The Egyptian Journal of Hospital Medicine (October 2025) Vol. 101, Page 5561-5569

Comparing 20% Albumin to Normal Saline for Volume Replacement in Critically Ill Patients with Sepsis/Septic Shock

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ABSTRACT

Background: Albumin (Alb) exerts oncotic and pleiotropic actions that could be advantageous in cases with sepsis or septic shock (SS), yet its superiority as opposed to crystalloid solutions remains unresolved.

Objective: Compare 20% Alb versus normal saline for intravascular volume resuscitation in critically ill adults with sepsis or SS.

Patients and Methods: Single-center randomized controlled trial at Benha University intensive care unit (January–July 2024). Adults with sepsis ± shock were randomized 1:1 to 20% Alb plus crystalloids (target serum Alb ≥30 g/L to day 28 or intensive care unit discharge) versus crystalloids alone. Eighty cases were randomized (Alb n=40; crystalloid n=40). Primary outcome was 28-day all-cause mortality. Key secondary outcomes included 90-day mortality; SAPS II; SOFA total and subscores; organ failures; vasopressor duration; mechanical ventilation (MV) days; renal replacement therapy; and ICU and hospital length of stay.

Results: SAPS II was diminished with Alb (46.7 ± 8.0 vs 50.4 ± 6.7; p=0.044). Measures exhibited comparability for heart rate, MAP, CVP, $ScvO_2$, total SOFA, organ dysfunction count, shock incidence, ventilation, urine output, lactate, and lengths of stay (all p>0.05). SOFA coagulation subscore was elevated with Alb (0.70 ± 0.08 vs 0.53 ± 0.07; p=0.046). Mortality exhibited comparability at 28 days (32.5% vs 35.0%; p=0.28) and 90 days (25.0% vs 30.0%; p=0.62). Prolonged vasopressor exposure was associated with 90-day death (log-rank χ^2=3.88; p=0.049).

Conclusion: Administration of 20% Alb did not reduce 28- or 90-day mortality versus crystalloids; most clinical outcomes exhibited comparability.

Keywords: Albumin; Crystalloids; Sepsis; Septic shock; Resuscitation.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, while septic shock (SS) is a subset of sepsis with concomitant circulatory, cellular, and metabolic derangements that increase mortality risk [1]. Sepsis and SS constitute an expanding global health burden and present considerable challenges for emergency and critical care clinicians, reflecting rising incidence together with substantial pathophysiological, molecular, genetic, and clinical heterogeneity. Reported cases of sepsis and SS have steadily increased, with an estimated 49 million episodes and 11 million deaths worldwide in 2017 [2].

From a mechanistic perspective, sepsis is now recognised as the consequence of multiple, contemporaneous processes that engage a broad array of pro- and anti-inflammatory mediators. Recent investigations have characterised sepsis-associated cellular alterations and underscored the critical role of the microcirculation in the evolution from sepsis to SS. Within this paradigm, the vascular endothelium has emerged as a central functional unit in sepsis pathobiology because of its integral role in microcirculatory regulation and its capacity to modulate coagulation pathways as well as pro- and anti-inflammatory signalling [3].

The diagnosis of sepsis is established when the Sequential Organ Failure Assessment (SOFA) score is ≥2. SS is defined clinically by the requirement for vasoactive therapy to sustain mean arterial pressure (MAP) ≥65 mmHg in conjunction with a serum lactate concentration ≥2 mmol/L [4]. Early intravenous fluid resuscitation, frequently described under the umbrella of early goal-directed therapy (EGDT), in cases with severe sepsis resulting in enhanced survival in critically ill cohorts. Nonetheless, the optimal choice of resuscitation fluid within EGDT frameworks remains unresolved; in contemporary practice 0.9% normal saline (NS) continues to be widely employed for immediate hemodynamic resuscitation in sepsis-related hypotension [5].

Prompt administration of intravenous fluids, commonly operationalised as a 30 mL/kg crystalloid bolus within the first hour, remains the exhibitedation of initial approaches for severe sepsis and SS. Crystalloid solutions are the favorite resuscitation fluids and are conventionally classified as non-balanced (e.g., 0.9% NS) or balanced preparations (e.g., lactated Ringer's [LR], Plasmalyte) [6].

