Review Article

Bull Emerg Trauma 2025;13(4):2-13.

Bulletin of Emergency And Trauma

The impact of Albumin Administration on Mortality and Resuscitation Volume in Burn Resuscitation: A Systematic Review and Meta-Analysis

***Aditya Wardhana*[1*], *Nadya Farhana*[1], *Putri Fernizi Harfah*[1], *Sheila Oklia*[1]**

[1]*Division of Plastic Reconstructive and Aesthetic Surgery, Department of Surgery, Cipto Mangunkusumo Hospital-Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*

***Corresponding author:** *Aditya Wardhana*
Address: Plastic Reconstructive and Aesthetic Surgery Division, Department of Surgery, Dr. Cipto Mangunkusumo Hospital – Faculty of Medicine, Universitas Indonesia, Diponegoro Road 71, Jakarta 10430 Indonesia. **Tel:** +62 213 146938;
e-mail: aditya_wrdn@yahoo.com

Received: July 29, 2025
Revised: September 14, 2025
Accepted: September 20, 2025

ABSTRACT

Objective: This systematic review and meta-analysis aimed to evaluate the impact of albumin administration on mortality and total resuscitation volume in burn patients.
Methods: We systematically searched ScienceDirect, Cochrane, PubMed, MEDLINE, Scopus, and ProQuest in June 2025 using the terms "Burns," "Resuscitation," and "Albumin." Studies were included if they investigated albumin as part of burn resuscitation in adult patients and reported on mortality and total resuscitation volume. Pediatric studies, studies using albumin for other purposes, and those using other colloids were excluded. Reviewers independently extracted data on study characteristics, patient demographics, and outcomes. The risk of bias was assessed using RoB 2 for RCTs and ROBINS-I for non-randomized studies (NRCTs). Pooled analyses were performed using Review Manager 9.3.0, applying random-effects models.
Results: Eleven of the 7,365 identified articles were included. Albumin administration did not significantly affect mortality (OR=1.19 [0.62–2.28], p=0.57) or total resuscitation volume (OR=0.69 [-0.93–2.31], p=0.34). However, albumin use was associated with a reduced incidence of sepsis (OR=1.18 [1.02–1.38], p=0.03) and ARDS (OR=2.64 [1.43–4.86], p=0.02).
Conclusion: The administration of albumin did not significantly impact mortality or resuscitation volume in burn patients. While there is some evidence of potential benefits in reducing complications, this is limited by heterogeneity, underscoring the need for further high-quality RCTs.

Keywords: Burns, Resuscitation, Albumin, Total resuscitation volume, Mortality.

Please cite this paper as:
Wardhana A, Farhana N, Harfah PF, Oklia S. The impact of Albumin Administration on Mortality and Resuscitation Volume in Burn Resuscitation: A Systematic Review and Meta-Analysis. *Bull Emerg Trauma*. 2025;13(4):2-13. doi: 10.30476/beat.2025.107914.1620.

Introduction

Albumin was first used in burn resuscitation in the 1940s, particularly during World War II, with the administration of freeze-dried plasma (FDP), which contained 25% albumin. It subsequently became a standard component of burn treatment [1-3]. However, in 1998, a Cochrane review suggested that albumin might increase mortality in critically ill patients [4-6]. Although the review was criticized for its weak evidence, it prompted many burn centers to reduce or discontinue albumin use [4-6].

Modern burn resuscitation formulas, along with the increasing tendency of burn centers to exclude colloids from their protocols, have been identified as key contributors to the rising incidence of 'fluid creep' observed in recent years [6, 7].

Burn injuries trigger a systemic inflammatory cascade mediated by cytokines, such as Interleukin-1, Tumor Necrosis Factor, Interleukin-6, and complement C5a. This inflammatory response, combined with the loss of serum proteins such as albumin, disrupts the colloid oncotic pressure (COP) within the capillary and interstitial spaces [8, 9]. The consequent loss of intravascular volume requires appropriate resuscitation to avoid 'fluid creep' [8-10]. The term "fluid creep" was first coined by Pruitt to describe the administration of excessive crystalloid volumes beyond the amounts calculated by the standard formula [11]. This over-resuscitation is associated with an increased risk of severe complications, including compartment syndrome and acute respiratory distress syndrome (ARDS) [11]. It has been proposed that fluid creep could be mitigated through a strategy known as "colloid rescue," which involves administering colloid solutions to restore appropriate intravascular volume and prevent further fluid overload. The administration of albumin, as early as 12 hours post-burn, has shown promising outcomes in managing fluid creep [12, 13].

Despite ongoing uncertainty about the benefits of albumin in burn patients, colloid solutions have been recommended in burn resuscitation formulas since the 1940s [14]. Nevertheless, many burn centers continue to exclude albumin from their protocols [4]. Therefore, this systematic review and meta-analysis aimed to evaluate the impact of albumin administration on mortality and total resuscitation volume in burn patients. This review hypothesized that the inclusion of albumin in burn resuscitation protocols is associated with reduced mortality and decreased total fluid requirements compared to protocols that exclude albumin.

Materials and Methods

This systematic review and meta-analysis was registered on the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420250651689) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

Eligibility Criteria

The inclusion criteria comprised trials that utilized albumin for burn resuscitation in adult patients and reported on the outcomes of total resuscitation volume and mortality. Only articles published in English were considered, with no restriction on the publication date.

Exclusion criteria were studies that used albumin for purposes other than burn resuscitation, those focusing on pediatric burn patients, and studies involving other colloids, such as fresh frozen plasma (FFP), hydroxyethyl starch, or hypertonic saline.

Information Sources and Search Strategy

A systematic literature search was performed in June 2025 across the ScienceDirect, Cochrane, PubMed, MEDLINE, Scopus, and ProQuest databases using the search terms 'Burns,' 'Resuscitation,' and 'Albumin'. The study selection process adhered to PRISMA guidelines and is detailed in Figure 1.

The following data were extracted from the included studies: year of publication, study design, number of patients, country of origin, treatment comparisons between the albumin and control groups, reported incidence of inhalation injury, mortality rate, total resuscitation volume, burn-related complications (such as incidence of sepsis, acute respiratory distress syndrome, abdominal compartment syndrome, and renal failure). The methodological quality of each trial was assessed using Cochrane's risk of bias tool. Disagreements between reviewers during data extraction or quality assessment were first resolved through discussion. If a consensus could not be reached, a third independent reviewer was consulted to make the final decision.

Data Collection and Risk of Bias Assessment

Risk of Bias was assessed using Cochrane's Revman Risk of Bias (RoB 2) Tool for Randomized Controlled Trials (RCTs). For non-randomized controlled trials (NRCTs), the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool was employed.

Outcomes and Data Synthesis

The primary outcomes were mortality and total resuscitation volume. Secondary outcomes included the incidence of sepsis, acute respiratory distress syndrome, abdominal compartment syndrome, and renal failure.

Data were analyzed using Cochrane Review Manager (RevMan, version 9.3.0). A random-effects model was applied to pool the results, reporting the odds ratio (OR) for binary outcomes and mean differences (MD) for continuous outcomes, both with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic. The publication bias was also assessed using Cochrane Review Manager 9.3.0.

