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A study protocol of the additional human albumin during resuscitation in patients with surgical septic shock: A randomized controlled trial (the ALBumin Use in Surgical septic shock, ALBUS study)

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The data and code were available upon reasonable request (Nattachai Hemtanon, email address: nattachai.hem@mahidol.ac.th)

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All authors have no conflicts of interest to declare.

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ABSTRACT:

Background: Surgical septic shock has a high mortality rate, which increases further in patients with low serum albumin levels. Current guidelines recommend crystalloids for initial fluid resuscitation, but excessive fluid administration can lead to complications such as volume overload and intra-abdominal hypertension. Human albumin solution (HA) may have benefits due to its oncotic properties, anti-inflammatory effects, and stabilization of the vascular endothelium. The latter may result in reduced mortality and improve clinical outcomes compared to standard care.

Objectives: To evaluate whether adjunctive administration of 20% HA in combination with standard care reduces 28-day all-cause mortality compared to standard care alone in adult patients with surgical septic shock.

Methods: This single-center, open-labeled, randomized controlled trial is conducted in surgical intensive care units (ICU) at Siriraj Hospital, Bangkok, Thailand. The patients admitted with confirmed or suspected surgical infection within 48 hours and fulfilling Sepsis-3 criteria for septic shock are enrolled. Patients are randomized at 1:1 to receive either protocolized 20% HA as an adjunct to standard care or standard care alone. The intervention is administered for 72 hours. The primary outcome is 28-day all-cause mortality. Secondary outcomes are hospital length of stay (LOS), ICU LOS, days alive and free of vasopressors and mechanical ventilation, cumulative 7-day fluid balance, rate of acute kidney injury requiring renal replacement therapy, and gastrointestinal function recovery. A total of 304 patients (152 per group), accounting for an estimated 10% dropout rate, is required. Analysis follows intention-to-treat principles.

Hypothesis: We hypothesized that adding 20% HA to standard care would improve clinical outcomes compared with standard care alone.

Conclusions: The ALBUS trial is the randomized controlled trial designed specifically to evaluate the addition of 20% HA to standard care during resuscitation in surgical septic shock. We aim to provide evidence to support the use of HA as an adjunctive resuscitation in reducing 28-day mortality and improving clinical outcomes in the surgical population.

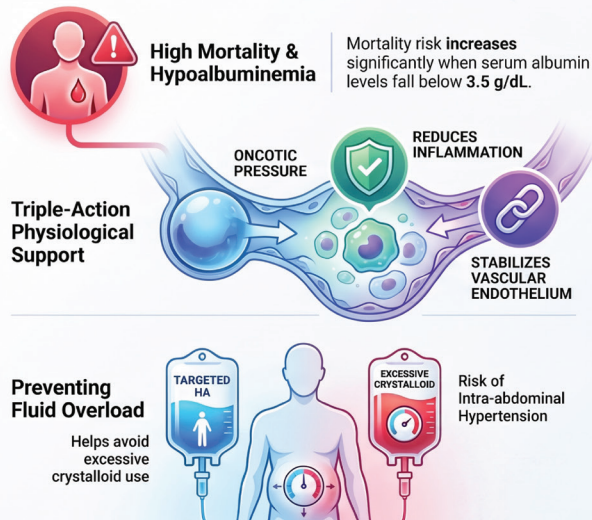
Ethics and dissemination: This trial received approval from the Siriraj Institutional Review Board.

Trial registration: NCT07212582

Keywords: Surgical septic shock; Human albumin; Fluid resuscitation; Mortality; Randomized controlled trial

A study protocol of the additional human albumin during resuscitation in patients with surgical septic shock: A randomized controlled trial (the ALBum in Surgical septic shock, ALBUS study)

RATIONALE: WHY HUMAN ALBUMIN?

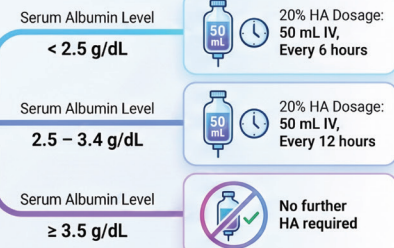


THE ALBUS TRIAL PROTOCOL

72-HOUR INTERVENTION WINDOW
Protocolized HA is administered during the acute 72-hour resuscitation phase of septic shock.

PRIMARY OUTCOME: 28-DAY MORTALITY
Evaluates HA's impact on all-cause mortality compared to standard care alone.

PRECISION TITRATED DOSING



Summarized infographic: Hemtanon, et al. Clin Crit Care 2026; 34: e260025

INTRODUCTION

Septic shock is a major cause of admission to intensive care units (ICUs), with a high mortality rate ranging from 20% to 50% [1-5]. Specifically in surgical ICUs, surgical septic shock, which is defined as septic shock requiring emergent surgical intervention or a procedure to eliminate, drain, or correct the source of infection, is frequently encountered. This condition carries a mortality rate of approximately 36% [6], which increased further in patients with low serum albumin levels, advanced age, high severity-of-illness scores, need for reoperation, and respiratory disease [7-9].