In septic states, it has been proposed that infusion of 4–5% human albumin (Alb) achieves an approximate 80% increment in plasma volume, whereas administration of 0.9% NS at an equivalent dose (30 mL/kg) increases intravascular volume only in direct proportion to the volume administered [7]. In Following bolus infusion in cases with sepsis, Alb tends to remain predominantly within the intravascular compartment for an estimated about 3 hours, as opposed to crystalloids which are rapidly redistributed into the extravascular space. Beyond its colloid oncotic effects,

Received: 15/06/2025
Accepted: 16/08/2025

Alb exhibits multiple biological actions that may be mechanistically advantageous; however, as a plasma-derived product it carries potential adverse effects, including hypersensitivity reactions and the risk of fluid overload [1].

This investigation compared 20% Alb with 0.9% NS for intravascular volume replacement in critically ill cases presenting with sepsis or SS.

PATIENTS AND METHODS

A randomized, controlled trial was carried out at the Intensive Care Unit, Banha University Hospital, enrolling cases admitted with a clinical diagnosis of sepsis with or without shock. Enrollment occurred following informed consent from cases or their legal representatives between January 2024 and July 2024.

Eligibility criteria:

Cases were eligible if they presented with severe sepsis or SS and fulfilled the following criteria: a proven or suspected infectious focus at one or more anatomical sites (pulmonary, abdominal, genitourinary, or other sites including bloodstream, central nervous system, soft tissue and skin, joints and bones, catheter-related, cardiac, or other); together with at least two systemic inflammatory criteria (elevated or diminished core temperature of 38 °C or elevated, or 36 °C or diminished; elevated heart rate of 90 beats/minute or elevated; elevated or diminished respiratory rate of 20 breaths/minute or elevated, or diminished arterial carbon dioxide pressure of 32 millimeters of mercury or diminished; need for mechanical ventilation (MV) due to an acute condition; or elevated or diminished white blood cell count of $12*10^{3}$/microliter or elevated, or $4*10^{3}$/microliter or diminished, or elevated immature neutrophils of more than 10 percent. In addition, participants had to exhibit at least one acute sepsis-related organ dysfunction, as assessed by the modified SOFA score. [8]

Exclusion criteria:

Cases were excluded if they were aged <18 years; had a documented hypersensitivity to Alb; had severe sepsis or SS attributable to confirmed or suspected head injury; had clinically active New York Heart Association class III or IV congestive heart failure; had conditions for which Alb is already an established indicated therapy (e.g., hepatic cirrhosis with tense ascites, nephrotic syndrome, intestinal malabsorption, extensive burns); presented more than 24 hours after meeting inclusion criteria; declined human blood-product administration for religious reasons; or were concurrently enrolled in another interventional study.

Baseline assessment and data collection

All enrolled participants underwent comprehensive baseline evaluation that included demographic information, relevant comorbidities, duration of illness prior to admission, and physiologic scoring (Acute Physiology measures and SOFA score) at the time of ICU admission. A full clinical history and focused assessment of cardiorespiratory status were recorded.

Clinical examination and monitoring

A complete clinical examination was performed with emphasis on vital signs (blood pressure, temperature, respiratory rate, HR) and targeted regional examinations (thoracic, abdominal, cardiac and neurological). Continuous hemodynamic monitoring and routine ICU care were provided according to institutional protocols.

Radiological and echocardiographic evaluation

Echocardiography (Vivid 7 Dimension ’06, GE Healthcare) was employed to evaluate left ventricular function, intravascular volume status, and cardiac output. Transthoracic echocardiography was repeated at intervals as clinically indicated during the management of acute circulatory failure.

Organ-system assessment

The respiratory, cardiovascular, hematologic renal, and hepatic subcomponents of the SOFA score were documented and serially monitored throughout the study period to quantify organ dysfunction and to guide clinical management [8].

Patients grouping

Participants were randomly allocated to one of two treatment arms: the Alb group, which received 20 percent human Alb in addition to standard crystalloid therapy, or the crystalloid-only group. Randomization continued until day 28 or ICU discharge, whichever occurred first. During the initial resuscitation phase, fluid management in both groups adhered to EGDT principles [9].