Results

Our initial search identified 503 studies. After removing 227 duplicates, we screened the abstracts of 276 studies. Of these, 212 studies were excluded, and 64 full-text articles were assessed for eligibility [16-26]. Eleven studies, published between 1975 and 2024, met the inclusion criteria. The included studies comprised three RCTs and eight NRCTs.

All studies compared the administration of albumin to crystalloid fluids for resuscitation in burn patients.

Table 1 summarizes the study design, interventions, control groups, and resuscitation endpoints. The analysis included 1,859 patients in the albumin group and 5,470 in the control group. Patient baseline characteristics, including age, total body surface area (TBSA) burned, percentage of full-thickness burns, and incidence of inhalation injury, are presented in Table 2. Age and inhalation injury incidence were notable baseline factors that varied across the studies. For instance, Yalan *et al.,* and Nakamura *et al.,* reported older patient populations in both study arms (mean ages 63.69±16.45 vs 61.07±19.04 and 66.7±18.5 vs 67.1±17.8, respectively) [25,26]. The reported incidence of inhalation injury also varied considerably. Goodwin *et al.,* reported no inhalation injuries in either group [17], whereas Cochran *et al.,* reported a high incidence, exceeding 50% in the albumin group [17, 19].

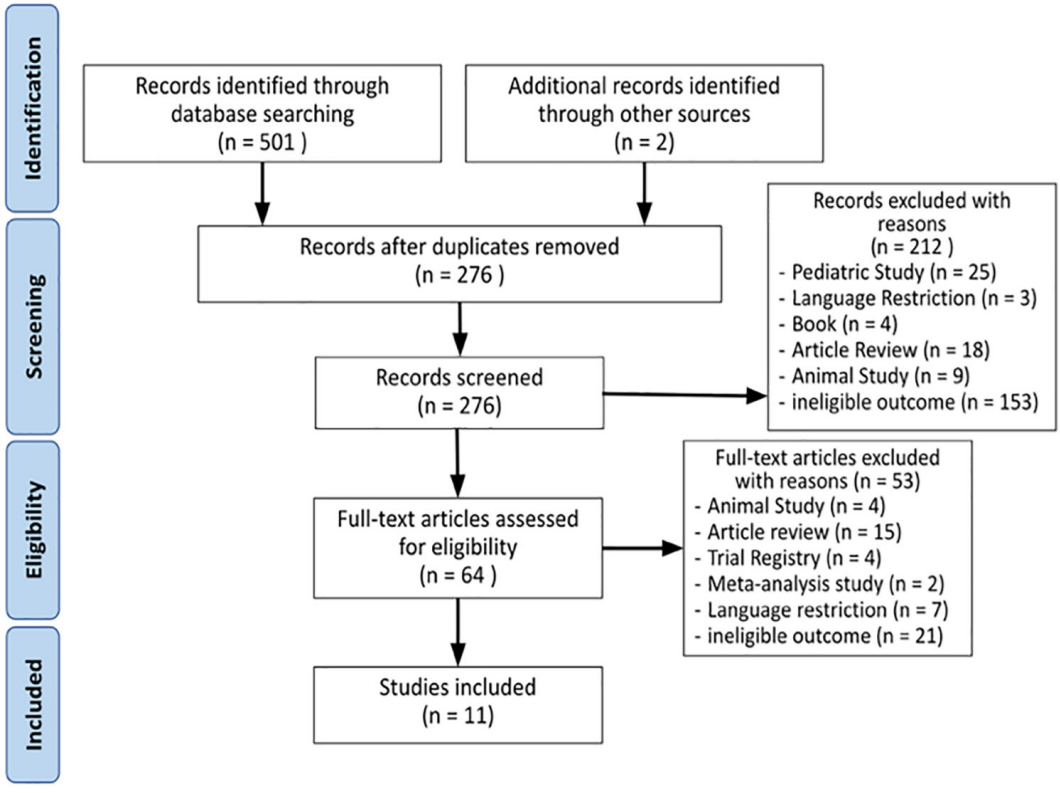

Fig. 1. PRISMA flowchart for study selection process

Table 1. Summary of eligible studies

Study, Year, Country	Study Design	Albumin (n)	Albumin intervention	Control (n)	Control	Main findings
Randomized controlled trials						
Recinos et al., 1975, USA [16]	RCT	14	2.3% albumin and Ringer's lactate	15	● Ringer lactate ● 4 mL/Kg/% TBSA, referring to the Baxter formula	The albumin group received less fluid than the control group, with an average of 3.4 vs 5.3 mL/Kg/% TBSA. In mortality, there is no statistically significant difference between these two groups.
Goodwin et al., 1982, USA [17]	RCT	40	2.5% albumin and Ringer's lactate	39	● Ringer lactate ● 2 mL/Kg/% TBSA	The albumin group required less fluid than the control group (2.98 vs. 3.81 mL/Kg body weight/% TBSA, $p<0.01$), and there were no significant differences in cardiac index found between these groups.

Study, Year, Country	Study Design	Albumin (n)	Albumin intervention	Control (n)	Control	Main findings
Cooper et al., 2006, Canada [18]	Multicenter unblinded RCT	19	5% human albumin and Ringer's lactate	23	● Ringer lactate ● 4 mL/Kg/% TBSA referring to Parkland Formula	The albumin group tended to have lower total fluid volume than the control group (232 mL, 95% CI: 0-6079 vs 2769 mL, 95% CI 0-14,314), but the trend was not significant (p=0.39).
Non-randomized controlled trials						
Cochran et al., 2006, USA [19]	Case control study	101	● 5% albumin and Ringer's lactate ● Albumin addition: 5% albumin at ⅓ current hourly rate, Ringer's lactate at ⅔ current rate	101	● Ringer lactate ● Parkland Formula	The albumin group had higher resuscitation volume (9.4 vs 6.4) than the control group.
Ennis et al., 2008, USA [20]	Retrospective cohort	56	5% of Albumin	62	No Information on Control Treatment	The albumin group had lower abdominal compartment syndrome and mortality than the control group (p=0.03).
Lawrence et al., 2010, USA [21]	Retrospective cohort	26	5% of Albumin and Ringer Lactate with a ratio of 1:2	26	● Ringer lactate ● Original Parkland Formula: 2-4 mL/Kg/% TBSA	The albumin group suffered more complications and had increased mortality (11.5 vs 3.8; p=0.61) than the control group.
Park et al., 2012, USA [22]	Retrospective cohort	98	5% human albumin	61	● Ringer Lactate ● 4 mL/Kg/% TBSA	The albumin group had lower mortality than the control group (p<0.01).
Comish et al., 2021, USA [23]	Case control study	30	25% albumin at 0.1 mL/Kg/% TBSA or 5% albumin at half the current crystalloid rate (based on burn surgeon preference)	61	● Ringer Lactate ● 4 mL/Kg/% TBSA as dictated by the Parkland formula	The total volume resuscitation was not significantly different between groups (15,914.43 vs. 11,828.71; p = 0.129)
Greenhalgh et al., 2023, USA [24]	Prospective non-interventional observational multicenter study	253	5%, 25%, or both Albumin combined	126	● Ringer Lactate ● 4 mL/Kg/% TBSA referring to Parkland Formula	The albumin group received more fluid (5.2±2.3 versus 3.7±1.7 mL/Kg/% TBSA burn/24 hours) and had more complications than the control group.
Yalan et al., 2024, China [25]	Retrospective cohort	692	● 5% Albumin ● In the first 24 hours	4426	Crystalloid solution	No statistically significant difference in mortality between the two groups.
Nakamura et al., 2024, Japan [26]	Retrospective cohort	530	4.4%, 5%, 20%, and 25% Albumin solution	530	Crystalloid solution	The 28-day mortality did not differ significantly between the two groups (albumin group vs. control group, 21.7% vs. 22.8%; risk difference, -1.1%; 95% CI, -6.1% to +3.9%).

