Supplement 1

Mortality Effect of Albumin Fluid Resuscitation in Adults with Septic Shock: A Systematic Review and Dual Frequentist–Bayesian Meta-Analysis of Randomised Trials

Authors:

Henrique Mendes, MD, MRCEM[1,2]

Henry Kinkei Wen, MD[1,2]

Harry de Souza, MD[1,2]

Yuanyuan Peng, MD[1,2]

Kush Deshpande, MD, FCICM[1,2]

Siebe G. Blok, MD, MSc[3]

Pieter R. Tuinman, MD, PhD[3,4]

Ary Serpa Neto, MD, PhD, FCICM[5,6,7,8]

Marcus J. Schultz, MD, PhD[9,10,11,12]

Manu L. N. G. Malbrain, MD, PhD[13,14]

Giacomo Grasselli, MD[15,16]

Frank M.P. van Haren, MD, PhD, FCICM[1,2,17,18]

[1]St George Hospital, Sydney, Australia [2]University of New South Wales, Sydney, Australia [3]Department of Intensive Care Medicine, Amsterdam UMC, Amsterdam, The Netherlands [4]Amsterdam Cardiovascular Sciences Research Institute, Amsterdam UMC, Amsterdam, The Netherlands [5]Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia [6]Department of Intensive Care, Austin Hospital, Melbourne, Australia [7]Department of Critical Care, Melbourne Medical School, University of Melbourne, Austin Hospital, Melbourne, Australia [8]Department of Critical Care Medicine, Hospital Israelita Albert Einstein, Sao Paulo, Brazil [9]Medical University Wien, Vienna, Austria [10]Cantonal Hospital St. Gallen, HOCH Health Ostschweiz, St. Gallen, Switzerland [11]University of Oxford, Oxford, UK [12]Mahidol University, Bangkok, Thailand [13]First Department of Anaesthesiology and Intensive Therapy, Medical University of Lublin, Jaczewskiego Lublin, Poland [14]International Fluid Academy, Lovenjoel, Belgium [15]Department of Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy [16]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy [17]Australian National University, Canberra, Australia [18]The George Institute for Global Health, Sydney, Australia

Table of Contents

S1. Search Strategies and Execution Metadata

Scope: No language or date restrictions. Inception to February 2026. Randomised trials comparing albumin-containing resuscitation strategies versus crystalloid-based resuscitation in adults with septic shock.

Execution Metadata (PRISMA-S)

Database	Interface / Platform	Run date	Searcher	Notes
PubMed/MEDLINE	NIH Entrez (pubmed.ncbi.nlm.nih.gov)	Feb 2026	HKW/HDS/YP	RCT filter applied
Embase	Elsevier Embase.com	Feb 2026	HKW/HDS/YP	Humans limit applied
CENTRAL	Cochrane Library (Advanced Search)	Feb 2026	HKW/HDS/YP	Records = Trials
Scopus	Elsevier Scopus	Feb 2026	HKW/HDS/YP	Document Type = Article

PubMed/MEDLINE (NIH interface)

RCT filter applied (Cochrane sensitivity-maximising). No language limits.

```
Block 1 — Population:
(
  "Shock, Septic"[Mesh]
  OR "septic shock"[tiab]
  OR "vasodilatory shock"[tiab]
  OR "distributive shock"[tiab]
  OR ( ("Sepsis"[Mesh] OR sepsis[tiab] OR "severe sepsis"[tiab]) AND shock[tiab] )
)

Block 2 — Intervention:
(
  "Albumins"[Mesh]
  OR "Serum Albumin"[Mesh]
  OR albumin[tiab]
  OR albumins[tiab]
  OR "human serum albumin"[tiab]
  OR "human albumin"[tiab]
  OR hyperoncotic[tiab]
  OR "iso-oncotic"[tiab]
  OR "colloid resuscitation"[tiab]
  OR "colloid solution"[tiab]
  OR "colloid solutions"[tiab]
  OR "Colloids"[Mesh]
  OR "Plasma Substitutes"[Mesh]
  OR "plasma expander"[tiab]
  OR "plasma expanders"[tiab]
  OR "volume expander"[tiab]
  OR "Fluid Therapy"[Mesh]
  OR "fluid resuscitation"[tiab]
```

)

Block 3 — RCT filter (Cochrane sensitivity-maximising):
(
 "Randomized Controlled Trial"[pt]
 OR "Controlled Clinical Trial"[pt]
 OR randomized[tiab]
 OR randomised[tiab]
 OR placebo[tiab]
 OR "drug therapy"[sh]
 OR randomly[tiab]
 OR trial[tiab]
 OR groups[tiab]
 NOT ("Animals"[Mesh] NOT "Humans"[Mesh])
)

Combined: Block 1 AND Block 2 AND Block 3

Embase (Embase.com)

Limits applied in interface: Humans.