In the Alb group, patients initially received 300 milliliters of 20 percent Alb solution immediately after randomization. From day 1 until day 28 or ICU discharge, daily Alb dosing was adjusted to maintain serum Alb concentrations of at least 30 grams/liter. Crystalloids were administered in both groups based on the clinical judgment of the attending physician, and the use of synthetic colloids was prohibited. All other treatments were left to the discretion of the clinical team.

Daily monitoring included HR, central venous pressure (CVP), MAP, volumes of study and non-study fluids, blood products administered, net fluid balance, requirement for MV, and renal replacement therapy, either intermittent or continuous, continuing until ICU discharge, death, or day 28.

Outcome Measures

The primary outcome was all-cause mortality within 28 days post-randomization. Secondary outcomes included 28-day survival, incidence of new organ failures (one to five organs), defined as an increase in the

cardiovascular, respiratory, renal, hematologic, or hepatic SOFA subscore from 0–2 to 3 or 4 during ICU stay, duration of MV, duration of renal replacement therapy, and ICU and hospital lengths of stay. All-cause 28-day mortality was also analyzed across six predefined subgroups stratified by trauma, severe sepsis, and acute respiratory distress syndrome at baseline.

Ethical Considerations

The research procedure was approved by Benha University's Research Ethics Committee. All participants or their legal representatives provided written informed permission before inclusion. The permission procedure clearly addressed participation in the research and the dissemination of de-identified data, assuring privacy and confidentiality. The study followed the Declaration of Helsinki and the World Medical Association's code of ethics for human subjects' research.

Sample Size Determination.

Based on prior literature by **Philips and co-authors** [1], who reported superior tachycardia resolution and improved short-term outcomes in cases receiving Alb as opposed to NS, the sample size was calculated via PASS 11.0 software. A total of 80 cases (40/group) was estimated to provide 80% study power at a 95% confidence interval, accounting for an anticipated 10% dropout rate.

Statistical Analysis

Data were compiled and analyzed via SPSS v25 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2019 (Redmond, WA, USA). Distribution normality was assessed via the Kolmogorov-Smirnov test. Quantitative variables were summarized via mean ± standard deviation, standard error, and median, while categorical variables were expressed as frequencies and percentages. Comparisons of categorical variables between groups employed the chi-square test or Fisher's exact test for 2×2 tables where expected cell counts exceeded 25% below five. Independent t-tests compared normally distributed continuous variables, whereas the Mann-Whitney U test was applied to non-normally distributed data. Kaplan-Meier survival curves and the log-rank test were used to analyze cumulative survival probabilities. Statistical significance was defined as a p-value <0.05.

RESULTS

The study flowchart is depicted in Figure 1. Of 97 cases initially assessed for eligibility, 17 were excluded (7 declined participation and 10 did not satisfy inclusion criteria). A total of 80 cases with sepsis or SS consented to participate and were randomly allocated into two groups: Alb Group (n = 40) and Crystalloid Group (n = 40).