TBSA:Total body surface area; HALFD: Hypertonic albuminated fluid demand; mEq: milliequivalent; Na:Natrium; NaCl: Natrium Chloride; D/W: Dextrose in water; CI: Confidence interval

Table 2. Patient's baseline characteristics

Study, Year	Age (Year)		TBSA (%)		Full thickness burns (%)		Incidence of inhalation injury (n)	
	Albumin	Control	Albumin	Control	Albumin	Control	Albumin	Control
Recinos et al., 1975 [16]	26.92±23.50	32.0±29.57	64.85±17.68	50.53±18.71	NI	NI	2/14	1/15
Goodwin et al., 1982 [17]	28±7	28±8	53±17	48±12	NI	NI	0/40	0/39
Cooper et al., 2006 [18]	36 (24-45)*	31 (25-39)*	39 (32-53)*	32 (26-34)*	15 (0-43)*	12 (0-20)*	12/19	11/23
Cochran et al., 2006 [19]	37.9±21.2	35.9±21.0	42.3±18.4	39.9±16.6	22.8±15.9	14.3±20.6	52/101	18/101
Ennis et al., 2008 [20]	25±5	28±8	52±17	50±17	43±21	40±22	20/56	26/62
Lawrence et al., 2010 [21]	42.2±2.66	42.3±2.96	39.7 (23-87)*	28.4 (20-59)*	15 (0-76)*	8 (0-24)*	12/26	7/26
Park et al., 2012 [22]	41±19	43±18	38±18	39±18	NI	NI	20/61	41/98
Comish et al., 2021 [23]	43.8±3.4	44.7±2.3	40.3 (20.8-92.5)*	34 (11-83.5)*	16.3 (0-84)*	1 (0-70)*	1/30	5/61
Greenhalgh et al., 2023 [24]	48.0±16.2	42.9±14.7	36.0 (19.5)**	24.7 (11.0)**	15.0 (26.0)**	0.0 (7.5)**	44 (17.4)**	4 (3.2)**
Yalan et al., 2024 [25]	63.96±16.45	61.07±19.04	NI	NI	NI	NI	NI	NI
Nakamura et al., 2024 [26]	66.7±18.5	67.1±17.8	29.5±15.9	28.5±16.2	NI	NI	117/530	109/530

*No mean and standard deviation data available; **Data are shown as median (IQR); NI: No information; TBSA: Total body surface area

Although all studies administered albumin in the treatment arm, the concentration and administration protocols differed. Most studies used 5% human albumin, with three studies combining it with Ringer's lactate [18-22, 24-26]. Other concentrations used included 2.3%, 2.5%, 4.4%, 20% and 25% albumin [16, 17, 23, 24, 26]. The crystalloid used in the control groups was Ringer's lactate in eight studies [16-19, 21-24], while three studies did not specify the crystalloid fluid or the full resuscitation protocol for the treatment group [20, 25, 26]. A summary of the resuscitation protocols and endpoints is provided in Table 3.

Randomized Study Quality

Three randomized controlled trials (RCTs) were evaluated, and the summary of the risk of bias is shown in Figure 2. The study by Recinos *et al.,* raised some concerns regarding the randomization process due to the use of a predictable allocation sequence. It was also judged to have a high risk of bias due to significant missing data resulting from patient mortality [16]. Nevertheless, these RCTs were assessed as having a low risk of bias.

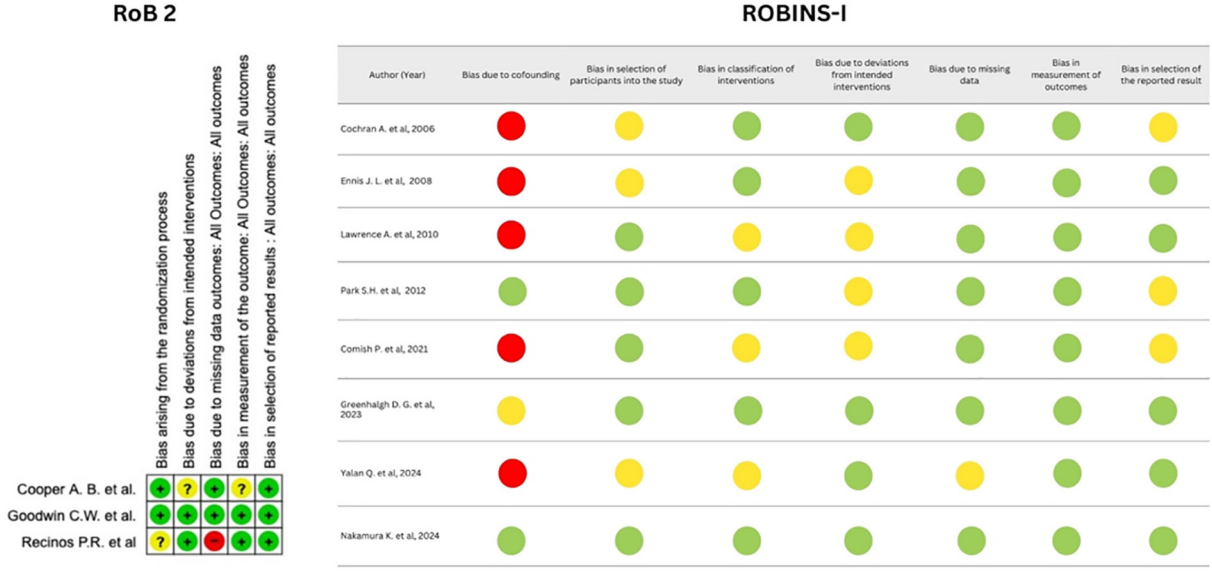

Fig. 2. Risk of bias assessment using RoB2 and ROBINS-I.

