | |
| Fungal | 1 (3.6) | 5 (16.7) | |

Descriptive statistics for continuous variables are depicted as means ± SD, and for categorical variables as number (percentage). *p* values were given for the comparison between the group of patients in 20% Albumin compared to plasmalyte group. *p* values for categorical variables were calculated using the Chi-square test. *p* values for continuous variables were calculated using the unpaired Student's *t* test.
$FiO_2$, fraction of inspired oxygen; MELD, model for end-stage liver disease; $PCO_2$, partial pressure of carbon dioxide; $PO_2$, partial pressure of oxygen; SOFA, sequential organ failure assessment.
*Ascites grades were defined in accordance with the guidelines proposed by the European Association for Study of the Liver.[27] Grade 1 ascites was defined as mild ascites only detectable by ultrasound; grade 2 ascites as moderate ascites as evident by moderate symmetrical distension of abdomen; grade 3 ascites as large or gross ascites with marked abdominal distension and refractory ascites was defined as ascites that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy.

function. The cumulative fluid volume administered at 24 hours was significantly lower in the 20% albumin group 616.50 ± 586.64 ml *vs.* 3.71 ± 1.55 L in the plasmalyte group ($p$ <0.001).

### Predictors of pulmonary complications in patients with cirrhosis and sepsis-induced hypotension

We performed logistic regression analysis to identify if albumin use was an independent predictor of pulmonary complications in patients with cirrhosis and sepsis-induced hypotension. Patients with a rapid decline in $PaO_2/FiO_2$ ratio at 6 hours requiring either discontinuation of protocol or reduction in the volume of fluid were defined as having a pulmonary complication. There were 22 (44%) patients in the albumin group (of whom 11 required discontinuation of albumin) and 10 (20%) patients in the plasmalyte group (none required discontinuation) who developed pulmonary complications. On univariate analysis, use of albumin (*vs.* plasmalyte), higher arterial lactate, lower serum bicarbonate, pneumonia, lower MAP, and Glasgow coma score, were predictors of worsening lung function after fluid resuscitation. On multivariate analysis, use of albumin (*vs.* plasmalyte) (odds ratio 4.65, 1.44-15.07), pneumonia as the cause of sepsis (odds ratio 5.26, 1.56-17.78) and lower serum bicarbonate (odds ratio 0.89, 0.81-0.96) predicted a higher incidence of pulmonary complications (Table S1).

### Factors predicting adverse effects of 20% albumin

We performed a univariate and multivariate logistic regression analysis in the subgroup of patients in the albumin group (n = 50) to identify factors predicting adverse effects of albumin. Patients with higher arterial lactate levels, serum creatinine, lower bicarbonate, higher model-for-end-stage liver disease (MELD), and SOFA scores had higher incidence of protocol violation due to adverse effects. Apart from this, patients with lower $PaO_2$ and pneumonia had a higher incidence of protocol violation. On multivariate logistic regression, avoiding multicollinearity, higher SOFA score, arterial lactate, lower $PaO_2$, and presence of pneumonia were recognized as independent factors predictive of adverse effects in different models in the albumin group (Tables S2 and S3).

### Per-protocol analysis

No significant difference was observed when the results were reanalyzed based on per-protocol analysis. The reversal of hypotension at 3 and 6 hours was higher in the albumin group compared to the plasmalyte group (23 [59%] *vs.* 11 [22%]; $p$ <0.001 and 25 [64%] *vs.* 14 [28%]; $p$ <0.001, respectively). The 28-day mortality was not significantly different between the 2 groups (albumin 20 [51%] *vs.* plasmalyte 31 [62%]; log-rank $p$ = 0.27). The proportion of deaths due to multi-organ failure and septic shock was not significantly different between the albumin and plasmalyte groups (0.49 *vs.* 0.48; $p$ = 0.95) and (0.03 *vs.* 0.14; $p$ = 0.06), respectively. It was interesting to observe a reduced proportion of patients requiring dialysis in the albumin group compared to the plasmalyte group (15 (39%) *vs.* 31 (62%); $p$ = 0.03) and also reduced length of stay in the ICU ($p$ = 0.04) (Table 3, Fig. 4).

### Predictors of 28-day mortality

On univariate analysis, arterial pH, bicarbonate levels, arterial lactate, lower MAP, increased diameter of IVC and severity as assessed by MELD and SOFA scores predicted worse outcomes. Shock reversal at 24 and 48 hours and lactate clearance at 48 hours were associated with improved outcomes. On multivariate analysis (Table 4), IVC diameter, shock reversal at 48 hours, and higher SOFA were independent predictors of 28-day mortality. The type of fluid for resuscitation, albumin *vs.* plasmalyte did not impact this outcome (Table 4).

## Discussion

The current RCT performed in critically ill patients with cirrhosis and sepsis-induced hypotension highlights that 20% albumin rapidly restores hemodynamics but causes more pulmonary complications than plasmalyte. The impact on renal functions was also modest. RRT had to be initiated earlier in patients given plasmalyte than patients receiving albumin. However, these effects did not result in an improvement in survival at 28 days. Moreover, rapid infusion of 20% albumin was associated with more frequent pulmonary complications requiring discontinuation in almost 1 in 5 patients. Higher SOFA score, arterial lactate, and patients with pneumonia had significantly higher odds of developing pulmonary complications.