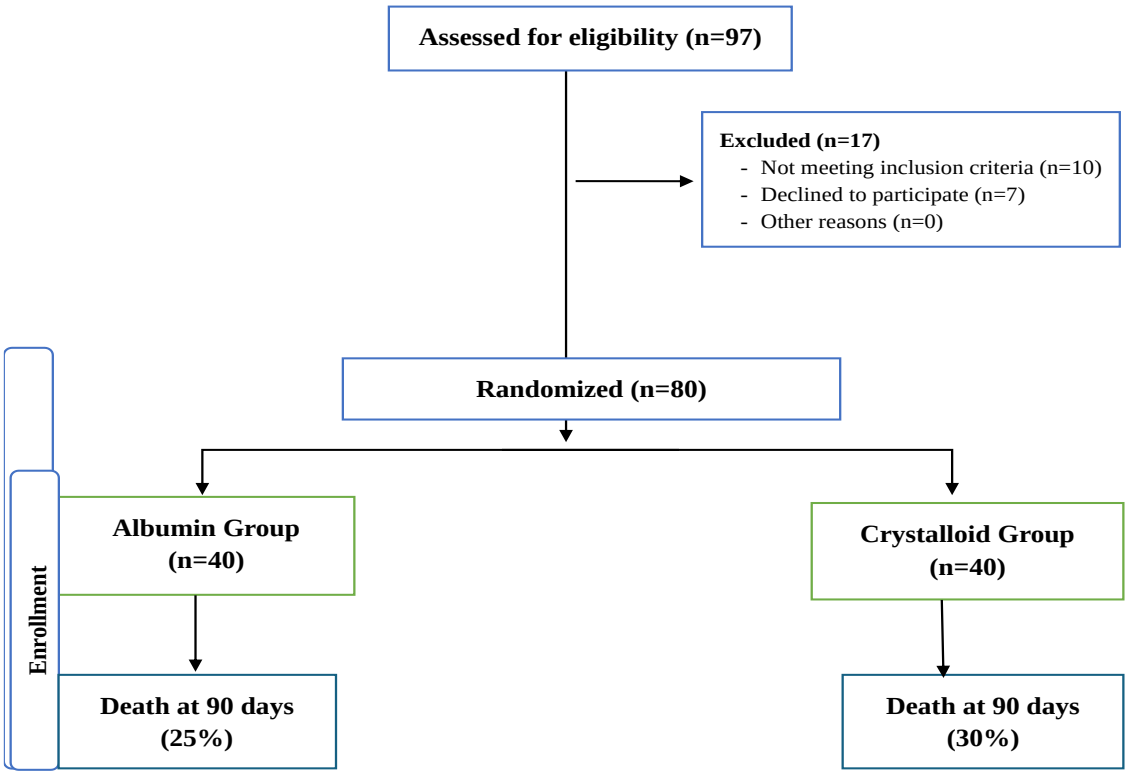

Figure 1. Flowchart of the study population.

The studied groups exhibited comparability in demographic data (p > 0.05) (Table 1).

Table 1. Baseline characteristics

	Albumin Group (n=40)		**Crystalloid Group (n=40)**		***P***
Age (years)					
Mean ± SD	65.85 ± 7.26		66.73 ± 5.57		0.547
Range	57-77		59-77		
Gender	**N**	**%**	**N**	**%**	
Male	25	62.50	23	57.50	0.648
Female	15	37.50	17	42.50	
Body-mass index					
Mean ± SD	21.90 ± 0.84		21.93 ± 0.92		0.899
Reason for ICU admission-no. (%)					
Medical	23	57.50	23	57.50	0.667
Elective surgery	4	10.00	2	5.00	
Emergency surgery	13	32.50	15	37.50	
Preexisting condition no. (%)					
No	19	47.50	18	45.00	
Liver disease	1	2.50	1	2.50	
COPD	5	12.50	5	12.50	0.921
Chronic renal failure	1	2.50	3	7.50	
Immunodeficiency	7	17.50	5	12.50	
Congestive or ischemic heart disease	7	17.50	8	20.00	

The independent t-test and chi-square test were employed to compare all data between the studied groups.

The SAPS II was significantly diminished in the Alb Group (46.73 ± 8.02) as opposed to the Crystalloid Group (50.40 ± 6.67) (p = 0.044). Other hemodynamic and clinical parameters including HR, MAP, CVP, central venous oxygen saturation, SOFA score, number of organ dysfunctions, presence of shock, requirement for MV, and fluid administration in the preceding 24 hours exhibited comparability between groups (p > 0.05) (Table 2).

Table 2. Clinical data

	Albumin Group (n=40)		Crystalloid Group (n=40)		***P***
SAPS II score					
Mean ± SD	46.73 ± 8.02		50.40 ± 6.67		**P^U=0.044***
Range	38-60		37-58		
Heart rate beats/min (Mean ± SD)	107.95 ± 15.24		101.95 ± 20.74		0.144
Mean arterial pressure (mm Hg) Mean ± SD	72.50 ± 11.23		72.25 ± 9.00		0.913
Central venous pressure (mm Hg) Mean ± SD	10.39 ± 3.31		9.91 ± 3.05		0.500
Central venous oxygen saturation					
Mean ± SD	71.83 ±4.65		73.65±4.06		0.062
Range	66-80		68-78		
SOFA score (Mean ± SD)	7.78 ±1.66		7.20 ± 1.71		**P^U**=0.127
Organ dysfunction, N (%)					
1	9	22.50	11	27.50	0.929
2	15	37.50	12	30.00	
3	11	27.50	11	27.50	
4	4	10.00	4	10.00	
5	1	2.50	2	5.00	
Shock, N (%)	26	65.00	23	57.50	0.491
Mechanical ventilation, N (%)	31	77.50	33	82.50	0.576
Fluid administration in previous 24 hr					
Albumin	6	15.00	7	17.50	0.762
Synthetic colloids	20	50.00	22	55.00	0.654

Independent t, chi-square and Mann-Whiteny U tests were employed to compare all data between the studied groups, *: Significant

Laboratory analyses demonstrated elevated urine output (UO), lactate, serum Alb, and hemoglobin in the Crystalloid Group as opposed to the Alb Group; however, these differences were not statistically significant ($p > 0.05$), (Table 3).