Table 3. Summary of resuscitation protocols and endpoints

Study, Year	Resuscitation phase duration	Fluid resuscitation formula / rate of infusion	Resuscitation endpoints
Randomized Controlled Trial			
Recinos et al., 1975 [16]	24 hours	Parkland Formula: 4 mL/Kg/% TBSA Addition of Albumin: 2.3% Albumin with hypertonic solution	● UO≥30-50 mL/h
Goodwin et al., 1982 [17]	48 hours	Resuscitation volume: 2 mL/Kg/% TBSA Addition of Albumin: 2.5% Albumin-lactated Ringer 0.3-0.5 mL/Kg/% TBSA	● UO ≥30-50 mL/h ● Stabilized vital sign
Cooper et al., 2006 [18]	<24 hours	Parkland Formula: 4 mL/Kg/% TBSA Addition of Albumin: 5% Albumin-lactated Ringer	● UO≥0.5 mL/Kg/h ● MAP≥70 mmHg
Non-Randomized Controlled Trial			
Cochran et al., 2006 [19]	<24 hours	Parkland Formula: 4 mL/Kg/% TBSA Addition of Albumin: 5% albumin at ⅓ current hourly rate, RL at ⅔ current rate	● UO≥30 mL/h, held for two hours and at least 24 hours post burn
Ennis et al., 2008 [20]	24 hours	No information on the resuscitation formula	● UO>30 mL/h
Lawrence et al., 2010 [21]	24 hours	Parkland formula: 4 mL/Kg/% TBSA Addition of Albumin: 5% albumin at ⅓ current hourly rate, RL at ⅔ current rate	UO 30-50 mL/Kg/h
Park et al., 2012 [22]	24 hours	Parkland Formula: 4 mL/Kg/% TBSA Addition of Albumin: 5% Albumin	● UO>1 mL/Kg for two consecutive hours ● Normal blood pressure
Comish et al., 2021 [23]	24 hours	Parkland Formula: 4 mL/Kg/% TBSA Addition of Albumin: 25% albumin at 0.1 mL/Kg/% TBSA or 5% albumin at half the current crystalloid rate (*based on burn surgeon preference*)	● UO≥0.5 mL/Kg/h ● Stable vital sign
Greenhalgh et al., 2023 [24]	24 hours	Parkland Formula: 4 mL/Kg/% TBSA Addition of Albumin: 5% and 25% Albumin to be given within 12 hours in a ratio of ⅓ albumin to ⅔ crystalloid	UO 0.5-1 mL/Kg/h
Yalan et al., 2024 [25]	24 hours	High volume fluid resuscitation: >60 mL/Kg in the first 24 hours Addition of Albumin: 5% albumin Early Albumin Group (before 24h) Late Albumin Group (after 24h)	No information on resuscitation endpoints
Nakamura et al., 2024 [26]	48 hours	No information on the resuscitation formula ● Low dose Albumin group: <50 g within 2 days of admission ● High dose Albumin: >50 g dosage within 2 days of admission	No information on resuscitation endpoints

TBSA: Total body surface area; UO: Urine output; BR: Basal rate; AFR: Additional fluid rate; TFV: Transport fluid volume; MAP: Mean arterial pressure

Non-Randomized Study Quality

The risk of bias in the ROBINS-I tool was used to evaluate eight NRCTs. These comprised five retrospective cohort studies, two case-control studies, and one prospective non-interventional observational multicenter study. The risk of bias, depicted in Figure 2, varied considerably. The most frequent bias was confounding bias. Studies by Cochran *et al.,* Ennis *et al.,* Lawrence *et al.,* Comish *et al.,* and Yalan *et al.*, were judged to have a serious risk of bias due to inadequate adjustment for key prognostic factors such as inhalation injury, full-thickness burns, and TBSA [19-21, 23, 25]. In contrast, Nakamura *et al.,* demonstrated a low risk of confounding bias due to the use of propensity score matching, which provided better methodological control [26]. Selection bias was generally low, though moderate concerns were noted for Cochran *et al.,* Ennis *et al.,* and Yalan *et al.,* due to non-random or time-based participant allocation [19, 20, 25]. Domains for intervention classification and outcome measurement were consistently low risk, reflecting clear definitions and objective measures (e.g., mortality) [19, 20, 25]. However, selective reporting bias was a moderate concern in many studies due to a lack of pre-registration and an emphasis on favorable findings despite non-significant results.

Mortality

Mortality was a primary outcome of this review. It was assessed in three RCTs [16-18] and seven NRCTs [19-23, 25, 26]. The forest plot for the overall effect on mortality is shown in Figure 3. A total of 29 deaths occurred in the randomized studies, while 1,148 deaths were reported in the non-randomized studies.

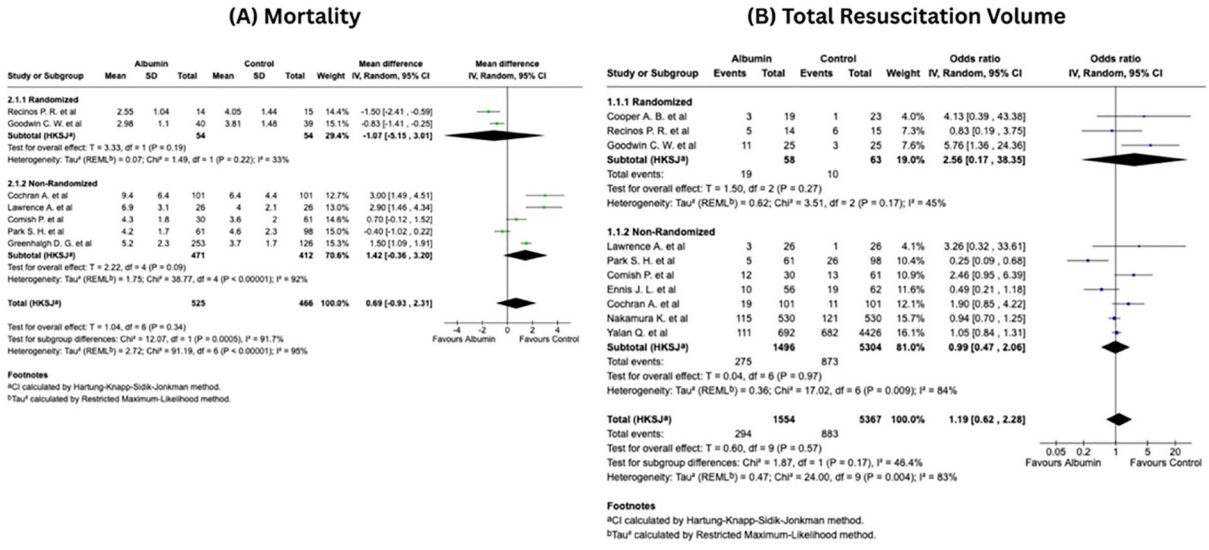

Fig. 3. Forest plots of albumin administration towards mortality and total resuscitation volume

Notably, one non-randomized study reported an incidence of inhalation injury nearly three times higher in the albumin group than the control group [19], while another reported an incidence almost twice as high [21].

In the randomized studies, the pooled odds ratio (OR) was 2.56 (95% CI: 0.17-38.35, p=0.27), suggesting a non-significant trend toward increased mortality with albumin, though the confidence interval was very wide. In the non-randomized studies, the pooled OR was 0.99 (95% CI: 0.47-2.06, p=0.97), indicating no clear effect. The overall pooled OR was 1.19 (95% CI: 0.62-2.28; p=0.57), with substantial heterogeneity (I^2=83%). No significant difference was observed between randomized and non-randomized subgroups (p=0.17).

The substantial heterogeneity, particularly among the NRCTs, is likely attributable to unadjusted baseline risk factors, such as TBSA, burn depth, and inhalation injury. For instance, Ennis *et al.,* reported a higher percentage of TBSA, while Park *et al.,* Yalan *et al.,* and Nakamura *et al.,* did not provide data on the baseline percentage of full-thickness burns [20, 21, 25, 26]. Furthermore, Cochran *et al.,* and Nakamura *et al.,* reported a higher rate of inhalation injury in the albumin group than the control group [19, 26]. These findings suggested that albumin use did not significantly impact mortality, but the evidence is limited by imprecision and heterogeneity, as well as potential bias from differences in baseline characteristics such as TBSA, burn depth, and inhalation injury.