In critically ill patients, limited studies have assessed the optimal choice of fluid. The data from patients without cirrhosis has not shown a consistent benefit of albumin for fluid resuscitation compared to crystalloids in patients with sepsis-induced hypotension.[6] Patients with cirrhosis are distinctly different compared to other populations.[1,3] They more frequently have hypoalbuminemia and severe

**Table 2. Changes in systemic hemodynamics, parameters of microcirculation, biochemical parameters, severity scores and fluid indices between the 2 groups.**

| Variable | 20% albumin (n = 50) | Plasmalyte (n = 50) | *p value | #p value |
|---|---|---|---|---|
| **Parameters of macro and microcirculation** | | | | |
| Mean arterial pressure (mmHg) | 51.40 ± 6.52 | 49.88 ± 4.45 | 0.18 | 0.001 |
| 30 mins | 60.20±5.11 | 58.28±4.55 | 0.05 | |
| 45 mins | 63.98±4.47 | 60.72±3.87 | <0.001 | |
| 1 hour | 65.28±4.10 | 62.58±4.21 | 0.002 | |
| 2 hours | 66.58±3.34 | 66.14±5.60 | 0.63 | |
| 3 hours | 68.04±2.41 | 65.68±4.83 | 0.003 | |
| 6 hours | 69.78±2.92 | 70.04±3.35 | 0.68 | |
| 12 hours | 69.08±11.20 | 71.06±4.49 | 0.25 | |
| 24 hours | 72.87±3.78 | 75.71±5.38 | 0.26 | |
| 48 hours | 73.22±3.38 | 74.28±5.38 | 0.37 | |
| Norepinephrine dose (μg/min) | | | | <0.001 |
| 30 mins | 0.00 (0.00) | 0.16±1.13 | 0.32 | |
| 45 mins | 0.20±0.61 | 0.72±1.60 | 0.03 | |
| 1 hour | 0.40±0.90 | 1.96±2.30 | <0.001 | |
| 2 hours | 0.60±1.36 | 2.96±2.33 | <0.001 | |
| 3 hours | 0.64±1.78 | 3.06±2.82 | <0.001 | |
| 6 hours | 1.72±3.16 | 4.08±4.70 | 0.004 | |
| 12 hours | 2.00±3.43 | 3.58±4.35 | 0.047 | |
| 24 hours | 1.60±3.48 | 2.12±3.22 | 0.44 | |
| 48 hours | 1.62±3.77 | 1.04±2.32 | 0.36 | |
| Vasopressin/terlipressin (asnorepinephrine equivalents μg/min) | | | | |
| 30 mins | 0.00±0.00 | 0.02±0.17 | 0.32 | 0.029 |
| 45 mins | 0.00±0.00 | 0.05±0.34 | 0.32 | |
| 1 hour | 0.17±0.58 | 0.05±0.34 | 0.21 | |
| 2 hours | 0.17±0.58 | 0.16±0.57 | 0.96 | |
| 3 hours | 0.19±0.59 | 0.41±0.78 | 0.12 | |
| 6 hours | 0.52±0.86 | 0.59±0.89 | 0.69 | |
| 12 hours | 1.15±1.73 | 0.85±0.99 | 0.29 | |
| 24 hours | 0.58±0.92 | 0.52±0.92 | 0.75 | |
| 48 hours | 0.53±0.85 | 0.53±0.97 | 0.99 | |
| Arterial lactate (mmol/L) | | | | |
| 0 hour | 6.16 ± 3.19 | 6.38±4.77 | 0.79 | <0.001 |
| 1 hour | 4.28±2.54 | 5.56±3.95 | 0.06 | |
| 3 hours | 2.90±1.60 | 4.90±3.72 | <0.001 | |
| 6 hours | 2.47±1.99 | 4.20±3.33 | 0.002 | |
| 12 hours | 2.34±2.07 | 3.84±3.46 | 0.01 | |
| 24 hours | 2.04±1.53 | 3.23±3.36 | 0.03 | |
| 48 hours | 1.85±1.68 | 3.04±3.33 | 0.03 | |
| **Fluid indices and oxygenation** | | | | |
| $PaO_2/FiO_2$ ratio | | | | |
| 0 hours | 352.30±78.71 | 328.44±157.95 | 0.34 | <0.001 |
| 1 hour | 323.75±93.75 | 290.40±91.15 | 0.07 | |
| 3 hours | 271.08±101.61 | 297.38±95.46 | 0.19 | |
| 6 hours | 294.22±140.44 | 298.20±105.48 | 0.87 | |
| 12 hours | 288.46±124.11 | 303.06±104.81 | 0.53 | |
| 24 hours | 322.40±123.41 | 282.48±84.16 | 0.06 | |
| 48 hours | 295.68±103.51 | 302.10±104.02 | 0.76 | |
| $PaCO_2$ — mmHg | | | | <0.001 |
| 0 hours | 26.22±3.83 | 26.17±3.80 | 0.95 | |
| 3 hours | 29.26 ± 4.73 | 26.85±3.46 | 0.004 | |
| 6 hours | 32.78±6.39 | 27.39±3.83 | <0.001 | |
| 12 hours | 32.57±6.53 | 29.38±5.09 | 0.008 | |
| 24 hours | 31.31±5.57 | 30.16±6.51 | 0.35 | |
| 48 hours | 29.46±6.10 | 30.93±7.14 | 0.27 | |
| Central venous pressure (cm $H_2O$) | | | | 0.1 |
| 0 hours | 9.70 ± 1.11 | 9.90 ± 1.13 | 0.37 | |
| 3 hours | 12.48±2.51 | 11.30±2.53 | 0.02 | |
| 6 hours | 12.72±2.89 | 11.50±2.53 | 0.03 | |
| 12 hours | 15.20±2.44 | 14.08±2.70 | 0.03 | |
| 24 hours | 17.00±3.86 | 15.32±3.82 | 0.03 | |
| 48 hours | 17.48±4.33 | 15.92±3.81 | 0.06 | |
| Inferior vena cava diameter (mm) | | | | <0.001 |
| 1 hour | 14.20±1.70 | 13.96±1.23 | 0.42 | |
| 3 hours | 18.20±4.53 | 14.92±1.71 | <0.001 | |
| 6 hours | 18.94±3.78 | 16.04±2.08 | <0.001 | |