Block 1 — Population:
(
 'septic shock'/exp
 OR 'septic shock':ti,ab
 OR 'vasodilatory shock':ti,ab
 OR 'distributive shock':ti,ab
 OR (('sepsis'/exp OR sepsis:ti,ab OR 'severe sepsis':ti,ab) AND shock:ti,ab)
)

Block 2 — Intervention:
(
 'albumin'/exp
 OR 'serum albumin'/exp
 OR albumin:ti,ab
 OR albumins:ti,ab
 OR 'human serum albumin':ti,ab
 OR 'human albumin':ti,ab
 OR hyperoncotic:ti,ab
 OR 'iso-oncotic':ti,ab
 OR 'colloid resuscitation':ti,ab
 OR 'colloid solution':ti,ab
 OR 'colloid solutions':ti,ab
 OR 'colloid'/exp
 OR 'plasma substitute'/exp
 OR 'plasma expander':ti,ab
 OR 'volume expander':ti,ab
 OR 'fluid therapy'/exp
 OR 'fluid resuscitation':ti,ab
)

Block 3 — RCT filter (Cochrane sensitivity-maximising, adapted for Embase):
(
 'randomized controlled trial'/exp
 OR 'controlled clinical trial'/exp

```
  OR randomized:ti,ab
  OR randomised:ti,ab
  OR placebo:ti,ab
  OR randomly:ti,ab
  OR trial:ti,ab
  OR groups:ti,ab
  NOT ('animal'/exp NOT 'human'/exp)
)
```

Combined: Block 1 AND Block 2 AND Block 3

Cochrane CENTRAL (Cochrane Library — Advanced Search)

Limits applied: Records = Trials. Enter as lines and combine.

```
#1  MeSH descriptor: [Shock, Septic] explode all trees
#2  ("septic shock"):ti,ab,kw OR ("vasodilatory shock"):ti,ab,kw OR ("distributive shock"):ti,ab,kw
#3  MeSH descriptor: [Sepsis] explode all trees
#4  (sepsis):ti,ab,kw OR ("severe sepsis"):ti,ab,kw
#5  (shock):ti,ab,kw
#6  #3 OR #4
#7  #6 AND #5
#8  #1 OR #2 OR #7
#9  MeSH descriptor: [Albumins] explode all trees
#10 MeSH descriptor: [Serum Albumin] explode all trees
#11 (albumin):ti,ab,kw OR (albumins):ti,ab,kw OR ("human serum albumin"):ti,ab,kw OR ("human albumin"):ti,ab,kw
#12 (hyperoncotic):ti,ab,kw OR ("iso-oncotic"):ti,ab,kw
#13 ("colloid resuscitation"):ti,ab,kw OR ("colloid solution"):ti,ab,kw OR ("colloid solutions"):ti,ab,kw
#14 MeSH descriptor: [Colloids] explode all trees
#15 MeSH descriptor: [Plasma Substitutes] explode all trees
#16 ("plasma expander"):ti,ab,kw OR ("plasma expanders"):ti,ab,kw OR ("volume expander"):ti,ab,kw
#17 MeSH descriptor: [Fluid Therapy] explode all trees
#18 ("fluid resuscitation"):ti,ab,kw
#19 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 #8 AND #19
```

Note: CENTRAL indexes only trials; no RCT filter required. Limit to Trials.

Scopus (Elsevier)

Filters applied: Document Type = Article.

```
( TITLE-ABS-KEY ( "septic shock" OR "vasodilatory shock" OR "distributive shock" )
  OR
  ( TITLE-ABS-KEY ( sepsis OR "severe sepsis" ) AND TITLE-ABS-KEY ( shock ) ) )
AND
( TITLE-ABS-KEY ( albumin OR albumins OR "human serum albumin" OR "human albumin" )
  OR TITLE-ABS-KEY ( hyperoncotic OR "iso-oncotic" )
  OR TITLE-ABS-KEY ( "colloid resuscitation" OR "colloid solution" OR "colloid solutions" )
  OR TITLE-ABS-KEY ( "plasma expander" OR "plasma expanders" OR "volume expander" )
  OR TITLE-ABS-KEY ( "fluid resuscitation" AND colloid* ) )
AND
( TITLE-ABS-KEY ( randomized OR randomised OR "controlled trial" OR "clinical trial" OR placebo ) )
```

S2. Trial Registries Search

ClinicalTrials.gov, WHO ICTRP, and EudraCT were searched using the following parameters:

Registry	Search Parameters
ClinicalTrials.gov	Condition = septic shock OR distributive shock; Intervention = albumin; Study Type = Interventional; Status = All
WHO ICTRP	Condition = septic shock; Intervention = albumin; Recruitment status = All
EudraCT	Medical condition = septic shock; IMP = albumin

S3. Screening and Deduplication

Deduplication: Records were exported to reference management software for semi-automated duplicate detection, followed by manual verification.