Total Resuscitation Volume

Total resuscitation volume was assessed as a co-primary outcome. It was evaluated in two RCTs [16, 17] and five NRCTs [19, 21-24]. The overall effects of albumin administration on total resuscitation volume in burn resuscitation are shown in Figure 3.

The randomized studies generally reported lower total resuscitation volumes in the albumin group, whereas all five non-randomized studies found higher volumes in the albumin group.

The overall effect on total resuscitation volume was not statistically significant (OR=0.69 [-0.93, 2.31], p=0.34). In the randomized studies, the pooled OR ratio was -1.07 (95% CI: -5.15, 3.01, p=0.19). Similarly, in the non-randomized studies, the pooled OR ratio showed an insignificant effect of albumin administration towards total burn resuscitation (OR=1.42 [-0.36, 3.20], p=0.09). The forest plot showed a trend favoring the control group over the albumin group. Statistically significant heterogeneity was observed between the randomized and non-randomized studies (p<0.000001, I^2=95%), which was likely due to confounding bias from differences in study design and patient characteristics.

Incidence of Sepsis

The incidence of sepsis was a secondary outcome, assessed in two RCTs [16, 18] and three NRCTs [19, 23, 25]. In randomized studies, sepsis occurred in 15.2% of patients in the albumin group versus 36.8% in the control group (OR=0.37 [0.06-2.17], p=0.27). In the non-randomized studies, the incidence was 48.8% versus 43.8%, respectively (OR=1.21 [1.04-1.41], p=0.01). The overall pooled analysis indicated a significantly higher incidence of sepsis with albumin administration (47.5% vs. 43.7%, OR=1.18 [1.02-1.38], p=0.03), as illustrated in Figure 4.

The randomized studies reported fewer sepsis incidents in the albumin group than the control group (30 vs 132 incidences). In contrast, one non-randomized study collectively showed a higher incidence in the albumin group. No significant heterogeneity was found among the non-randomized studies (I^2=0%, p=0.45). However, variations in the definition of sepsis and incomplete reporting across studies might have introduced bias.

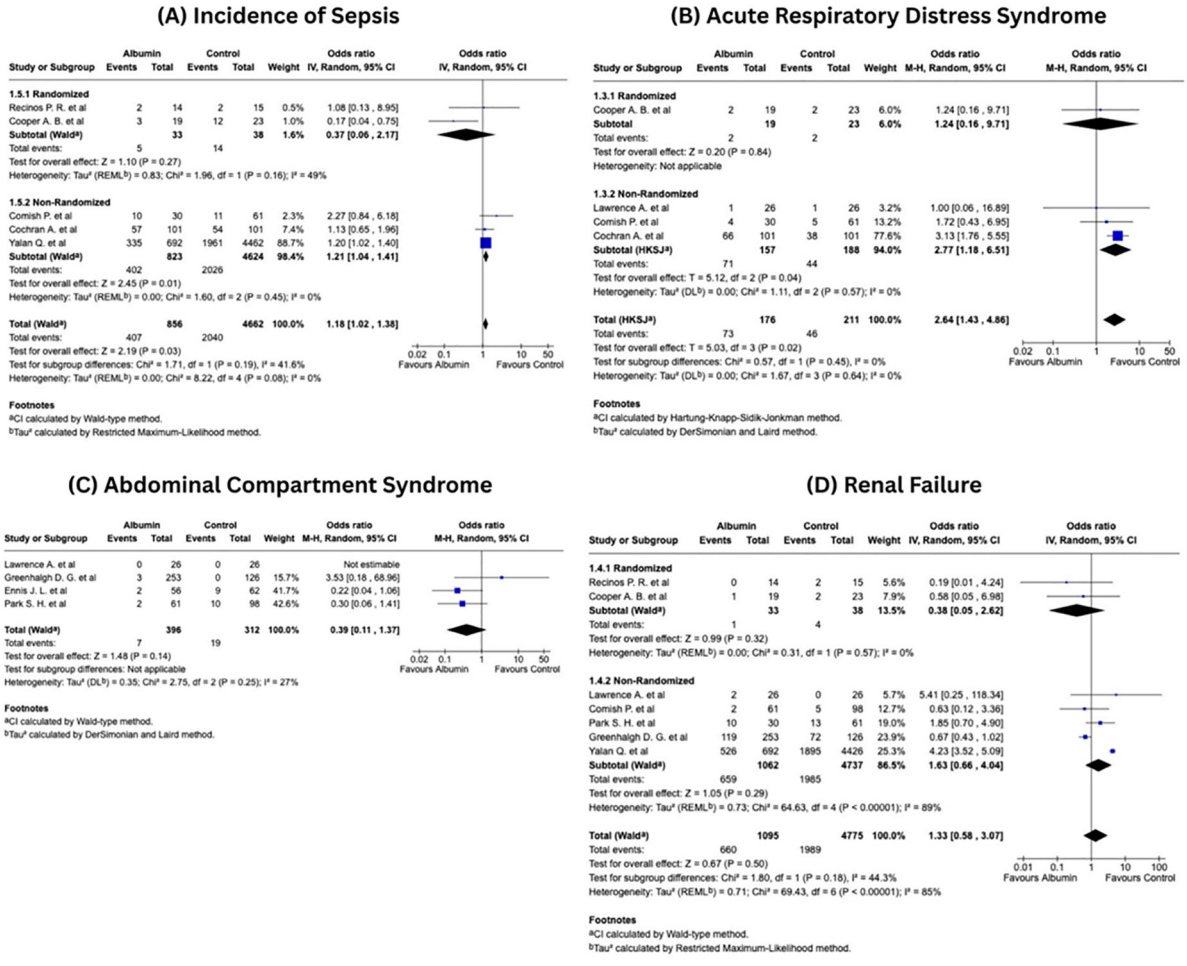

Fig. 4. Forest plots of albumin administration towards incidence of sepsis, ARDS, ACS, and renal failure.

Acute Respiratory Distress Syndrome

The incidence of acute respiratory distress syndrome (ARDS) was evaluated as a secondary outcome in one RCT [18] and three NRCTs [19, 21, 23]. In the randomized study, ARDS occurred in 10.5% of patients in the albumin group versus 8.7% in the control group, with no significant difference (OR=1.24 [0.16-9.71], p=0.84). In non-randomized studies, the incidence was significantly higher in the albumin group (45.2% vs. 23.4%, OR=2.77 [1.18-6.51], p=0.04). The overall pooled analysis showed a significantly higher incidence of ARDS in the albumin group (41.5% vs. 21.8%, OR=2.64 [1.43-4.86], p=0.02), as shown in Figure 4.

The single RCT reported a lower incidence of ARDS in the control group. In contrast, both groups in the RCT study had the same incidence (4 vs 113 incidences). In contrast, the non-randomized studies consistently observed a higher incidence in the albumin group. For instance, one NRCT reported a higher incidence of ARDS in the albumin group, but also reported a higher baseline incidence of inhalation injury in that group [19]. No significant heterogeneity was found among the non-randomized studies (I^2=0%, p=0.57). These observed associations might be confounded by the higher rate of inhalation injury in the albumin groups of these studies.

Abdominal Compartment Syndrome

The incidence of abdominal compartment syndrome (ACS) was evaluated as a secondary outcome. It was assessed in four NRCTs [20-22, 24]; no RCTs reported on this outcome. A total of 708 cases of ACS were reported across the non-randomized studies. The overall effect of albumin administration on ACS is shown in Figure 4.