(*continued on next page*)

**Table 2.** (*continued*)

| Variable | 20% albumin (n = 50) | Plasmalyte (n = 50) | *p value | #p value |
|---|---|---|---|---|
| 12 hours | 19.14±3.34 | 17.08±3.19 | 0.002 | |
| 24 hours | 20.14±3.31 | 17.76±3.86 | 0.001 | |
| 48 hours | 19.06±2.38 | 17.26±2.87 | <0.001 | |
| Arterial pH | | | | <0.001 |
| 0 hour | 7.36±0.15 | 7.33±0.09 | 0.16 | |
| 3 hours | 7.33±0.07 | 7.37±0.14 | 0.05 | |
| 6 hours | 7.35±0.06 | 7.36±0.06 | 0.51 | |
| 12 hours | 7.36±0.05 | 7.38±0.05 | 0.04 | |
| 24 hours | 7.39±0.03 | 7.39±0.04 | 0.73 | |
| 48 hours | 7.41±0.03 | 7.39±0.08 | 0.11 | |
| Volume of fluid (in ml) | | | | <0.001 |
| 30 mins | 72.00±89.31 | 437.00±251.28 | <0.001 | |
| 45 mins | 64.00±69.28 | 366.00±163.96 | <0.001 | |
| 1 hour | 55.80±30.78 | 366.56±204.53 | <0.001 | |
| 2 hours | 59.40±27.93 | 326.20±193.68 | <0.001 | |
| 3 hours | 34.40±21.18 | 191.20±164.94 | <0.001 | |
| 6 hours | 20.70±16.81 | 109.30±61.79 | <0.001 | |
| 12 hours | 85.90±129.66 | 665.10±480.34 | <0.001 | |
| 24 hours | 101.50±182.91 | 457.80±506.40 | <0.001 | |
| 48 hours | 87.70±159.15 | 243.90±373.85 | 0.008 | |
| **Biochemical parameters** | | | | |
| Hemoglobin (g/dl) | | | | |
| Day 1 | 7.92±1.47 | 8.29±2.14 | 0.32 | |
| Day 2 | 8.37±1.05 | 8.51±1.03 | 0.52 | |
| Day 3 | 8.43±1.24 | 8.60±0.96 | 0.43 | |
| Day 4 | 8.44±0.82 | 8.76±0.88 | 0.07 | 0.481 |
| Day 5 | 8.40±0.73 | 8.65±0.95 | 0.14 | |
| Day 6 | 8.41±0.69 | 8.71±0.90 | 0.06 | |
| Day 7 | 8.44±0.84 | 8.61±0.97 | 0.35 | |
| Platelet count ($x10^3$) | | | | |
| Day 1 | 78.88±48.22 | 91.02±61.28 | 0.27 | |
| Day 2 | 72.36±43.50 | 91.28±61.93 | 0.08 | |
| Day 3 | 73.58±46.57 | 87.18±58.62 | 0.20 | 0.029 |
| Day 4 | 76.10±45.67 | 70.36±46.64 | 0.54 | |
| Day 5 | 76.30±46.77 | 70.46±55.33 | 0.57 | |
| Day 6 | 75.10±47.07 | 66.42±43.62 | 0.34 | |
| Day 7 | 78.64±44.59 | 69.32±41.98 | 0.28 | |
| Total bilirubin (mg/dl) | | | | 0.149 |
| Day 1 | 9.50±7.57 | 13.02±10.82 | 0.062 | |
| Day 2 | 10.14±8.40 | 12.14±10.15 | 0.29 | |
| Day 3 | 10.40±8.78 | 13.64±11.14 | 0.11 | |
| Day 4 | 10.65±9.29 | 14.60±12.02 | 0.07 | |
| Day 5 | 11.00±9.41 | 15.10±12.15 | 0.06 | |
| Day 6 | 10.88±9.94 | 14.85±12.57 | 0.08 | |
| Day 7 | 11.01±9.91 | 15.11±12.51 | 0.07 | |
| International normalized ratio | | | | |
| Day 1 | 2.46±0.62 | 2.68±0.92 | 0.17 | 0.0196 |
| Day 2 | 2.63±1.08 | 2.86±1.21 | 0.33 | |
| Day 3 | 2.34±1.02 | 3.14±1.34 | 0.001 | |
| Day 4 | 2.39±1.04 | 2.83±1.23 | 0.06 | |
| Day 5 | 2.41±1.12 | 2.94±1.43 | 0.04 | |
| Day 6 | 2.37±1.06 | 2.91±1.27 | 0.02 | |
| Day 7 | 2.58±1.12 | 3.02±1.41 | 0.08 | |
| Serum creatinine (mg/dl) | | | | |
| Day 1 | 1.79 ± 1.04 | 2.29 ± 1.63 | 0.07 | |
| Day 2 | 2.01±1.2 | 1.74±1.24 | 0.39 | 0.78 |
| Day 3 | 1.82±0.86 | 1.91±1.20 | 0.73 | |
| Day 4 | 1.54±0.69 | 1.91±1.11 | 0.12 | |
| Day 5 | 1.44±0.97 | 1.45±0.91 | 0.99 | |
| Day 6 | 1.57±1.22 | 1.59±1.09 | 0.95 | |
| Day 7 | 1.33±0.92 | 1.55±1.26 | 0.45 | |
| Serum albumin (g/dl) | | | | |
| Day 1 | 2.13±0.49 | 2.26±0.49 | 0.18 | 0.054 |
| Day 2 | 2.38±0.45 | 2.44±0.46 | 0.53 | |
| Day 3 | 2.45±0.54 | 2.63±0.55 | 0.11 | |
| Day 4 | 2.47±0.56 | 2.65±0.61 | 0.15 | |

(*continued on next page*)