Screening: Two independent reviewers (HKW/HDS) screened titles/abstracts and full texts. Disagreements were resolved by consensus or referral to a third reviewer (YP).

S4. Extracted Data

Table S4.1: Primary Outcome Data (Longest Follow-Up Mortality, Up to 90 Days)

Trial	Year	N (Alb)	Deaths (Alb)	N (Ctrl)	Deaths (Ctrl)	Timepoint	RR (95% CI)
Rackow et al.	1983	7	5	4	3	Hospital	0.95 (0.46–1.99)
SAFE	2004	209	70	229	90	28-day	0.85 (0.66–1.09)
EARSS	2011	399	96	399	105	28-day	0.91 (0.72–1.16)
ALBIOS	2014	558	243	563	281	90-day	0.87 (0.77–0.99)
ICARUS-ED	2025	197	35	189	30	30-day	1.12 (0.72–1.75)
Cusack et al.	2025	50	15	50	12	ICU	1.25 (0.65–2.39)
ARISS	2026	210	91	209	96	90-day	0.94 (0.76–1.17)
Total		**1,630**	**555**	**1,643**	**617**		

Notes: Rackow et al. (1983): septic subgroup only (albumin 7, saline 4); hetastarch arm excluded per protocol. Hospital mortality used as the longest available follow-up. SAFE: septic shock subgroup mortality (70/209 albumin vs 90/229 saline at 28 days) reported by Xu et al. (2014, Critical Care) from personal communication with Prof. S. Finfer; only 28-day mortality was available for this subgroup. EARSS: abstract-only data; 28-day mortality. ALBIOS: septic shock subgroup defined as cardiovascular SOFA score 3 or 4 at randomisation; 90-day mortality (243/558 vs 281/563). ICARUS-ED: refractory hypotension subgroup (SBP <90 mmHg after ≥1000 mL fluid); 30-day mortality. Cusack et al.: ICU survival reported (35/50 vs 38/50); deaths derived as 15/50 and 12/50. ARISS: 90-day mortality; the trial was stopped early after 440 randomised patients (planned n = 1,662), and the 90-day analysis used the modified intention-to-treat population of 210 vs 209.

Table S4.2: Secondary Outcome Data (28-Day Mortality or Equivalent)

Trial	Year	N (Alb)	Deaths (Alb)	N (Ctrl)	Deaths (Ctrl)	Timepoint
SAFE	2004	209	70	229	90	28-day
EARSS	2011	399	96	399	105	28-day
ICARUS-ED	2025	197	35	189	30	30-day
ARISS	2026	213	66	210	80	28-day

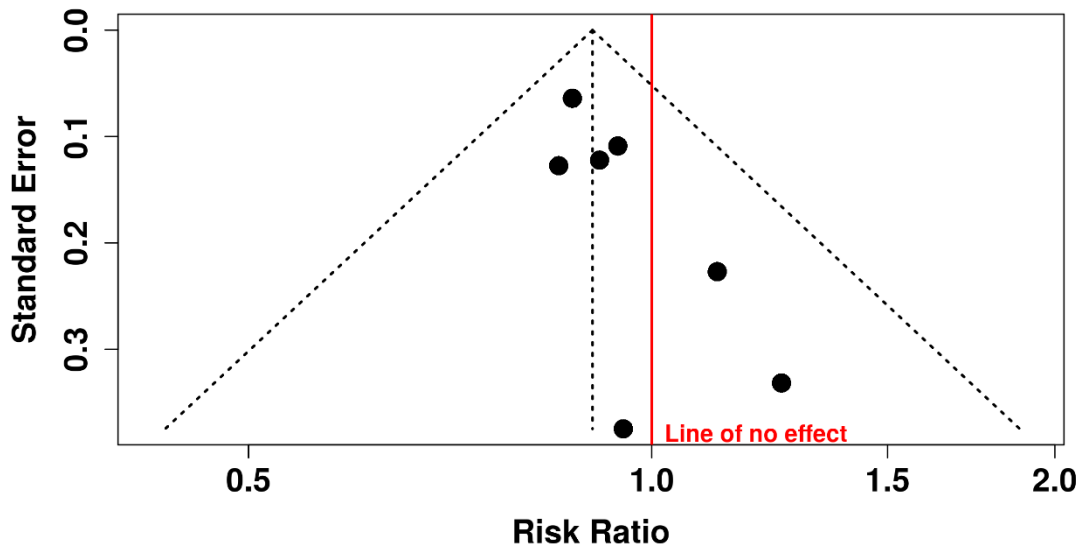
Notes: ALBIOS septic shock subgroup excluded from 28-day analysis because only 90-day mortality was reported for this subgroup. Cusack et al. excluded because only ICU survival was reported; 28-day mortality event counts were listed as a secondary endpoint but not numerically reported. Rackow et al. excluded because study-period (in-hospital) mortality is a variable-duration endpoint, not a calendar-fixed timepoint. ARISS contributes 213 albumin / 210 control to the 28-day analysis, whereas the 90-day primary analysis uses the modified intention-to-treat population (210 / 209); the difference reflects the analysis populations reported by Sakr et al. at each timepoint.