Two out of the four studies reported a lower incidence of ACS in the albumin group than in the control group. The overall pooled effect on ACS was not statistically significant (OR=0.39 [0.11-1.37], p=0.14). No significant heterogeneity was observed between studies (I^2=27%, p=0.25). As the evidence is derived solely from non-randomized studies, the findings remain susceptible to selection bias.

Renal Failure

The incidence of renal failure was evaluated as a final secondary outcome. It was assessed in two RCTs [16, 18] and five NRCTs [21-25]. The randomized studies reported 5 cases of renal failure, while the non-randomized studies reported 2,644 cases.

The overall effect of albumin administration on renal failure is shown in Figure 4. In randomized studies, the pooled odds ratio was 0.38 [95% CI: 0.05, 2.62, p=0.32]. In the non-randomized studies,

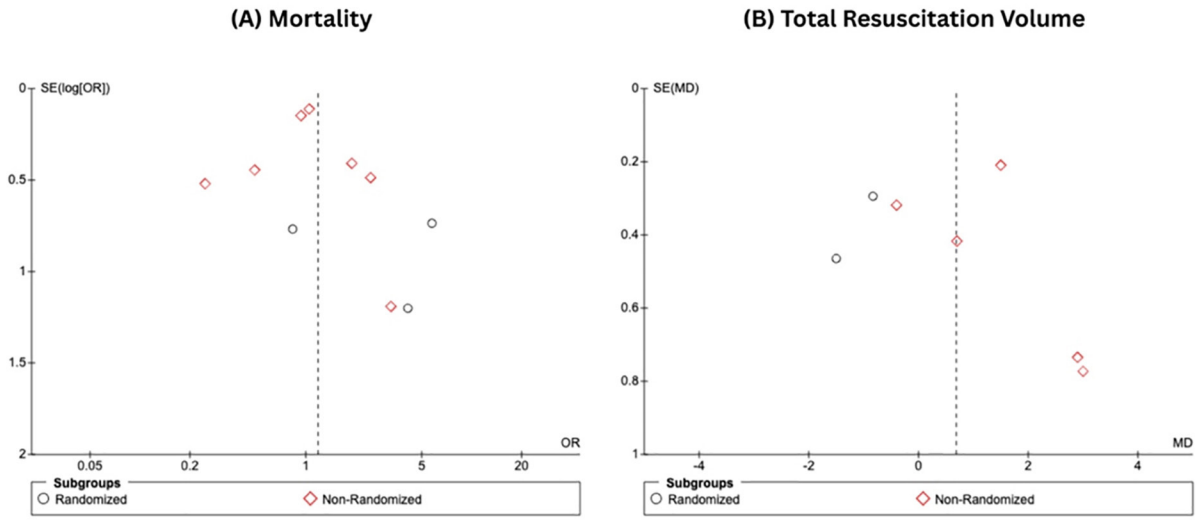

Fig. 5. Funnel plot in mortality and total resuscitation volume

the pooled OR was 1.63 [95% CI: 0.66- 4.04, p=0.29]. Significant heterogeneity was found among the non-randomized studies (I^2=89%, p=<0.00001), which was likely attributable to confounding bias from differences in patient characteristics and study methodology.

Publication Bias

Publication bias was assessed using Cochrane Review Manager 9.3.0 by generating funnel plots to evaluate the distribution of studies. Figure 5 illustrates the funnel plots for the primary outcomes of mortality and total resuscitation volume. The funnel plot for total resuscitation volume shows an asymmetrical distribution, with an imbalance toward the left of the centerline, suggesting potential bias. In contrast, the funnel plot for mortality indicates a symmetrical distribution of studies. This asymmetry observed for total resuscitation volume implies that the pooled result for this outcome may be influenced by publication bias, as smaller studies showing certain effects may be missing from the literature.

Discussion

This systematic review and meta-analysis evaluated the hypothesis that albumin administration in burn resuscitation would reduce mortality, total resuscitation volume, and the incidence of complications, such as sepsis, acute respiratory distress syndrome, acute compartment syndrome, and incidence of renal failure. The analysis also highlighted significant limitations within the existing literature. We identified eleven relevant studies, comprising three RCTs and eight NRCTs. The RCTs were generally of high quality, though some concerns were raised regarding the randomization process, deviations from intended interventions, missing outcome data, and outcome measurement. The NRCTs demonstrated a serious risk of confounding bias, largely due to imbalances in key prognostic factors such as TBSA and inhalation injury, though they showed a moderate to low risk of bias in other domains.

The primary outcomes were mortality, assessed in ten studies [16-23, 25, 26], and total resuscitation volume, assessed in seven studies [16, 17, 19, 21-24]. Secondary outcomes included the incidence of sepsis, ARDS, ACS, and renal failure. The intervention was consistent across studies, with the treatment group receiving albumin. Most control groups used Ringer's lactate, except for three studies that did not specify the crystalloid used [20, 25, 26].

Non-randomized studies contributed over 97% of the total patient population, providing substantial statistical power to this meta-analysis. Although RCTs are preferred, this does not suggest that high-quality non-randomized studies contribute less in this analysis.

Unlike the three prior meta-analyses on albumin administration in burn patients, we specifically examined albumin as a burn resuscitation strategy compared to a control group (primarily Ringer's Lactate) in adults [1, 13]. For instance, Wilkes *et al.,* included all patients who received albumin administration, not exclusively for resuscitation, thereby incorporating pediatric patients and those with hypoalbuminemia [27]. Meanwhile, Navickis *et al.,* and Elajiek *et al.,* pooled studies on albumin administration in burn patients but focused on outcomes such as mortality and total resuscitation volume [1, 13].

Methodologically, the majority of the included studies utilized the Parkland formula or a modification to estimate fluid requirements, though Ennis *et al.,* Yalan *et al.,* and Nakamura *et al.,* did not specify their calculation method [20, 25, 26]. Resuscitation protocols were largely consistent, with nine of the eleven studies defining a 24-hour resuscitation phase and using urine output (UOP) as the primary endpoint for adequacy, except for Yalan *et al.,* and Nakamura *et al.,* who didn't specify their resuscitation endpoints.

Regarding mortality, our findings indicated that albumin administration did not significantly affect mortality, despite a non-significant trend toward higher mortality in the albumin group. This contrasted with the meta-analysis by Navickis *et al.,* who incorporated seven similar studies and reported contradictory findings [1]. The relationship between mortality and burn severity is complex. Tasleem *et al.,* found no significant association between mortality and the degree of burns. However, they reported a significant correlation with the TBSA affected, identifying sepsis as a primary contributing factor [28]. Patients with severe burns involving more than 20% TBSA were at an increased risk of excessive fluid loss, leading to hypovolemic shock and elevated troponin I levels, which collectively increased the risk of cardiac arrest [28, 29].