Intravenous fluid administration is a cornerstone in the management of surgical septic shock, aiming to enhance peripheral oxygen delivery and maintain sufficient blood pressure for organ perfusion. The current guideline for septic shock management recommends crystalloid solutions as the initial and primary fluid choice [10]. If a patient has received a substantial volume of crystalloids (generally about 30 mL/kg), the attending physician may consider human albumin solutions (HA) as supplementary fluid to avoid excessive fluid administration, which can negatively impact patient outcomes. In addition, aggressive fluid resuscitation and the presence of shock are statistically significant risk factors for developing intra-abdominal hypertension (IAH), particularly in patients with intra-abdominal infection [8,11]. The recent 2024 recommendation for intravenous fluid therapy in intra-abdominal infection cautions against fluid overload, as fluid leakage into the abdominal cavity can elevate intra-abdominal pressure [12]. This can worsen patient outcomes by increasing inflammation, raising the risk of acute kidney injury and elevating 28- and 90-day mortality rates [13,14].

Many retrospective studies have demonstrated a statistically significant inverse relationship between low serum albumin level (< 3.5 g/dL) and mortality, with the risk esca-

KEY MESSAGES:

- Surgical septic shock carries high mortality, especially in patients with hypoalbuminemia. HA has the property to increase oncotic pressure; beyond that, it also carries anti-inflammatory and endothelial glycocalyx-stabilizing properties, hypothesized to reduce total crystalloid requirements, shorten vasopressor and organ support dependency.
- This randomized controlled trial evaluates adjunctive 20% HA plus standard of care versus standard care alone over 72 hours, with dosing titrated by daily serum albumin level, aiming to explore the beneficial outcomes of this intervention.

lating at very low levels (< 2.5 g/dL) [15-19]. This evidence has led to the use of HA as an additional fluid replacement. The primary goal of using HA is to raise serum albumin levels and enhance fluid retention within a patient's vasculature. Its potential benefits include increasing oncotic pressure, reducing inflammatory processes and stabilizing the vascular endothelial glycocalyx layer [20-22]. These factors can maintain the patient's blood pressure and reduce the total volume of crystalloid needed, potentially leading to a shorter duration of vasopressor use [23,24], reduced mechanical ventilation time [23], and improvement of tissue perfusion [25].

Evidence from the SAFE trial [26], which compared 4% HA versus crystalloids in 6,997 ICU patients. Although the results showed no significant difference in 28-day mortality (20.9% vs. 21.1%, relative risk (RR) 0.99, 95%

confidence interval (CI) 0.91 – 1.09, p-value 0.87), hospital length of stay (LOS), or other outcomes, a subgroup analysis of patients with severe sepsis showed a non-significant trend toward lower mortality in the HA group (30.7% vs 35.3%, RR 0.87, 95%CI 0.74-1.02, p-value 0.09) and a significantly lower net fluid balance. Another large trial, the ALBIOS trial [27], investigated severe sepsis patients. The study compared 20% HA combined with crystalloids to maintain serum albumin > 3 g/dL versus the use of crystalloids alone. The mean baseline serum albumin level in this trial was 2.4 g/dL. Although overall mortality was not statistically different between the groups, a subgroup analysis of patients with septic shock found that the albumin group had a significantly lower mortality rate (RR 0.87, 95%CI 0.77-0.99). Despite these promising findings, surgical patients represented only 32% of the ALBIOS population, which may not adequately capture the specific clinical outcomes and therapeutic requirements of human albumin therapy in surgical septic shock patients managed in the ICU setting. Beyond the uncertainty of its clinical efficacy, the cost-effectiveness analyses from the COASST [28] and EMAISS [29] trials indicated that the administration of HA remains cost-effective in severe sepsis and septic shock patients.

To date, HA is recommended for some specific indications such as volume replacement during large volume abdominal paracentesis in cirrhosis, treatment of hepatorenal syndrome and spontaneous bacterial peritonitis, use in therapeutic plasma exchange, replacement in severe hypoalbuminemia from malabsorption syndrome, nephrotic syndrome, burns, and post-cardiac or thoracic surgery. Some guidelines suggest considering HA in septic shock patients refractory to initial crystalloid resuscitation; however, there is no clear evidence that it significantly reduces mortality, and it is not considered a standard treatment according to current clinical guidelines [10,27]. Therefore, this study aims to evaluate the potential benefits of additional administration of 20% HA combined with standard care during fluid resuscitation in patients with surgical septic shock admitted to the surgical ICUs, focusing on whether maintaining serum albumin above 3.5 g/dL. We hypothesize that it will reduce 28-day all-cause mortality and improve clinical outcomes in these patients.

OBJECTIVES

Primary objective

To evaluate whether adjunctive administration of 20% HA in combination with standard care reduces 28-day all-cause mortality compared to standard care alone in adult patients with surgical septic shock.

Secondary objective

To compare the following outcomes between the groups:

1. Both hospital and ICU LOS
2. Organ support-free days: specifically, days of alive and free (DAF) of vasopressors and DAF of mechanical ventilation within the first 28 days
3. Cumulative fluid balance during the initial 7 days of treatment
4. Incidence of acute kidney injury (AKI) requiring renal replacement therapy (RRT)

5. Gastrointestinal (GI) function recovery is assessed using objective parameters, including the day of achievement of 80% of the enteral nutritional target and the incidence of enteral feeding intolerance.