**Table 2.** (*continued*)

| Variable | 20% albumin (n = 50) | Plasmalyte (n = 50) | *p value | #p value |
|---|---|---|---|---|
| Day 5 | 2.51±0.57 | 2.65±0.61 | 0.24 | |
| Day 6 | 2.52±0.57 | 2.77±0.67 | 0.046 | |
| Day 7 | 2.54±0.56 | 2.74±0.66 | 0.12 | |
| **Severity scores** | | | | |
| SOFA score | | | | 0.052 |
| Day 1 | 10.80 ± 2.96 | 11.10 ± 4.21 | 0.68 | |
| Day 2 | 11.58 ±6.80 | 12.60 ±7.55 | 0.48 | |
| Day 3 | 12.02 ± 6.63 | 11.70 ±7.23 | 0.82 | |
| Day 4 | 10.76 ±6.32 | 12.01 ±7.22 | 0.36 | |
| Day 5 | 11.08 ± 6.52 | 12.22 ±7.55 | 0.42 | |
| Day 6 | 10.60 ± 6.43 | 11.92 ±7.41 | 0.34 | |
| Day 7 | 12.22 ± 7.82 | 12.72 ±8.09 | 0.75 | |

Descreptive statistics are presented as means ±SD. *$p$ values were given for the comparison between the 2 groups (20% albumin *vs.* plasmalyte) at each time point derived from unpaired Student's $t$ test.

$FiO_2$, fraction of inspired oxygen; $PCO_2$, partial pressure of carbon dioxide; $PO_2$, partial pressure of oxygen; SOFA, sequential organ failure assessment.

#$p$ value denotes statistical significance of interaction effect of albumin group and time in influencing the level of the considered parameter (*i.e.*, whether the changes in the considered parameter over time is a matter of albumin group or not), and is obtained using repeated measure analysis.

vasodilatation. The superiority of administering albumin to prevent renal dysfunction in patients with spontaneous bacterial peritonitis (SBP), paracentesis-induced-circulatory dysfunction, and the management of AKI is well-established.[14] However, the data is limited in the context of sepsis-induced hypotension. In an RCT, we demonstrated the superiority of 5% albumin compared to normal saline in improving the parameters of microcirculation, lactate clearance, and MAP in patients with cirrhosis.[9] 5% albumin could be an ideal fluid for resuscitation, but it is non-balanced. It has a higher concentration of sodium and chloride, which predisposes patients to the risk of hyperchloremic acidosis. Hyperchloremia is associated with worsening coagulation and renal dysfunction in critically ill patients with cirrhosis. In a large cohort of critically ill patients with cirrhosis, hyperchloremia is an important determinant of AKI progression.[12] 20% albumin is a more balanced fluid with a markedly lower sodium concentration in the preparation. Similar benefits have been shown for plasmalyte over normal saline for fluid resuscitation. However, albumin has pleiotropic effects on the vascular endothelium, capillary leak, and antioxidant effects. It could theoretically be superior to balanced crystalloids for volume expansion in the context of sepsis-induced hypotension in critically ill patients with cirrhosis.[7] In the current RCT, we observed only temporary benefits of 20% albumin compared to plasmalyte in the reversal of hypotension and lactate clearance. The effects became negligible at 24 hours. The association of arterial lactate and its clearance on clinical outcomes has been well-documented in patients with cirrhosis and septic shock.[15,16] Lactate was cleared in both groups, even though clearance was faster and significantly higher in the 20% albumin group. Lactate clearance at 48 hours and reversal of hypotension were identified as predictors of improved survival. This finding suggests that even though early fluid resuscitation is crucial, mortality is associated with sustained hemodynamic improvement at 48 hours. In the ALBIOS trial, the benefits of resuscitation with intravenous albumin when combined with crystalloids were observed in patients with severe hypoalbuminemia.[11]

Strategies targeting serum albumin have been proposed to improve outcomes in the context of patients with stable decompensated cirrhosis.[17] In the current study, it was interesting that serum albumin levels were not significantly different between the 2 groups and did not predict worse outcomes. This is possible because the effective albumin concentration rather than the serum albumin concentration determines patient outcomes.[18] However, in our study, the dose of albumin was not guided by serum albumin concentration, and we did not measure the effective albumin concentration. The ATTIRE study performed in hospitalized patients with decompensated cirrhosis showed a high incidence of pulmonary complications with albumin, which was dosed targeting the serum albumin concentration in this trial.[19] Albumin also failed to demonstrate an improvement in composite outcome, which included developing renal dysfunction, infections, and mortality. We also observed a high incidence of pulmonary complications in the albumin group, which led to discontinuation in 20% of patients by 6 hours. After albumin administration, the high partial pressure of carbon dioxide may be implicated in hypoventilation driven by hypoxia.[20] In the albumin arm, decreased $PaO_2/FiO_2$ ratio was associated with a concomitant increase in partial pressure of carbon dioxide. In prior studies, albumin could not improve outcomes in patients with cirrhosis and infections other than SBP; rather, a high incidence of pulmonary complications was observed.[21] The majority of patients in our study had non-SBP infections. Pneumonia was the most common cause of infection in the enrolled cohort. Patients with pneumonia may have poor tolerance to albumin given as rapid infusion for fluid resuscitation, possibly because of the impaired alveolo-capillary barrier and leaky capillaries. This may result in albumin extravasation to the interstitial space, worsening pulmonary function.[22] We found the presence of lower partial pressure of oxygen and pneumonia as a risk factor for pulmonary complications. Also, sicker patients with higher MELD, SOFA scores, and arterial lactate more often developed pulmonary complications. Based on our data, these patients should not be given a