Despite its use in clinical practice, our analysis found that albumin administration did not significantly reduce the total resuscitation volume in burn patients. The evidence was conflicting: while RCTs suggested lower volumes with albumin [16, 17], NRCTs consistently reported higher volumes [19, 21-24], resulting in an overall non-significant effect. A trend favoring the control group was noted, suggesting albumin might not reduce resuscitation volume. To date, only one previous meta-analysis has evaluated this outcome, incorporating three similar RCTs, and reported that burn patients receiving albumin required significantly less fluid during resuscitation [13]. In our analysis, we also included five additional NRCTs. Cochran *et al.,* and Comish *et al.,* found no significant difference in total resuscitation volume between the crystalloid and colloid groups [19, 23]. However, Comish *et al.,* noted that the use of 25% albumin, as a "rescue colloid," resulted in a lower in/out ratio (IOR) in the albumin than in the control group [23]. Lawrence *et al.,* reported that adding colloid to Parkland resuscitation rapidly reduced hourly fluid requirements, restored normal resuscitation ratios, and ameliorated fluid creep [21]. These findings might be contextualized by Greenhalgh *et al.,* who observed that patients receiving albumin tended to be older with larger, deeper burns and more severe organ dysfunction, often requiring 24-hour resuscitation volumes at or above the Parkland formula estimate, regardless of treatment [24].

We also examined sepsis as a secondary outcome and found that albumin administration was associated with a significantly higher incidence. This finding must be interpreted with caution, as it may be confounded by baseline patient characteristics. For instance, three studies reported a higher incidence of inhalation injury in the albumin group, a known risk of septic complications [19]. Heimburg *et al.,* reported that all patients with inhalation injury in their study developed sepsis [30]. Furthermore, the relationship between serum albumin levels and infection is well-established. Zega *et al.,* found a substantial correlation between albumin levels and sepsis in burn patients, reporting that 90.6% of patients with low albumin levels developed sepsis [31]. Therefore, while our pooled analysis did not show a protective effect of albumin administration against sepsis, it is plausible that exogenous albumin could help mitigate risk in patients with hypoalbuminemia [13].

The incidence of ARDS was another secondary outcome, and our analysis found it to be significantly higher in patients who received albumin. This contrasts with some physiological hypotheses. For example, Wang *et al.,* reported that early administration of albumin, particularly during the resuscitation phase, could reduce disease severity in ARDS patients and enhance vascular function in those with septic shock [32]. The same study also suggested that human albumin was associated with better outcomes in patients with a SOFA score ≤10, including improved organ function, better drug responsiveness, and fewer adverse events [32]. The discrepancy between these potential benefits and our findings might again be explained by the greater initial injury severity in the albumin groups within the included studies.

Another secondary outcome was the incidence of ACS. Although the difference was not statistically significant, both studies reported a lower incidence of ACS in patients who received albumin than in those in the control group. This potential benefit could be understood in the context of fluid management. Vatankhah *et al.,* reported that patients requiring large-volume resuscitation, such as those with extensive burns, are at greater risk for developing ACS [33]. Aggressive crystalloid resuscitation could lead to considerable edema in both burned and unburned tissues, reducing oxygen supply and increasing intra-abdominal pressure [33]. As a severe manifestation of this edema, ACS could be a life-threatening complication. The use of albumin was consistently associated with a substantial reduction in this complication and might help reduce the need for subsequent interventions such as escharotomy or fasciotomy.

The final secondary outcome was renal failure. The present study found that albumin administration did not have a significant effect on its incidence. According to Frenette *et al.,* albumin administration was associated with a dose-dependent increased risk of AKI [34]. Other risk factors for AKI included reduced left ventricular ejection fraction (LVEF), diuretic use, anemia, heart valve surgery, longer duration of extracorporeal circulation, hemodynamic instability, and the use of albumin, pentastarch 10%, and transfusions [34]. Conversely, Gomez *et al.,* reported that although a higher rate of AKI at any stage was observed in patients receiving albumin administration, it did not typically progress to persistent renal dysfunction [35]. These conflicting findings suggested that the impact of albumin on renal function remained uncertain and might be context-dependent.

This systematic review and meta-analysis had several strengths. First, it employed a comprehensive search strategy and a rigorous process involving duplicate study screening, eligibility assessments, and data extraction to minimize selection bias. The methodological quality of the included trials was also critically appraised using established tools (RoB 2 and ROBINS-I). Furthermore, this systematic review and meta-analysis provided an update to the existing evidence on albumin use in burn resuscitation. Unlike previous meta-analyses, it incorporated pivotal recent studies [22-26], thereby offering a more current and comprehensive evidence base. It also expanded the scope of outcomes by evaluating both primary and secondary endpoints in detail, which allowed for a more nuanced interpretation of the findings. These approaches strengthened the evidence supporting the role of albumin in improving patient outcomes, particularly in reducing total resuscitation volume and mortality.

However, several limitations must be acknowledged. The inclusion of non-randomized studies (NRCTs), which constituted the majority of the evidence, introduces a significant risk of bias, particularly from confounding. Important baseline characteristics, such as %TBSA burned and the presence of inhalation injury, often differed between intervention groups in these studies. These imbalances, coupled with variations in resuscitation protocols, make it difficult to isolate the true effect of albumin and likely influenced the pooled results.

In addition, incomplete data reporting in some studies, such as the significant missing outcome data in Recinos *et al.,* increased the risk of bias [16]. Clinical heterogeneity was also substantial, stemming from variations in albumin concentration, dosage, timing of administration, and inconsistently described resuscitation protocols in the control groups. These factors likely contributed to the high statistical heterogeneity observed in the meta-analyses.

Despite these limitations, our findings suggested that albumin could have a beneficial role when used selectively in burn resuscitation, particularly in patients with large TBSA burns or those at high risk of fluid overload and its complications.

Future research should prioritize well-designed, adequately powered RCTs that employ consistent albumin administration and clearly defined control groups. Such studies are essential to establish a more robust and reliable evidence base. In the meantime, this systematic review provided a comprehensive summary of the current evidence and might inform the design of future clinical studies.

In conclusion, this meta-analysis found that albumin administration did not have a significant effect on mortality and total resuscitation volume in burn patients. In contrast, a significant association was observed between albumin use and a higher incidence of sepsis and ARDS. However, these findings are likely confounded by the greater baseline injury severity in patients receiving albumin, as evidenced in the non-randomized studies. Therefore, the current evidence does not support the routine use of albumin in burn resuscitation to reduce mortality or fluid volume. Any potential benefit must be carefully weighed against the possibility of increased complications, a relationship that future high-quality RCTs must clarify.

Declaration

Ethical approval and participation consent: Not applicable.

Consent for publication: All authors have agreed to the publication of this manuscript.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Funding: This work did not receive any specific funding from governmental, commercial, or non-profit organizations.

Authors' Contribution: AW: Conceptualization, investigation, writing-original draft, visualization, formal analysis, project administration, supervision, methodology, and proof-reading; NF: Investigation, writing-review, proof-reading, and editing; PFH: Investigation, writing-review, and editing; SO: Supervision, investigation, writing-review, and editing. All authors played a vital role in the study's conception and design, critically reviewed the manuscript for significant intellectual contributions, and provided final approval for submission.