6. Incidence of adverse reactions associated with 20% HA administration

MATERIALS AND METHODS

Study design and setting

This single-center, open-label, randomized trial will be conducted at general surgical ICUs in Siriraj Hospital, Bangkok, Thailand, which primarily admits patients after surgery excluding cardiothoracic surgery, neurological surgery, and trauma. The study was approved by the Siriraj Hospital Ethics Committee (COA No. SI 823/2025) and was registered with the US Clinical Trial Registry (ClinicalTrials.gov NCT07212582). This protocol has been structured, written, and formatted in strict accordance with the SPIRIT 2025 (Standard Protocol Items: Recommendations for Interventional Trials) statement [30]. The completed SPIRIT 2025 Checklist detailing the location of all recommended items within this manuscript is provided as Supplementary Material 1.

Study population

Patients are eligible for enrollment if they meet all the following criteria:

1. Age $\geq$ 18 years old and admitted to the surgical ICUs.
2. Patients with confirmed or suspected surgical infection who are scheduled to undergo a surgical procedure or intervention within the next 48 hours, or who have undergone surgery within 48 hours prior to study enrollment
3. Patients met the clinical criteria for septic shock [10,31], defined as:
 - o Mean arterial pressure (MAP) < 65 mmHg after initial fluid resuscitation or requiring vasopressors to maintain for at least 1 hour.
 - o and meet one of the following organ dysfunction or tissue hypoperfusion criteria:
 - Organ dysfunction: Sequential Organ Failure Assessment (SOFA) score change $\geq$ 2 points (suggestive of organ failure).
 - Tissue Hypoperfusion (meet any one of these following):
 - Serum lactate > 2 mmol/L.
 - Urine output < 0.5 mL/kg/h for > 2 hours.
 - Clinical signs of hypoperfusion, such as a decline in consciousness, skin mottling, or capillary refill time > 2 seconds.

We will exclude the patients from the study if they meet any of the following criteria:

1. Patient or patient's representative refusal to participate in the trial or documentation of a Do Not Resuscitate (DNR) status.
2. Meeting the inclusion criteria for longer than 24 hours before enrollment
3. Contraindication to or refusal to receive HA
4. History of severe anaphylaxis or uncontrollable adverse reaction of HA

5. Any existing indication where HA might be potentially beneficial, including:
 - a. Cirrhosis
 - b. Large volume paracentesis (> 5 L)
 - c. Hepatorenal syndrome
 - d. Spontaneous bacterial peritonitis
 - e. Therapeutic plasma exchange or plasmapheresis
 - f. Malabsorption syndrome or protein-losing enteropathy
 - g. Nephrotic syndrome
 - h. Burns
 - i. Post cardiac or thoracic surgery
6. Clinical signs or symptoms of volume overload or cardiogenic pulmonary edema, specifically defined by
 - a. Physical examination revealing bilateral lung crepitations and chest radiograph demonstrating bilateral opacity consistent with pulmonary edema
 - b. Combined with central venous pressure (CVP) >15 mmHg or pulmonary occlusive pressure (PAOP) >18 mmHg or N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 900 pg/mL
7. End-stage renal disease or current requirement for RRT
8. Pregnancy or breastfeeding status

Death after enrollment will not be classified as withdrawal; participants who die will be retained in the intention-to-treat population, and 28-day mortality will be ascertained regardless of the timing of death. The study intervention (HA infusion) will be discontinued if a participant or their representative issues a DNR order or declines further life-sustaining treatment, and outcome data will continue to be collected through Day 28, hospital discharge, or death. True withdrawal from the study is limited to voluntary withdrawal of consent by the participant or their representative, in which case no further data will be collected, but data already obtained will be retained for analysis to the extent permitted by the participant.

The administration of the study intervention will be terminated if the participant experiences any of the following:

1. Suspected anaphylaxis of HA, whose symptoms occur following administration and cannot be attributed to other underlying medical causes
2. Intractable adverse reaction associated with HA administration, whose symptoms are refractory to medical treatment, including severe cutaneous adverse reaction and recurrent symptoms upon re-challenge (symptoms subside with medication but relapse following the next dose of HA)

Informed consent will be obtained from all eligible participants or their authorized proxies prior to enrollment. Given that surgical septic shock patients are frequently unable to provide consent due to altered consciousness or hemodynamic instability, consent may be obtained from the patient's legally authorized representative, such as a spouse, adult child, or next of kin, in accordance with the Siriraj Hospital Ethics Committee guidelines and Thai research ethics regulations. Once the patient recovers capacity, re-consent will be sought to confirm continued

participation. The consent process will be conducted by a designated member of the research team who is not involved in the clinical care of that patient, ensuring that the decision to participate is made freely and without coercion. A copy of the signed informed consent form will be provided to the participant or their representative and retained in the study records.