**Table 3. Between group comparisons (20% albumin and plasmalyte) with respect to the primary and secondary outcomes in intention-to-treat and per-protocol analysis.**

| | Intention-to-treat analysis | | | Per-protocol analysis | | |
|---|---|---|---|---|---|---|
| **Primary outcome** | **20% albumin (n = 50)** | **Plasmalyte (n = 50)** | ***p* value** | **20% albumin (n = 39)** | **Plasmalyte (n = 50)** | ***p* value** |
| Reversal of hypotension at 3 hours | 31 (62) | 11 (22) | <0.001 | 23 (59) | 11 (22) | <0.001 |
| **Secondary outcomes** | | | | | | |
| Reversal of hypotension | | | | | | |
| 6 hours | 33 (66) | 14 (28) | <0.001 | 25 (64) | 14 (28) | 0.001 |
| 12 hours | 38 (76) | 15 (30) | <0.001 | 30 (77) | 15 (30) | <0.001 |
| 24 hours | 40 (80) | 29 (58) | 0.017 | 32 (82) | 29 (58) | 0.015 |
| 48 hours | 40 (80) | 36 (72) | 0.35 | 32 (82) | 36 (72) | 0.27 |
| Dialysis | | | | | | |
| Need for dialysis at day 7 | 24 (48) | 31 (62) | 0.16 | 15 (38) | 31 (62) | 0.03 |
| Time to initiation of dialysis (in hours) | 97.76± 63.5 | 68.13±47.79 | 0.06 | 84.25±49.19 | 68.13±47.79 | 0.29 |
| Mortality (Log-rank, *p* value) | | | | | | |
| *28-day | 29 (58) | 31 (62) | 0.68 | 20 (51) | 31 (62) | 0.31 |
| Length of stay in the intensive care unit (days) | 5.68±4.93 | 6.76±5.91 | 0.32 | 4.56±3.99 | 6.76±5.91 | 0.049 |
| Duration of hospital stay (days) | 11.46±5.75 | 11.84±6.51 | 0.76 | 7.15±3.84 | 8.84±6.51 | 0.15 |

Descreptive statistics for continuous variables are depicted as means ± SD, and for categorical variables as number (percentage). *p* values are calculated using Chi-square test for categorical variables and independent Student's *t* test for continuous variables. The *p* value for 28-day mortality is derived from Cox-regression analysis. Data has been presented as number (percentage) for categorical variables and mean±SD for continuous variables.

rapid infusion of 20% albumin. This is because most of the complications occurred in the first 6 hours of transfusion. Whether a slow and targeted strategy of albumin delivery could prevent these complications should be evaluated in future studies. We would suggest using IVC diameter, collapsibility, and point of care ultrasound to decide the volume of fluid in these patients.[23–26] We propose future studies comparing 5% albumin to a combination of plasmalyte and slow infusion of 20% albumin in patients with sepsis-induced hypotension.

In the current study, even though RRT incidence was not different in the intention-to-treat analysis between the 2 groups, patients in the plasmalyte group required early initiation of dialysis. Further, on per-protocol analysis, a significantly lower incidence of dialysis was noted in the albumin group. The benefits of albumin for volume expansion in the context of sepsis-related hepatorenal syndrome (HRS-AKI) are known. Albumin ameliorates AKI by improving cardiac function, restoring the preload and combating inflammatory cytokines.[27]

We observed higher SOFA scores, reversal of shock at 48 hours, and IVC diameter as independent predictors of mortality. A mortality benefit was not observed even though albumin caused a faster shock and arterial lactate reversal.

The limitations of our study include the single-center design and lack of data on cardiac pump function. We also chose the effect size based on assumption and did not have any reference to support the hypotheses. This is because of the complete lack of data on plasmalyte and 20% albumin in patients with cirrhosis and septic shock. We had arbitrarily selected the dose of albumin for the study. We measured IVC diameter as a surrogate for right atrial pressure. IVC distensibility correlates with the severity of venous congestion and cardiac filling pressures in critically ill patients.[23–26] IVC also had prognostic implications and was an independent predictor of worse outcomes in our study. Measurements of IVC are an easy and objective tool for guiding fluid management in the emergency department. An intriguing finding was a near-normal value of the diameter of IVC and central venous pressure in the enrolled patients despite them being in shock. These values are consistent with the previously reported data in patients with cirrhosis and ascites. Our study did not measure IVC collapsibility, which is a limitation.[26]

Further, the dosage we chose for either albumin or plasmalyte was not guided by dynamic indices and could have been over or underestimated, which is a limitation. We would also propose a titrated dose based on hemodynamic monitoring for these patients. However, despite these limitations, the current study has many strengths. Managing patients with cirrhosis and septic shock is a real challenge, particularly due to the lack of literature on these patients. In most studies performed in critically ill patients, those with advanced cirrhosis are excluded. Our study, thus, provides robust data on the comparison of albumin with plasmalyte for fluid resuscitation in patients with cirrhosis and sepsis-induced hypotension. We demonstrated the superiority of albumin in achieving a rapid improvement in microcirculation, lactate clearance, and reversal of shock compared to plasmalyte but a higher risk of pulmonary complications. However, there were no differences in improvement in overall clinical outcomes. Whether combining slow albumin infusion with plasmalyte