Table 3. Laboratory investigations.

	Albumin Group (n=40)	Crystalloid Group (n=40)	***P***
Urine output-ml/hr Mean ± SD Range	50.30 ± 27.41 23-100	60.35 ±21.38 24-100	0.071
Lactate mmol/liter (Mean ± SD)	2.66 ±0.97	2.92 ±0.88	P^U=0.216
Serum albumin-g/liter (Mean ± SD)	22.71 ± 4.03	23.63 ± 3.72	0.252
Hemoglobin-g/dl (Mean ± SD)	10.72 ±1.22	10.98 ± 1.23	0.350

Independent t, and Mann-Whiteny U tests were employed to compare all data between the studied groups.

Primary or secondary outcomes exhibited comparability ($p > 0.05$), with the exception of coagulation, which was significantly diminished in the Crystalloid Group (0.53 ± 0.07) as opposed to the Alb Group (0.70 ± 0.08) ($p <0.001$) (Table 4).

Table 4. Outcomes.

Outcome		Albumin Group (n=40)		Crystalloid Group (n=40)		***P***
		N	%	N	%	
Death at 28 days		13	32.50	14	35.00	0.813
Death at 90 days		10	25.00	12	30.00	0.617
New organ failures	None	18	45.00	19	47.50	1
	1	14	35.00	13	32.50	
	2	6	15.00	5	12.50	
	3	2	5.00	2	5.00	
	4	1	2.50	1	2.50	
	5	1	2.50	1	2.50	
SOFA score	Mean ± SD Range	6.15±2.55 4-8.7		5.6±2.9 4-8.5		0.067
Cardiovascular subscore	Mean ± SD Range	1.35±1.05 0.45-2.4		1.45±1.13 0.55-2.58		0.063
Respiratory subscore	Mean ± SD Range	2±0.48 1.56-2.48		2±0.5 1.57-2.50		1.00
Renal subscore	Mean ± SD Range	0.83±0.67 0.15-2.50		0.77±0.43 0.10-2.20		0.059
Coagulation subscore	Mean ± SD Range	0.7±0.08 0.1-1.68		0.53±0.07 0.1-1.60		**<0.001***
Liver subscore	Mean ± SD Range	0.3±0.01 0.00-1.00		0.22± 0.06 0.00-0.98		**<0.001***
ICU stay/days	Mean ± SD Range	9.75±3.43 4-19		9.83±2.85 4-20		0.849
Hospital stay/day	Mean ± SD Range	23.73±7.68 10-37		24.33 ±7.70 9-38		0.276
Renal-replacement therapy		10	25.00	8	20.00	0.592
Acute kidney injury		9	22.50	9	22.50	1.00
Duration of mechanical ventilation days	Mean ± SD Range	6.50±2.25 1-15		7.53±2.94 2-15		0.200
Time to suspension of vasopressor or inotropic agents/days	Mean ± SD Range	4.00±1.04 1-6		3.98±1.10 2-7		0.628

All data between the studied groups were compared via independent t test, chi-square test and Man-Whiteny U test, *Significant.

Kaplan–Meier survival curves demonstrated that the estimated mean and median hazard related to the time to suspension of vasopressors or inotropes was significantly elevated in cases who died at 90 days (mean hazard 4.273, 95% CI: 3.693–4.852) as opposed to survivors (mean hazard 3.879, 95% CI: 3.648–4.111) (log-rank test = 3.877, p =

0.049) (Table 5, Figure 2).

Table 5: Means and medians for estimated hazard related to the time to suspension of vasopressors or inotropes via Kaplan–Meier survival analysis among the studied groups.