Intervention

After enrollment, participants were assigned to one of two groups (open-labeled): the control group (standard care) or the intervention group (standard care with a protocolized 20% HA infusion). The random allocation sequence was generated using the Research Electronic Data Capture (REDCap) randomization module, hosted at the Research Data Management Unit (RDMU), Faculty of Medicine Siriraj Hospital [32]. It was implemented at a 1:1 ratio using a block size of 4 to ensure balanced group assignments, with randomization triggered at the point of enrollment. The investigator on the team serving in the surgical ICU that month was not involved in the randomization or the treatment intervention.

All enrolled patients will receive routine standard care of septic shock management according to international guidelines [10]. This includes source identification and control; intravenous empirical broad-spectrum antibiotics; intravenous balanced crystalloids as fluid resuscitation; vasopressors; lactate monitoring; and other adjunctive therapies (e.g., corticosteroids, thiamine, and ventilatory and renal support) as clinically indicated. To ensure maximum patient safety and accommodate acute clinical fluctuations inherent to critical illness, subsequent therapeutic adjustments—including the weaning of vasopressors, fluid administration, and titration of mechanical ventilatory support—were tailored to individual patient needs at the clinical discretion of the attending intensive care team.

In the control group, standard care alone, HA may be given according to the discretion of the treating physician based on the separate indications regarding the hospital's rational drug utilization (RDU) protocol (e.g., receiving crystalloids > 60 mL/kg in perioperative patients, severe hypoalbuminemia < 2.5 g/dL with capillary leakage syndrome).

In the intervention group, patients will receive 20% HA (Human Albumin Grifols® concentration 20 g/100 mL, 50 mL/bottle) intravenously in accordance with the prescribed study protocol, serving as an adjunctive therapy to the routine standard care. The first dose of HA will be given to patients immediately once enrollment regardless of baseline serum albumin level since the low baseline albumin levels were demonstrated in septic shock patients in previous literature [17,27,33,34]. Following the initial dose, subsequent HA infusion will be determined by the patient's serum albumin level at enrollment according to the following criteria:

- If the serum albumin level is ≥ 3.5 g/dL: no further HA will be required
- If the serum albumin level is 2.5–3.4 g/dL: the patient will receive 20% HA 50 mL intravenous drip over 4 hours every 12 hours
- If the serum albumin level is < 2.5 g/dL: the patient

will receive 20% HA 50 mL intravenously drip over 4 hours every 6 hours

Serum albumin cut-off values of 3.5 and 2.5 g/dL were selected based on previous retrospective literature demonstrating their significant association with clinical mortality [18]. The serum albumin level will be re-evaluated on Day 2 and Day 3 at 06:00 A.M. to determine the subsequent 24-hour dosing schedule as described above. The intervention will continue until 72 hours after enrollment, which this timeframe aligns with the resuscitation phase, during which patients are highly susceptible to pathological fluid accumulation. The HA infusion will be omitted if the patient has clinical signs or symptoms of volume overload or a serum sodium > 150 mEq/L. Beyond the defined 72-hour protocol period, subsequent human albumin administration was permitted at the discretion of the attending physicians, strictly guided by the hospital's RDU criteria. To address potential contamination between the study groups, the total amount of HA administered was

meticulously monitored. The adherence to the institutional RDU guidelines served as a pragmatic strategy to minimize non-protocol albumin utilization and mitigate contamination risks. The overall study protocol is summarized in Figure 1.

The serum C-reactive protein (CRP) and serum albumin levels will be measured on Day 2, 3 and 7. Intra-abdominal pressure (IAP) will be measured by aseptic intravesical methods if indicated, such as by abdominal distention, feeding intolerance, or ascites noted during physical examination or ultrasound. Routine intra-abdominal pressure (IAP) monitoring was not universally performed to avoid secondary infection risks in patients with ongoing septic shock. Instead, we adopted an indication-driven approach, reserving IAP measurement for patients exhibiting clinical signs suggesting intra-abdominal hypertension. The standard care protocol is attached as Supplementary Table 1.