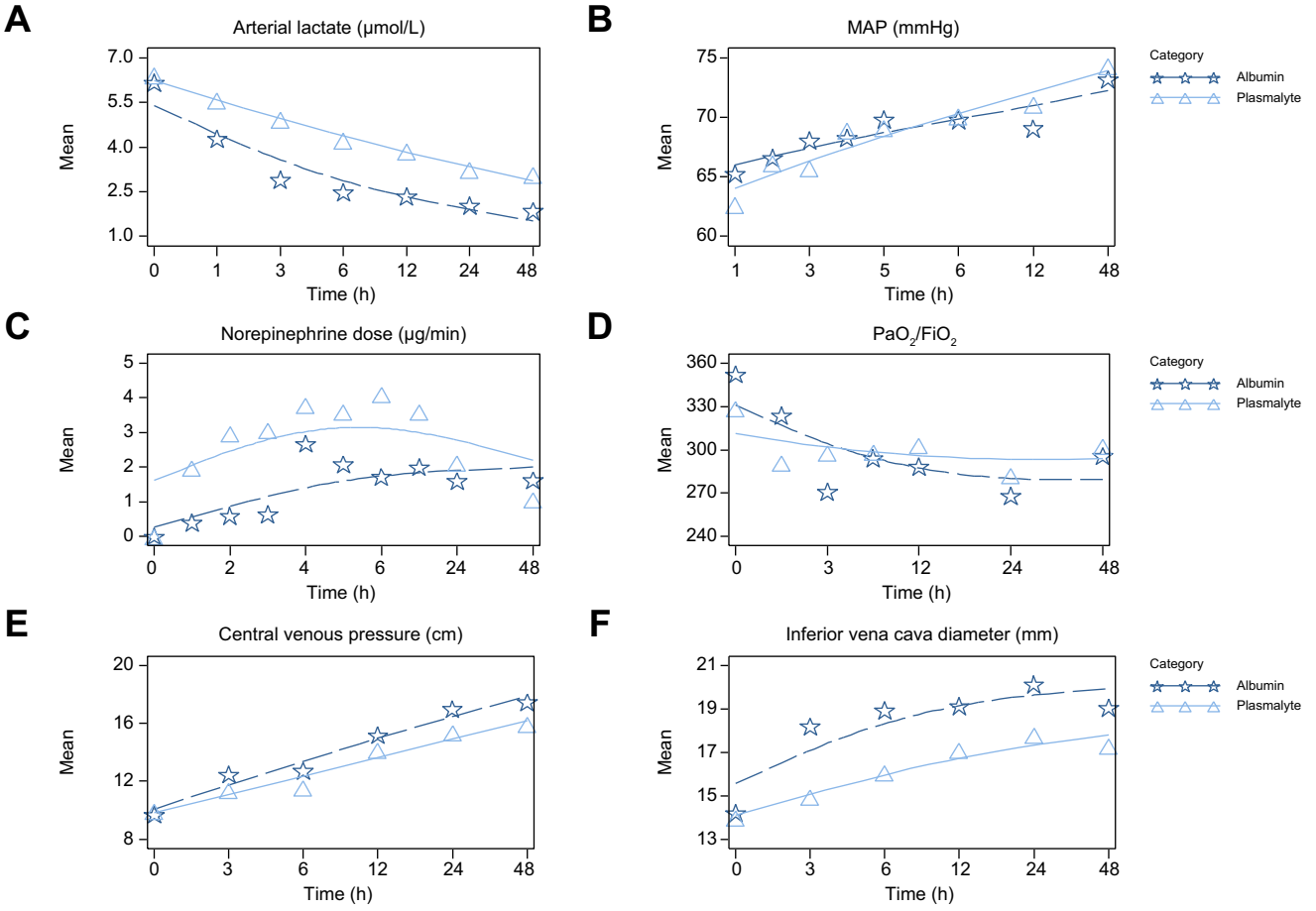
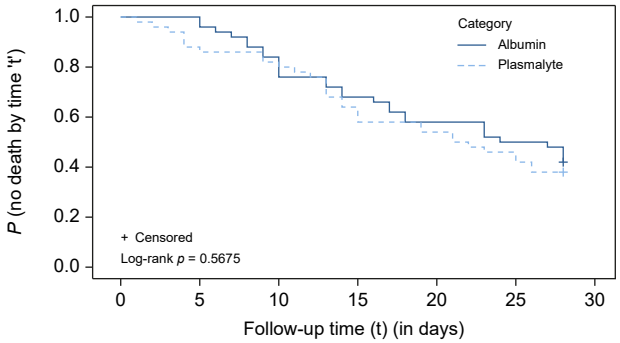


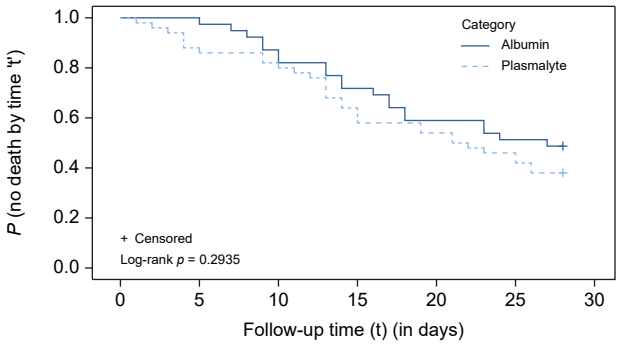

**Fig. 2. Changes in arterial lactate, mean arterial pressure, ratio of partial pressure of oxygen on inspired oxygen, central venous pressure and inferior vena cava diameter between 20% albumin *vs.* plasmalyte group.** The x-axis denotes time in hours after enrolment to the trial and y-axis denoted means of different parameters (A) arterial lactate (µmol/L), (B) MAP (mmHg), (C) Norepinephrine dose (µg/min), (D) $PaO_2/FiO_2$, (E) central venous pressure (cm), (F) inferior vena cava diameter (in mm). MAP, mean arterial pressure; $PaO_2/FiO_s$, partial pressure of oxygen to fractional inspired oxygen. Repeated measures ANOVA is used to test the interaction effect of group (20% albumin *vs.* plasmalyte) and time in influencing the level of the considered parameter (*i.e.*, whether the changes in the considered parameter over time is a matter of the group or not). The results of are presented in the form of *p* value. The significance was observed for arterial lactate ($p < 0.001$), mean arterial pressure ($p = 0.001$), norepinephrine dose ($p < 0.001$), ratio of partial pressure of oxygen on inspired oxygen ($p < 0.001$), and inferior vena cava diameter ($p < 0.001$) but not in case of central venous pressure ($p = 0.1$).