Death at 90 days	Mean				Median			
	Estimate Hazard	Std. Error	95% CI (Tau protein)		Estimate Hazard	Std. Error	95% CI (Tau protein)	
			Diminished	Upper			Diminished	Upper
No	3.879	0.118	3.648	4.111	4.000	0.111	3.783	4.217
Yes	4.273	0.296	3.693	4.852	4.000	0.199	3.611	4.389
Overall	3.988	0.119	3.755	4.220	4.000	0.099	3.806	4.194
Log Rank (Mantel-Cox)	X^2=3.877				**P=0.049***			

CI: Confidence Interval, *Significant.

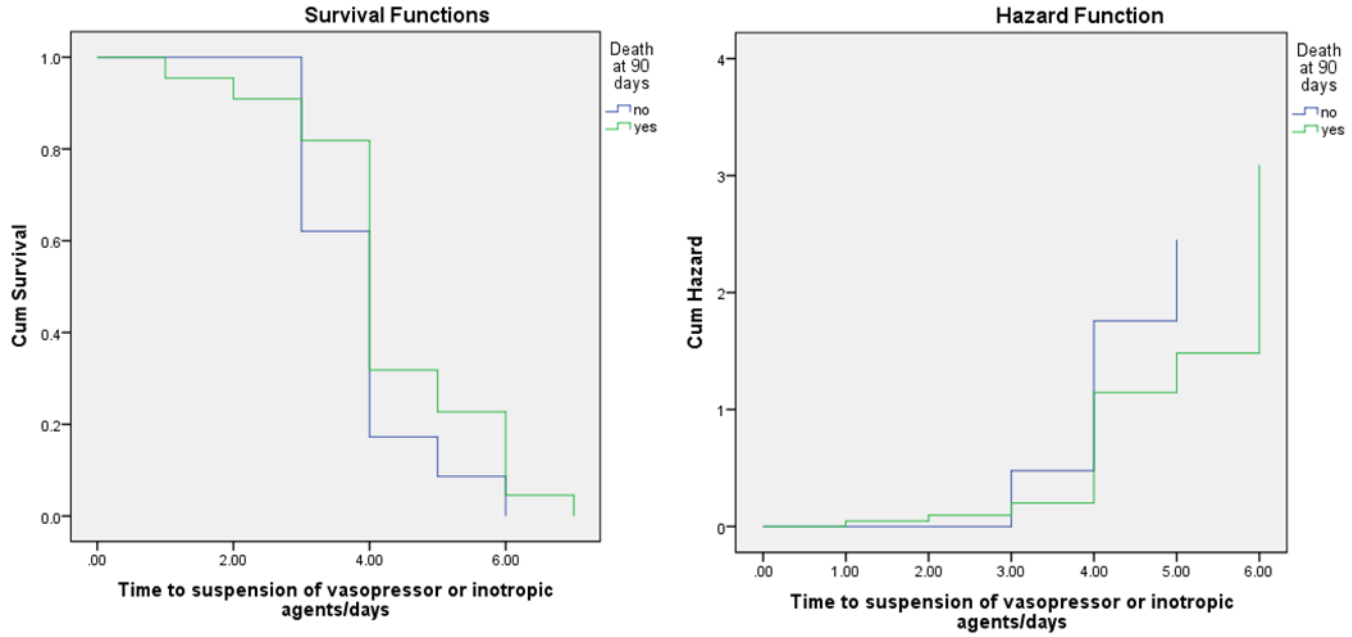

Figure 2: Means and medians for estimated hazard via Kaplan–Meier survival analysis based on the time to suspension of vasopressor or inotropic agents among the studied groups.