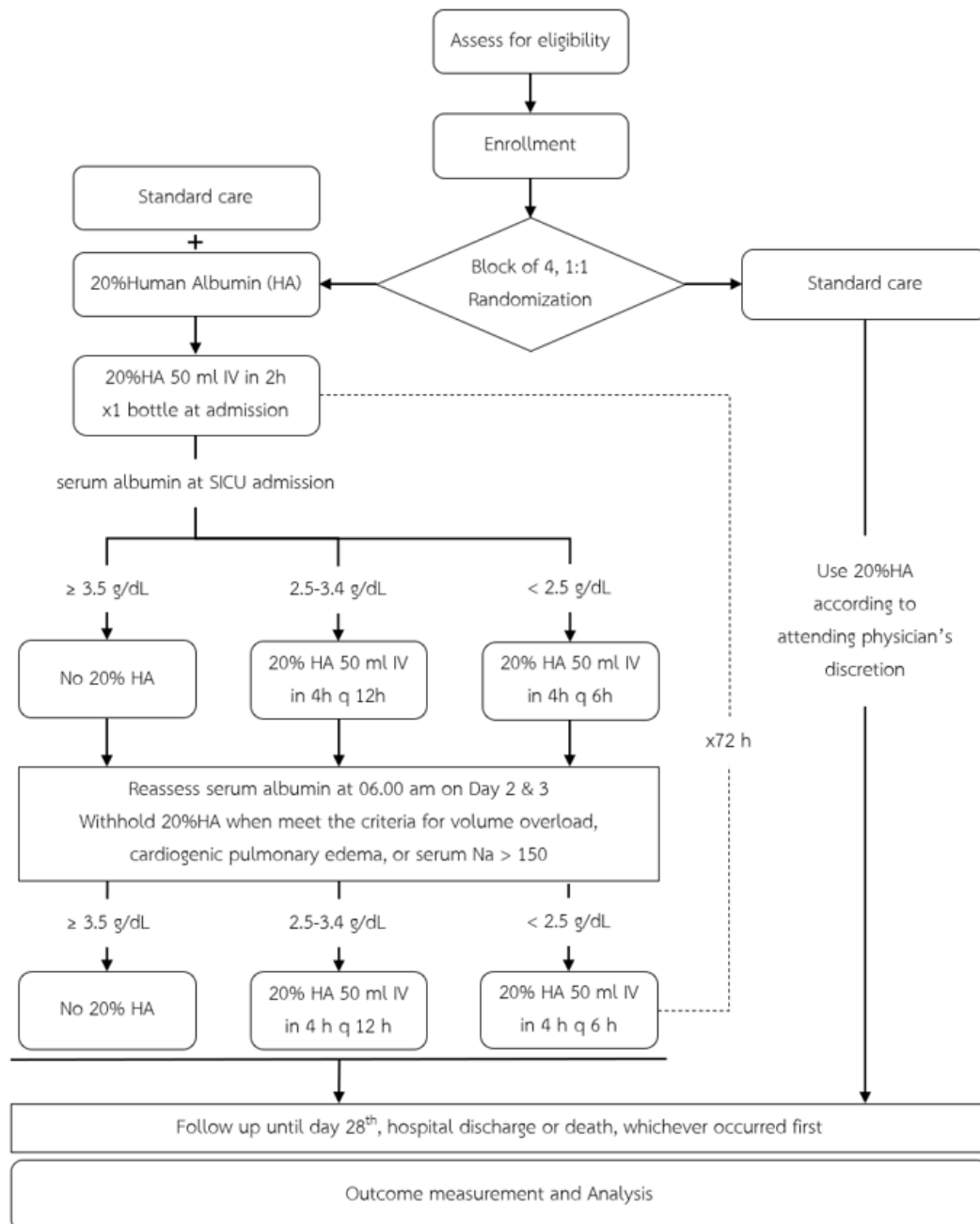


Figure 1. Patient flow, the standard care (control group) and the protocolized 20% HA administration adjunct to standard care (intervention group)

Outcome assessment and monitoring

At the time of enrollment, the baseline characteristics will be assessed, including the patient's demographics, SOFA score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, pre-existing conditions, source of infection, and details of surgical intervention. The baseline hemodynamic variables, resuscitated fluid, vasopressors, and management will be recorded.

After enrollment, the participants will be sequentially monitored, including fluid and hemodynamic management, including amount of fluid intake and output; type and dosage of vasopressors; and details of ventilatory support, including mode and setting of mechanical ventilator, positive end-expiratory pressure (PEEP) level, and the partial pressure of arterial oxygen to fraction of inspired oxygen ratio ($\text{PaO}_2/\text{FiO}_2$, P/F ratio). The focused laboratory marker will be measured, including serum lactate level every 6 hours until the level decreases to < 2 mmol/L, CRP, and serum albumin level, which will be measured every morning on Day 2, 3 and 7. The clinical progression will be assessed daily by SOFA score through Day 7. The surgical complications will also be monitored, including the event of anastomotic leakage, surgical site infection, and the requirement for reoperation.

All participants will be followed until Day 28 after enrollment, hospital discharge, or death, whichever occurs first. The primary outcome is 28-day all-cause mortality, comparing patients receiving adjunctive 20% HA plus standard care with those receiving standard care alone. The prespecified secondary outcomes include hospital LOS, ICU LOS, DAF of vasopressors, DAF of mechanical ventilation, cumulative fluid balance during the first 7 days, AKI requiring RRT, and recovery of GI function. Days alive and free of mechanical ventilation and vasopressors will be calculated through Day 28; patients who die within

this period will be assigned zero free days. Recovery of GI function will be assessed using objective parameters, including the time to achievement of 80% of the enteral nutritional target and the incidence of enteral feeding intolerance. Enteral feeding intolerance is defined as a gastric residual volume > 500 mL, new-onset vomiting, or abdominal distension with an intra-abdominal pressure > 15 mmHg requiring reduction or cessation of enteral feeding. Achievement of the nutritional target is defined as the first 24-hour period in which delivered enteral calories reach $\geq 80\%$ of the calculated energy target. Brief interruptions for scheduled procedures or operating room transport will not be classified as feeding intolerance unless accompanied by the criteria above.

All outcome assessments will be performed by investigators blinded to treatment allocation to minimize detection and adjudication bias. The blinded outcome assessor role will be rotated among the investigator team on a monthly basis to ensure independence and consistency throughout the study period.