| N° at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Albumin | 50 | 50 | 42 | 34 | 29 | 25 | 0 |
| Plasmalyte | 50 | 44 | 41 | 32 | 27 | 23 | 0 |

| | Subjects | Event | Censored | Median survival | 95% CI |
|---|---|---|---|---|---|
| Albumin | 50 | 29 | 21 | 25.50 | 17 |
| Plasmalyte | 50 | 31 | 19 | 21.50 | 14 |

**Fig. 3. Kaplan-Meier survival curve between 20% albumin and plasmalyte groups on intention-to-treat analysis.** *p* value is derived from the log-rank test for testing the equality of survival curves of the two considered groups (20% albumin *vs.* plasmalyte).




| N° at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Albumin | 39 | 39 | 34 | 28 | 23 | 20 | 0 |
| Plasmalyte | 50 | 44 | 41 | 32 | 27 | 23 | 0 |

| | Subjects | Event | Censored | Median survival | 95% CI |
|---|---|---|---|---|---|
| Albumin | 39 | 20 | 19 | 27 | 17 |
| Plasmalyte | 50 | 31 | 19 | 21.50 | 14 |

**Fig. 4. Kaplan-Meier survival curve between 20% albumin and plasmalyte groups on per-protocol analysis.** *p* value is derived from the log-rank test for testing the equality of survival curves of the two considered groups (20% albumin *vs.* plasmalyte).

**Table 4. Predictors of 28-day mortality – univariate and multivariate cox-regression analysis.**

| Variables | *p* value | Crude HR (95% CI) | Adjusted HR (95% CI) | *p* value |
|---|---|---|---|---|
| Age (years) | 0.58 | 0.99 (0.97-1.02) | | |
| Sex (male) | 0.3 | 1.62 (0.65-4.04) | | |
| Etiology of cirrhosis Ref. category: alcohol | 0.81 | 0.94 (0.55-1.59) | | |
| **Physiological parameters** | | | | |
| Mean arterial pressure (mmHg) | 0.04 | 0.95 (0.91-1) | | |
| Fraction of inspired oxygen | 0.06 | 1.03 (0.99-1.07) | | |
| Heart rate (per minute) | 0.006 | 1.002 (1.001-1.003) | | |
| Respiratory rate (per minute) | <0.001 | 1.18 (1.08-1.3) | | |
| Central venous pressure (cm of $H_2O$) | 0.96 | 1.005 (0.81-1.25) | | |
| Inferior vena cava diameter (in mm) | 0.005 | 1.3 (1.08-1.57) | 1.36 (1.12-1.65) | 0.002 |
| **Arterial blood gas parameters** | | | | |
| pH | 0.01 | 0.04 (0.003-0.47) | 0.55 (0.05-6.66) | 0.64 |
| Arterial lactate (mmol/L) | <0.001 | 1.13 (1.06-1.19) | | |
| Serum bicarbonate (mEq/L) | 0.002 | 0.9 (0.84-0.96) | | |
| Partial pressure of oxygen (mmHg) | 0.78 | 1.002 (0.99-1.02) | | |
| Partial pressure of carbon dioxide (mmHg) | 0.07 | 1.07 (0.99-1.15) | | |
| Central venous oxygen saturation ($ScvO_2$) | 0.04 | 0.94 (0.88-0.99) | | |
| $PaO_2/FiO_2$ (log transformed) | 0.001 | 0.40 (0.23-0.68) | | |
| **Biochemical parameters** | | | | |
| Hemoglobin (g/dl) | 0.9 | 1.01 (0.87-1.17) | | |
| Platelet count ($x10^9$/L) | 0.94 | 1 (0.99-1.005) | | |
| Serum creatinine (mg/dl) | 0.004 | 1.31 (1.09-1.56) | | |
| International normalized ratio | <0.001 | 2.42 (1.73-3.39) | | |
| Serum bilirubin (mg/dl) | <0.001 | 1.06 (1.03-1.09) | | |
| Serum albumin (g/dl) | 0.57 | 0.86 (0.49-1.48) | | |
| Glasgow coma score | <0.001 | 0.89 (0.85-0.94) | | |
| SOFA | 0.005 | 1.12 (1.04-1.22) | 1.12 (1.02-1.22) | 0.012 |
| MELD | <0.001 | 1.08 (1.05-1.11) | | |
| 20% albumin *vs.* plasmalyte | 0.57 | 0.87 (0.52-1.44) | 0.95 (0.55-1.61) | 0.84 |
| Reversal of shock 24 hours | 0.008 | 2.01 (1.2-3.37) | | |
| Reversal of shock 48 hours | <0.001 | 4.21 (2.46-7.19) | 4.38 (2.32-8.25) | <0.001 |
| Lactate clearance at 24 hours | 0.08 | 0.43 (0.16-1.18) | | |
| Lactate clearance at 48 hours | 0.03 | 0.36(0.14-0.92) | 0.95 (0.29-3.10) | 0.94 |

$FiO_2$, fraction of inspired oxygen; MELD, model for end-stage liver disease; $PCO_2$, partial pressure of carbon dioxide; $PO_2$, partial pressure of oxygen; SOFA, sequential organ failure assessment.
*p* values were derived from the Cox-regression analysis. Variables were chosen in the models avoiding multicollinearity. Considering 60 deaths, we considered 6 variables for multivariate analysis, we included pH, SOFA score, treatment group albumin *vs.* plasmalyte, lactate clearance at 48 hours, reversal of shock at 48 hours and inferior vena cava diameter.

would be a better strategy should be investigated in future RCTs. We also propose evaluating the role of 20% albumin compared to plasmalyte in the resuscitation of patients with SBP and shock in future studies.