DISCUSSION

Sepsis constitutes the tenth leading cause of mortality in high-income nations and is the foremost etiology of death within intensive care units, thereby imposing a considerable burden on healthcare infrastructures. Despite extensive evaluation of numerous sepsis-targeted therapeutic interventions over recent decades, these approaches have generally failed to achieve the anticipated clinical benefits. In addition to its primary oncotic function, Alb possesses multiple biological properties, including the capacity to bind and transport endogenous molecules, exert antioxidant and anti-inflammatory effects, and regulate nitric oxide metabolism [10]. These biological properties are particularly pertinent in critically ill populations, notably among cases with sepsis. In 1998, a Cochrane meta-analysis indicated an association between Alb administration and heightened mortality risk in critically ill cases [11]. However, subsequent analyses, including additional clinical trials incorporated by **Wilkes and Navickis,** demonstrated that Alb therapy is safe, although no corresponding improvement in survival was noticed [12]. Notably, a later meta-analysis conducted by **Vincent and co-authors** [13] suggested that human Alb administration may reduce morbidity in critically ill individuals. Furthermore, a pilot study evaluating Alb therapy aimed at maintaining serum Alb concentrations above 30 g/L confirmed a significant enhancement in organ function among critically ill cases [14]. Based on this evidence, the current research compared the efficacy of 20% Alb with that of NS for volume replacement in critically ill cases with sepsis or SS.

In the current investigation, the groups exhibited comparability with respect to HR or MAP. In contrast, **Philips and co-authors** [1] noticed better MAP in critically ill cases managed with Alb. In contrast, **Leibovici and co-authors** [15] demonstrated that relative tachycardia in severe sepsis constitutes an independent risk factor for mortality in critically ill cases. Similarly, **Philips and co-authors** [1] noticed that cases in the Alb group experienced greater improvement in tachycardia and demonstrated superior short-term outcomes as opposed to the NS group. The

SAFE study [16] also corroborated the beneficial effects of Alb infusion on HR. Moreover, **Philips and co-authors** [1] demonstrated that hypotension reversal was achieved in a greater proportion of cases receiving 5% Alb as opposed to those administered NS at both one- and three-hours post-infusion. Furthermore, at one week, the Alb group exhibited elevated survival rates relative to the NS cohort. Smaller studies involving healthy volunteers and cases with shock confirmed that Alb is both well tolerated and effective as a resuscitation fluid [17]. Additionally, **Finfer and colleagues** [18] noticed a favorable trend in mortality among adult cases with severe sepsis managed with Alb; however, Alb administration appeared detrimental in cases with traumatic brain injury.

In our study, UO and lactate titres were diminished in the Alb group as opposed to the crystalloid group, though the differences did not reach statistical significance. Previous investigations have identified both lactate reduction and its temporal changes as reliable predictors of survival in cases with sepsis [19,20]. Consistently, **Philips and co-authors** [1] reported that cases resuscitated with Alb demonstrated a greater decline in arterial lactate and more favorable lactate kinetics over time as opposed to those receiving NS. Supporting these observations, **Zhou and colleagues** [21] demonstrated in an experimental sepsis model that NS boluses exacerbated hyperlactatemia, a finding comparable to our observations with NS use in cases with cirrhosis. **Philips and co-authors** [1] demonstrated that UO a simple bedside indicator of recovery from shock, was modestly improved in cases receiving albumin, though without statistical significance relative to NS.

The study groups exhibited comparability with respect to the incidence of new organ failures and SOFA scores. Although fluid resuscitation remains a fundamental component of sepsis management, predictors of fluid responsiveness are largely derived from dynamic assessments of cardiopulmonary interactions in mechanically ventilated cases, such as the passive leg-raising maneuver [22]. The SOFA score has been established as a reliable predictor of tissue hypoperfusion at admission, correlating with increased hospital mortality among septic cases [23]. Our findings exhibited comparability with these observations, underscoring the prognostic utility of the SOFA score in anticipating both fluid non-responsiveness and overall hospital outcomes. In line with prior evidence, the SAFE trial [24] demonstrated that the frequency of new single- or multi-organ failures, as assessed by SOFA scores, exhibited comparability between cases managed with Alb and those receiving NS (P = 0.85, Fisher's exact test). During the 28-day observation period, the mean ICU stay was 6.5 ± 6.6 in the Alb group and 6.2 ± 6.2 days in the NS group (P = 0.44), while mean hospital stay was 15.3 ± 9.6 and 15.6 ± 9.6 days, respectively (P = 0.30). Likewise, the durations of MV and renal-replacement therapy exhibited comparability between the groups.