The safety outcome of HA administration will be observed, including any adverse reactions, serum sodium level, and incidence of volume overload during the intervention period. Safety outcomes will be adjudicated using the following prespecified definitions: (1) volume overload/pulmonary edema – bilateral crepitations on examination and chest radiograph demonstrating bilateral opacities consistent with pulmonary edema, combined with CVP > 15 mmHg, PAOP > 18 mmHg, or NT-proBNP > 900 pg/mL; (2) hyponatremia – serum sodium > 150 mEq/L; (3) HA-related adverse reaction – anaphylaxis or cutaneous/systemic reaction temporally associated with HA infusion and not attributable to another cause. The planned outcome assessment is summarized in Table 1.

Table 1. Follow up and assessment plan during study period.

Timepoint	Study period								
	D0	D1	D2	D3	D4	D5	D6	D7	D28
Eligibility screen-ing	X								
Informed and consent	X								
Randomization	X								
Intervention		X	X	X					
Baseline data		X							
Hemodynamic and ventilation		X	X	X	X	X	X	X	
Fluid balance, adverse reaction		X	X	X	X	X	X	X	
Mortality, Hospital LOS, ICU LOS, AKI with RRT, DAF of ventilator, DAF of vasopressors, GI function									X
Safety outcome		X	X	X					

Abbreviation: AKI: Acute kidney injury; DAF: Day of alive and free; D0: At ICU admission; D(number): Day after enrollment; GI: Gastro-intestinal tract; ICU: Intensive care unit; LOS: Length of stay; RRT: Renal replacement therapy

DATA ANALYSIS PLAN

Sample size calculation

The sample size was calculated based on an expected 28-day mortality rate of 35% in the control group, drawn from previous literature [6]. We expected to detect a clinically significant reduction in mortality of 40%, corresponding to a 28-day mortality rate of 20% in the intervention group. The calculation used a statistical power of 80% and a two-sided Type I error rate (α) of 0.05.

$$n = \frac{\left[Z_{\alpha/2} \sqrt{P(1-P)} + (Z_{\beta} \sqrt{P_1(1-P_1) + P_2(1-P_2)}) \right]^2}{(P_1 - P_2)^2}$$

$$P = \frac{P_1 + P_2}{2} = \frac{0.35 + 0.20}{2} = \frac{0.55}{2} = 0.275$$

$$n = \frac{\left[1.96 \sqrt{2(0.275)(1-0.275)} + 0.84 \sqrt{0.35(1-0.35) + 0.20(1-0.20)} \right]^2}{(0.35 - 0.20)^2}$$

This analysis determined a requirement for a minimum of 138 participants per group. To compensate for an estimated 10% dropout rate, 152 participants per group will be recruited. In summary, a total of 304 septic shock patients will be enrolled in this study.

OUTCOME ANALYSIS PLAN

Statistical analysis

All analyses will follow the intention-to-treat principle. All randomized patients will be analyzed according to their assigned group. Baseline characteristics will be summarized descriptively as counts with percentages, mean with standard deviation, or median with interquartile range, as appropriate. No formal significance testing will be performed for baseline comparisons.

The primary analysis will use a Bayesian framework. The primary outcome, 28-day all-cause mortality, will be analyzed using Bayesian logistic regression with treatment group as the main predictor. The treatment effect will be reported as an odds ratio with a 95% credible interval and the posterior probability that adjunctive 20% HA administration reduces 28-day mortality compared with standard care. Weakly informative priors will be used for the primary analysis. The treatment effect on the log-odds scale will use a normal (0, 0.7) prior, centered at no effect and corresponding approximately to a 95% prior odds ratio range of 0.25 to 3.94. The intercept will use a normal (qlogis(0.35), 1.0) prior on the log-odds scale, reflecting the anticipated control-group mortality used in the sample size calculation while allowing uncertainty around this estimate. Prior sensitivity will be assessed using a skeptical treatment-effect prior, normal (0, 0.35), corresponding approximately to a 95% prior odds ratio range of 0.50 to 1.99.

For the primary outcome, posterior probabilities will be used to quantify evidence of benefit. A posterior probability of benefit $\geq 95\%$ will be considered strong evidence, while 90% to $< 95\%$ will be considered suggestive evidence. These thresholds are intended to guide interpretation and will not serve as formal decisions or stopping rules. Findings

will be interpreted according to effect size, uncertainty, safety outcomes, and consistency across analyses. Secondary outcomes will be analyzed using Bayesian regression models appropriate to outcome type and distribution. No formal adjustment for multiplicity will be applied to secondary outcomes or subgroup analyses; these findings will be considered supportive or exploratory and interpreted cautiously. Binary outcomes will be analyzed using logistic regression. Continuous, skewed, and count outcomes will be analyzed using Gaussian, Student's t, log-normal, Poisson, or negative binomial models, as appropriate. Outcome-specific model specifications, prior distributions, and sensitivity analyses will be prespecified in a detailed statistical analysis plan before database lock. Results will be reported as posterior estimates with 95% credible intervals and posterior probabilities of benefit where applicable. Adjusted analyses of the primary outcome will be performed as supportive analyses, adjusting for prespecified clinically important variables including baseline serum albumin, SOFA score, lactate level, source of infection, pre-enrollment fluid resuscitation, and vasopressor dose at enrollment. Additional adjustments for clinically important baseline imbalances may be considered if needed.