### Abbreviations

ALBIOS, Albumin Italian Outcome Sepsis; AKI, acute kidney injury; CRRT, continuous RRT; HRS-AKI, hepatorenal syndrome-acute kidney injury; ICU, intensive care unit; IVC, inferior vena cava; MAP, mean arterial pressure; MELD, model for end-stage liver disease; $PaO_2/FiO_2$, partial pressure of oxygen and fraction of inspired oxygen; RCT, randomized-controlled trial; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; SLED, sustained low-efficiency dialysis; SOFA, sequential organ failure assessment.

## Financial support

The authors received no financial support to produce this manuscript.

## Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

SKS and RM made the study concept and design; acquisition of data done by AV and AKH, Statistical analysis done by SSP and GK; drafting of the manuscript done by RM Critical revision of manuscript done for crucial intellectual content done by SKS, administrative and technical support by SKS.

## Data availability statement

The data that support the findings of this study are available from the corresponding author.

## Disclaimer

The work was presented as an oral paper at the ILC 2021.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.03.043.

## References


[1] Simonetto DA, Piccolo Serafim L, Gallo de Moraes A, Gajic O, Kamath PS. Management of sepsis in patients with cirrhosis: current evidence and practical approach. Hepatology 2019;70:418–428.

[2] Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Sepsis definitions task force. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775–787.

[3] Moreau R, Hadengue A, Soupison T, Kirstetter P, Mamzer MF, Vanjak D, et al. Septic shock in patients with cirrhosis: hemodynamic and metabolic characteristics and intensive care unit outcome. Crit Care Med 1992;20:746–750.

[4] Olson JC, Wendon JA, Kramer DJ, Arroyo V, Jalan R, Garcia-Tsao G, et al. Intensive care of the patient with cirrhosis. Hepatology 2011;54:1864–1872.

[5] Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004 27;350:2247–2256.

[6] Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Crit Care Med 2011;39:386–391.

[7] Vincent JL, De Backer D, Wiedermann CJ. Fluid management in sepsis: the potential beneficial effects of albumin. J Crit Care 2016;35:161–167.

[8] Fernández J, Clària J, Amorós A, Aguilar F, Castro M, Casulleras M, et al. Effects of albumin treatment on systemic and portal hemodynamics and systemic inflammation in patients with decompensated cirrhosis. Gastroenterology 2019;157:149–162.

[9] Philips CA, Maiwall R, Sharma MK, Jindal A, Choudhury AK, Kumar G, et al. Comparison of 5% human albumin and normal saline for fluid resuscitation in sepsis induced hypotension among patients with cirrhosis (FRISC study): a randomized controlled trial. Hepatol Int 2021;15:983–994.

[10] Levin M, Cunnington AJ, Wilson C, Nadel S, Lang HJ, Ninis N, et al. Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial. Lancet Respir Med 2019;7:581–593.

[11] Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al., ALBIOS Study Investigators. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014 10;370:1412–1421.

[12] Maiwall R, Pasupuleti SSR, Chandel SS, Narayan A, Jain P, Mitra LG, et al. Co-orchestration of acute kidney injury and non-kidney organ failures in critically ill patients with cirrhosis. Liver Int 2021;41:1358–1369.

[13] Reddy SK, Bailey MJ, Beasley RW, Bellomo R, Henderson SJ, Mackle DM, et al. A protocol for the 0.9% saline versus Plasma-Lyte 148 for intensive care fluid therapy (SPLIT) study. Crit Care Resusc 2014;16:274–279.

[14] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406–460.

[15] Choudhury A, Kedarisetty CK, Vashishtha C, Saini D, Kumar S, Maiwall R, et al. A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int 2017;37:552–561.

[16] Vincent JL, Quintairos E Silva A, Couto Jr L, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care 2016 13;20:257.

[17] Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al., ANSWER Study Investigators. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet 2018;391:2417–2429.

[18] Baldassarre M, Naldi M, Zaccherini G, Bartoletti M, Antognoli A, Laggetta M, et al. Determination of effective albumin in patients with decompensated cirrhosis: clinical and prognostic implications. Hepatology 2021;74:2058–2073.

[19] China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, et al., ATTIRE Trial Investigators. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. N Engl J Med 2021 4;384:808–817.

[20] Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. Eur Respir J 2014;44:1023–1041.

[21] Wong YJ, Qiu TY, Tam YC, Mohan BP, Gallegos-Orozco JF, Adler DG. Efficacy and Safety of IV albumin for non-spontaneous bacterial peritonitis infection among patients with cirrhosis: a systematic review and meta-analysis. Dig Liver Dis 2020;52:1137–1142.

[22] Polito C, Martin GS. Albumin: physiologic and clinical effects on lung function. Minerva Anestesiol 2013;79:1180–1186.

[23] Bortoluzzi A, Ceolotto G, Gola E, Sticca A, Bova S, Morando F, et al. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. Hepatology 2013;57. 266-76a.

[24] Long E, Oakley E, Duke T, Babl FE, Paediatric Research in Emergency Departments International Collaborative (PREDICT). Does respiratory variation in inferior vena cava diameter predict fluid responsiveness: a systematic review and meta-analysis. Shock 2017;47:550–559.

[25] Ilyas A, Ishtiaq W, Assad S, Ghazanfar H, Mansoor S, Haris M, et al. Correlation of IVC diameter and collapsibility index with central venous pressure in the assessment of intravascular volume in critically ill patients. Cureus 2017 Feb 12;9:e1025.

[26] Premkumar M, Rangegowda D, Kajal K, Khumuckham JS. Noninvasive estimation of intravascular volume status in cirrhosis by dynamic size and collapsibility indices of the inferior vena cava using bedside echocardiography. JGH Open 2019 12;3:322–328.

[27] European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. Hepatol 2010;53:397–417.