Furthermore, **Caironi and co-authors** [25], exhibited that the rate of new organ failures throughout the research was comparable across the Alb and crystalloid groups. They also exhibited significantly elevated mean SOFA subscores for liver and coagulation in the Alb group, suggesting slightly raised serum bilirubin titres and marginally diminished platelet counts (PLT) compared to the crystalloid group. However, the absolute increase in serum bilirubin in the Alb group was minimal (median, 1.0 mg/dL [0.6-1.7] as opposed to 0.9 mg/dL [0.5-1.5], P<0.001). This is likely due to the preparation methods of Alb solutions, which may not adequately remove bilirubin from plasma [26,27]. The slight decrease in PLT in the Alb group may indicate a greater expansion of the intravascular compartment as opposed to the crystalloid group, leading to a minor dilution of hemoglobin.

The present study showed that 90-day mortality was 25% in the Alb group and 30% in the crystalloid group, with the two groups exhibiting comparability. In agreement, **Caironi and co-authors** [25] exhibited that administering Alb-crystalloids over the first 28 days to maintain serum Alb titres ≥30 g/L is safe but does not provide a survival benefit over crystalloids alone in a 90-day follow-up. Similar results were reported in subgroups stratified by the time between attaining clinical criteria for severe sepsis and initiating therapy. Additionally, **Xu and co-authors** [17] exhibited a tendency toward diminished 90-day mortality in severe sepsis victims resuscitated with Alb rather than crystalloid or NS, with a substantial decrease in death among individuals with SS. **Kaukonen *and co-authors*** [28] noticed 14-30% fatality rates in severe sepsis without shock, which increased to 22-40% in SS. In our investigation, the groups showed comparable 90-day death rates, which may seem to contradict the specified subgroup analysis from the SAFE trial [24], which demonstrated a survival advantage with an Alb-based approach in severe sepsis. This notion, however, is backed by established hemodynamic benefits [16] and evidence that treating hypoalbuminemia may lessen the severity of organ failure [14,29].

Comparable favorable simpacts have also been highlighted by **Delaney and co-authors** [30] who exhibited that the administration of Alb-containing solutions may be related with reduced mortality in comparison to other fluid regimes. Furthermore, **Caironi and co-authors** [25] reported that post hoc univariate and multivariate analyses of data from 1,121 cases with SS demonstrated significantly diminished 90-day mortality in the Alb group as opposed to the crystalloid group. In contrast, in the subgroup of cases with severe sepsis without shock, mortality appeared elevated among those receiving Alb as opposed to those managed with crystalloids alone; however, this difference exhibited comparability and was far from statistically significant. As this analysis was not

prespecified, it may be subject to recognized biases. Nevertheless, SS represents a clearly defined clinical entity, and if the oncotic, anti-inflammatory, and nitric oxide–scavenging properties of Alb are clinically relevant, their benefits are likely to be maximized in the most severe conditions, such as in cases with cardiovascular dysfunction.

Several plausible mechanisms may explain the favorable outcomes noticed with Alb use in SS. Fluid expansion remains a critical, life-saving intervention in the resuscitation of cases with SS, with the primary aim of expanding intravascular volume and restoring effective circulating volume. In sepsis, however, a substantial portion of fluid frequently shifts into the extravascular space, contributing to tissue edema. By leveraging oncotic pressure gradients [31], Alb achieves more effective intravascular volume expansion and facilitates restoration of circulating fluid. These properties enhance the efficiency and timeliness of fluid resuscitation. Moreover, Alb functions as an important binder and transporter of active molecules [32]. It exhibits radical-scavenging antioxidant activity and plays a role in inhibiting platelet aggregation while preserving capillary membrane integrity, all of which may collectively improve case outcomes [28].

This study has certain limitations. It was conducted as a single-center trial with a relatively small sample size, which may constrain the generalizability of the results and diminished the capacity to identify subtle outcome differences between groups. The open-label design introduces the potential for bias in treatment administration and clinical decision-making. While serum Alb titres and hemodynamic parameters were monitored during ICU stay, long-term follow-up beyond 90 days and evaluation of inflammatory or endothelial biomarkers were not performed. Furthermore, the exclusion of cases with liver cirrhosis or other conditions requiring Alb may have restricted the assessment Alb's broader therapeutic effects in a heterogeneous septic population.

CONCLUSION

Our findings indicate a trend toward diminished 90-day mortality in cases with severe sepsis who were resuscitated with Alb as opposed to crystalloid and NS but with no significant difference.

Financial support and sponsorship: Nil.
Conflict of Interest: Nil.

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