Acknowledgment: Non applicable

References

1. N Navickis RJ, Greenhalgh DG, Wilkes MM. Albumin in burn shock resuscitation: a meta-analysis of controlled clinical studies. *J Burn Care Res*. 2016;**37**(3):e268–e278.
2. Rossis CG, Yiacoumettis AM. Burns caused by napalm bombs. *Burns*. 1980;**6**(4):251-2.
3. Peng HT, Singh K, Rhind SG, da Luz L, Beckett A. Dried plasma for major trauma: past, present, and future. *Life (Basel)*. 2024;**14**(5):619.
4. Cartotto R, Johnson LS, Savetamal A, Greenhalgh D, Kubasiak JC, Pham TN, Rizzo JA, Sen S, Main E. American Burn Association Clinical Practice Guidelines on Burn Shock Resuscitation. *J Burn Care Res*. 2024;**45**(3):565-89.
5. Daniels M, Fuchs PC, Lefering R, Grigutsch D, Seyhan H, Limper U, et al. Is the Parkland formula still the best method for determining the fluid resuscitation volume in adults for the first 24 hours after injury? A retrospective analysis of burn patients in Germany. *Burns*. 2021;**47**(4):914-21.
6. Hunter JE, Drew PJ, Potokar TS, Dickson W, Hemington-Gorse

SJ. Albumin resuscitation in burns: a hybrid regime to mitigate fluid creep. *Scars Burn Heal*. 2016;**2**:2059513116642083.
7. Saffle JI. The phenomenon of "fluid creep" in acute burn resuscitation. *J Burn Care Res*. 2007;**28**(3):382-95.
8. Fishel RS, Are C, Barbul A. Vessel injury and capillary leak. *Crit Care Med*. 2003;**31**(8 Suppl):S502-11.
9. Ravage ZB, Gomez HF, Czermak BJ, Watkins SA, Till GO. Mediators of microvascular injury in dermal burn wounds. *Inflammation*. 1998;**22**(6):619-29.
10. Saffle JR. Fluid creep and over-resuscitation. *Crit Care Clin*. 2016;**32**(4):587-98.
11. Pruitt BA Jr. Protection from excessive resuscitation: "pushing the pendulum back". *J Trauma*. 2000;**49**(3):567-8.
12. Atiyeh BS, Dibo SA, Ibrahim AE, Zgheib ER. Acute burn resuscitation and fluid creep: it is time for colloid rehabilitation. Ann Burns Fire Disasters. 2012;**25**(2):59-65.
13. Eljaiek R, Heylbroeck C, Dubois MJ. Albumin administration for fluid resuscitation in burn patients: A systematic review and meta-analysis. *Burns*. 2017;**43**(1):17-24.
14. Cartotto R, Greenhalgh D. Colloids in acute burn resuscitation. *Crit Care Clin*. 2016;**32**(4):507-23.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;**6**(7):e1000097.
16. Recinos PR, Hartford CA, Ziffren SE. Fluid resuscitation of burn patients comparing a crystalloid with a colloid containing solution: a prospective study. *J Iowa Med Soc*. 1975;**65**(10):426–32.
17. Goodwin CW, Dorethy J, Lam V, Pruitt BA Jr. Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury. *Ann Surg*. 1983;**197**(5):520-31.
18. Cooper AB, Cohn SM, Zhang HS, Hanna K, Stewart TE, Slutsky AS; ALBUR Investigators. Five percent albumin for adult burn shock resuscitation: lack of effect on daily multiple organ dysfunction score. *Transfusion*. 2006;**46**(1):80-9.
19. Cochran A, Morris SE, Edelman LS, Saffle JR. Burn patient characteristics and outcomes following resuscitation with albumin. *Burns*. 2007;**33**(1):25-30.
20. Ennis JL, Chung KK, Renz EM, Barillo DJ, Albrecht MC, Jones JA, et al. Joint Theater Trauma System implementation of burn resuscitation guidelines improves outcomes in severely burned military casualties. *J Trauma*. 2008 Feb;64(2 Suppl):S146-51; discussion S151-2.
21. Lawrence A, Faraklas I, Watkins H, Allen A, Cochran A, Morris S, Saffle J. Colloid administration normalizes resuscitation ratio and ameliorates "fluid creep". *J Burn Care Res*. 2010;**31**(1):40-7.
22. Park SH, Hemmila MR, Wahl WL. Early albumin use improves mortality in difficult to resuscitate burn patients. *J Trauma Acute Care Surg*. 2012;**73**(5):1294-7.
23. Comish P, Walsh M, Castillo-Angeles M, Kuhlenschmidt K, Carlson D, Arnoldo B, et al. Adoption of rescue colloid during burn resuscitation decreases fluid administered and restores end-organ perfusion. *Burns*. 2021;**47**(8):1844-50.
24. Greenhalgh DG, Cartotto R, Taylor SL, Fine JR, Lewis GM, Smith DJ Jr, et al. Burn Resuscitation Practices in North America: Results of the Acute Burn Resuscitation Multicenter Prospective Trial (ABRUPT). *Ann Surg*. 2023;**277**(3):512-9.
25. Yalan Q, Yinzhou L, Binfei T, Yunxing C, Wenqi H, An Z. Early high-volume resuscitation with crystalloid solution combined with albumin improves survival of critically ill patients: A retrospective analysis from MIMIC-IV database. *Burns*. 2024;**50**(4):893-902.
26. Nakamura K, Isogai T, Ohbe H, Nakajima M, Matsui H, Fushimi K, et al. Effect of fluid resuscitation with albumin on mortality in patients with severe burns: A nationwide inpatient data analysis. *Burns*. 2024;**50**(9):107227.
27. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. Ann Intern Med. 2001;**135**(3):149-64.
28. Tasleem S, Siddiqui AI, Zuberi MAW, Tariq H, Abdullah M, Hameed A, et al. Mortality patterns and risk factors in burn patients: A cross-sectional study from Pakistan. *Burns Open*. 2024;**8**(1):13-18.
29. Hughes A, Almeland SK, Leclerc T, Ogura T, Hayashi M, Mills JA, et al. Recommendations for burns care in mass casualty incidents: WHO Emergency Medical Teams Technical Working Group on Burns (WHO TWGB) 2017-2020. *Burns*. 2021;**47**(2):349-70.
30. Von Heimburg D, Stieghorst W, Khorram-Sefat R, Pallua N. Procalcitonin--a sepsis parameter in severe burn injuries. *Burns*. 1998;**24**(8):745-50.
31. Zega Y, Dachlan I. Sepsis risk factor in Mount Merapi eruption victims with 2nd or 3rd degree burn injury. *J Med Sci*. 2018;**50**(1):86-92.
32. Wang X, Zhang T, Gao X, Cai H, Guo M, Liu Q, et al. Early human albumin administration is associated with reduced mortality in septic shock patients with acute respiratory distress syndrome: A retrospective study from the MIMIC-III database. *Front Physiol*. 2023;**14**:1142329.
33. Vatankhah S, Sheikhi RA, Heidari M, Moradimajd P. The relationship between fluid resuscitation and intra-abdominal hypertension in patients with blunt abdominal trauma. *Int J Crit Illn Inj Sci*. 2018;**8**(3):149-53.
34. Frenette AJ, Bouchard J, Bernier P, Charbonneau A, Nguyen LT, Rioux JP, et al. Albumin administration is associated with acute kidney injury in cardiac surgery: a propensity score analysis. *Crit Care*. 2014;**18**(6):602.
35. Gomez H, Priyanka P, Bataineh A, Keener CM, Clermont G, Kellum JA. Effects of 5% Albumin Plus Saline Versus Saline Alone on Outcomes From Large-Volume Resuscitation in Critically Ill Patients. *Crit Care Med*. 2021;**49**(1):79-90.