Conventional frequentist analyses will be performed as supportive analyses. The primary outcome will be analyzed using logistic regression and reported as an odds ratio with 95% confidence interval and two-sided p-value. Risk difference and relative risk with 95% confidence intervals may also be reported for clinical interpretation. Frequentist analyses of secondary outcomes may be performed using generalized linear models appropriate to each outcome.

Prespecified subgroup analyses will explore heterogeneity of treatment effect according to source of infection, baseline serum albumin, baseline lactate, and vasopressor dose at enrollment, with the Holm-Bonferroni correction applied to adjust the statistical significance thresholds and control for Type I error inflation. These analyses will include treatment-by-subgroup interaction terms and will be considered exploratory.

An interim analysis will be performed after enrollment of approximately 50% of the target sample size. This analysis will focus primarily on safety, including adverse reactions, hypernatremia, volume overload, and unexpected mortality imbalance. Bayesian posterior summaries for the primary outcome may be reviewed for monitoring, but the trial is planned as a fixed-sample trial. No formal early stopping rule for efficacy or futility will be applied. The trial will continue to the planned sample size unless the monitoring committee recommends modification or termination for safety or ethical reasons.

Missing data will be summarized by treatment group, including the extent and reasons for missingness. The primary analysis will use all observed outcome data. If missing primary outcome data exceed 5%, sensitivity analyses using multiple imputation under a missing-at-random assumption will be performed. All analyses will be performed using R, with Bayesian models fitted using brms, rstanarm, or equivalent packages.

Data management and data monitoring

1. Input data

The investigator will collect participant information based on cases recorded and approved by IRB as follows:

- Baseline characteristics: age, sex, weight, height, American Society of Anesthesiologists (ASA) physical status, source of infection, baseline hemodynamics, SOFA score, APACHE II score, vasopressor and steroid usage, pre-existing condition, diagnosis, operation procedure, and fluid before enrollment.
- Outcome variables: 28-day mortality, length of hospital and ICU stay, DAF of ventilator, DAF of vasopressor, fluid balance in the first 7 days, AKI requiring RRT, recovery of bowel function, and adverse events.
- Abdominal function: enteral feeding, total calories per day, passing stool, prokinetic agent usage, and IAP monitoring if done.
- Surgical complications such as anastomosis leakage, surgical site infection, and re-surgery.
- The information was collected and managed using REDCap hosted at the Research Data Management Unit (RDMU), Faculty of Medicine, Siriraj Hospital

2. Confidentiality: The patient data collected will be recorded using code numbers. No information that could identify the patient, such as names or hospital numbers, will be recorded, ensuring confidentiality.

3. Cost to participants: All protocol-mandated 20% HA during the first 72 hours was provided at no cost to participants via the study budget. Conversely, HA administered in the control group, or in the intervention group after 72 hours, was left to physician discretion and billed through standard institutional reimbursement pathways.

4. Dissemination policy: Results from this trial will be disseminated through presentations and a peer-reviewed medical publication. Authorship will adhere strictly to the Mahidol University policy, and the funder will be acknowledged in all publications.

DISCUSSION

Surgical sepsis has a high mortality rate, approximately one-third of the patients, which is worsened by hypoalbuminemia [7-9,15-19,35]. No randomized controlled trial has investigated the potential benefit of HA replacement exclusively in this population. Previous trials such as SAFE [26], ALBIOS [27], and ARISS [36] enrolled mixed medical and surgical ICU patients, with surgical patients accounting for 32% of the ALBIOS population and 63% of the ARISS trial. Although the ARISS trial was early terminated due to low enrollment rates, its result may be underpowered.

Our study focuses on patients with surgical septic shock, as this condition distinctly differs from medical septic shock in several clinical aspects. First, operative or procedural source control introduces substantial peri-procedural fluid redistribution, placing surgical patients at high risk for dilutional hypoalbuminemia and fluid accumulation of resuscitation volume. Second, the prevalence of intra-abdominal infection in this population makes IAH, a complication of over-resuscitation, a concern more than in medical patients. Third, the need for repeated surgical intervention amplified cumulative inflammatory burden and protein

catabolism. These differences suggest that the mortality benefit of HA may be greater in surgical than medical patients [35,37]. Moreover, the advantages of HA are increasing oncotic pressure, reducing inflammation, and stabilizing the vascular endothelium to aim to enhance intravascular fluid retention, maintain blood pressure, and reduce fluid balance. A lower accumulative fluid balance should reduce the incidence of IAH, tissue edema, and secondary organ dysfunction by maintaining serum albumin above 3.5 g/dL [23-25]. Furthermore, minimizing fluid accumulation may facilitate surgical anastomotic healing, thereby positively impacting clinical outcomes. By mitigating tissue edema—a known exacerbating factor for anastomotic leakage—a 'near-zero fluid balance' strategy, as advocated by the Enhanced Recovery After Surgery (ERAS) framework [38,39], plays a pivotal role in reducing surgical complications. Consistent with established evidence, the implementation of these protocols significantly shortens the LOS and accelerates the recovery of GI function [40]. Thus, this randomized controlled trial is conducted to evaluate the outcomes of an additional 20% HA in combination with standard care during resuscitation in surgical sepsis patients. We hypothesized that our treatment would reduce mortality, hospital and ICU LOS, organ support-free days, cumulative fluid balance, and improve GI function.

A notable distinction of our study is the protocol design intervention for the first 72 hours after enrollment, which aligns with the acute resuscitation phase of septic shock. The window corresponds to the period of maximal capillary leak, vasopressor dependency, and fluid accumulation, where timely HA administration appears to matter [10,38]. The optimal timing for HA initiation was investigated in the ALBIOS trial, which demonstrated that patients receiving HA within 6 to 24 hours of sepsis diagnosis exhibited superior survival outcomes. Previous trials continued albumin infusion for up to 28 days; however, prolonged infusion beyond the resuscitation phase may not confer additional benefit once hemodynamic stability is achieved and may introduce risks of volume overload [27,36]. In addition, we use serum albumin above 3.5 g/dL as the upper treatment target, which differs from the 3.0 g/dL threshold used in previous studies [27,36]. This decision is based on evidence from retrospective studies showing that the mortality risk associated with albumin level falls below 3.5 g/dL. This level is likely to preserve endothelial integrity and oncotic pressure more than the 3.0 g/dL threshold. The lower 2.5 g/dL cut-off is used to trigger more intensive dosing (every 6 hours), as very low albumin levels are associated with marked mortality [15-19]. The stepwise dosing strategy aims to match treatment intensity to the severity of albumin deficiency by avoiding unnecessary albumin use in patients.

The main strength of our study is the randomized controlled design with a homogenous surgical septic shock population. We used to protocolize and adjust the dosing regimen based on serum albumin level. The primary outcome is objective, which minimizes interpretation bias. The secondary outcomes include organ support burden, fluid balance, and GI recovery.

There are some limitations in this study. We utilized open-label medication because the study drug could not be

blinded and a controlled substance was unavailable. Nonetheless, the outcome measures are objective, which should minimize bias. Second, the single-center design may limit generalizability to different healthcare settings. Third, the 40% relative risk reduction assumed for sample size calculation is quite optimistic; if the true effect is smaller, a larger sample size would be

CONCLUSION

The ALBUS study is the first randomized controlled trial designed to evaluate adjunctive 20% HA during the resuscitation phase of surgical septic shock. It aims to provide evidence on whether albumin-augmented resuscitation can improve outcomes in surgical critical care.

Confidentiality: The informed consents were obtained in a separate, private space in the surgical ICU. Codes were used as an alternative to patient names, hospital identification number, and admission number. The data was recorded in the research record form, which was kept in REDCap hosted at the Research Data Management Unit (RDMU), Faculty of Medicine Siriraj Hospital. After the research, the information was deleted from the computer and physical documents destroyed.

Dissemination Policy: The findings of this study will be disseminated through presentations at national or international conferences and submitted for publication in peer-reviewed journals.

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SUPPLEMENTARY MATERIALS

Supplementary Table1: Supplementary table1

Source identification and control
- o Hemoculture (at least) x2 specimens and microbial culture from the suspected source - o CBC, BUN, Cr, Electrolytes, iCa, Mg, P, LFT, CRP, PT, aPTT, Fibrinogen, ABG, lactate - o CXR or UA when indicated - o Intravenous broad spectrum antibiotics administration as soon as possible
o IAP measurement bid x3 days if indicated
Hemodynamic management and organ support
- o Isotonic balanced crystalloids at least 30 mL/kg within 3 hours after shock recognition - o Arterial cannulation for continuous blood pressure monitoring - o Central venous cannulation when indicated - o Thiamine 200 mg IV q 12h x3 days - o Follow serum lactate q 6h until shock reversal and serum lactate < 2 mmol/L
o Norepinephrine administration after adequate fluid resuscitation
o Consider albumin administration when indicated: (1) receiving crystalloids > 60 mL/kg in peri-operative patients, or (2) serum albumin < 2.5 g/dL + capillary leakage syndrome, or (3) receiving crystalloids > 30 mL/kg in non-operative patients
When Norepinephrine ≥ 0.25 mcg/kg/min, consider - o 2nd vasopressor administration: Epinephrine or another - o Hydrocortisone administration if required NE ≥ 0.25 mcg/kg/min longer than 4h
If lactate clearance < 10% from baseline or lactate remain > 2 mmol/L, consider - o Dobutamine administration if ScvO₂ < 70% + PaCO₂ gap > 6 - o PRC transfusion to maintain Hb 9-10 g/dL if ScvO₂ < 70% + normal PaCO₂ gap - o Reduce vasopressor dose if ScvO₂ > 75%
- o Light sedation keeps RASS 0 – (-2) - o Early enteral nutrition within 48h when norepinephrine < 0.1 mcg/kg/min, SpO₂ $\geq$ 94%, IAP < 15 mmHg, without contraindication - o POCT glucose q 6h keep 100-180 mg/dL - o Blood for serum albumin, CRP at day 2, 3 and 7