S5. Publication Bias Assessment

Publication bias was assessed in accordance with the prespecified protocol. Because only seven trials contributed to the primary outcome, formal small-study effect testing (e.g., Peters' test) was not performed, given its poor reliability with fewer than 10 studies. Instead, we undertook a qualitative assessment including visual inspection of the funnel plot (eFigure S1). Visual inspection was largely equivocal; while there was a slight rightward imbalance among the less precise studies, this did not constitute a clear or convincing asymmetry. This pattern may simply reflect chance variation or methodological heterogeneity across a small set of trials. If it were nevertheless primarily driven by publication bias, its direction would suggest that the current pooled estimate may underestimate, rather than exaggerate, the true beneficial effect of the intervention.

In addition, trial registries and protocols/registrations (where available) were checked against publications to identify completed but unpublished studies and to assess selective outcome reporting; these considerations were incorporated within the RoB 2.0 Domain 5 judgement for each trial. Overall, there was no strong evidence of small-study effects or reporting bias, although these possibilities cannot be excluded confidently given the limited number of studies.

eFigure S1: Funnel plot (longest follow-up mortality)



S6. PRISMA 2020 Checklist

The 'location where the item is reported' refers to the section(s) in the main manuscript.

Section and Topic	Item #	Checklist Item	Location
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Methods, para 1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review.	Methods
Information sources	6	Specify all databases, registers, and other sources searched.	Methods; Supplement S1
Search strategy	7	Present the full search strategies for all databases.	Supplement S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria.	Methods
Data collection	9	Specify the methods used to collect data from reports.	Methods; Supplement S4
Data items	10a	List and define all outcomes for which data were sought.	Methods
	10b	List and define all other variables for which data were sought.	Methods; Table 1
Risk of bias	11	Specify the methods used to assess risk of bias.	Methods; Supplement 3
Effect measures	12	Specify for each outcome the effect measure(s) used.	Methods
Synthesis methods	13a–f	Describe the processes used for synthesis.	Methods; Results
Reporting bias	14	Describe methods to assess risk of bias due to missing results.	Results; Supplement S5
Certainty assessment	15	Describe methods to assess certainty in the body of evidence.	Methods; Table 3
RESULTS			
Study selection	16a–b	Describe the results of the search and selection process.	Results; Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Results; Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results; Table 2; Supplement 3
Results of syntheses	20a–d	Present results of all statistical syntheses conducted.	Results; Figures 2–3
Reporting biases	21	Present assessments of risk of bias due to missing results.	Supplement S5
Certainty of evidence	22	Present assessments of certainty in the body of evidence.	Table 3
DISCUSSION			
Discussion	23a–d	Provide general interpretation; discuss limitations and implications.	Discussion
OTHER INFORMATION			

Registration	24a–c	Provide registration information for the review.	Abstract; Methods; PROSPERO CRD420261325998

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. Licensed under CC BY 4.0.

S7. Protocol Summary

This section summarises key methodological details from the pre-registered protocol (PROSPERO CRD420261325998).

Eligibility Criteria (PICOS)

Population: Adults (≥18 years) with septic shock managed in ICU, ED, or HDU settings. For the purposes of this review, septic shock required documented evidence of acute circulatory failure in the context of sepsis, defined by at least one of: (a) vasopressor requirement to maintain a target mean arterial pressure; (b) persistent hypotension (SBP <90 mmHg or MAP <65 mmHg) despite initial fluid resuscitation; or (c) evidence of tissue hypoperfusion (e.g., lactate ≥4 mmol/L) attributed to sepsis. Mixed ICU populations were eligible if a septic shock subgroup comprising ≥70% of the enrolled cohort or if the septic shock population was reported separately with extractable outcome data.

Intervention: Albumin administered as part of a resuscitation strategy, in hyperoncotic (20–25%) or iso-oncotic (4–5%) formulations, compared directly against crystalloid-based resuscitation.

Comparison: Crystalloid-only resuscitation, including normal saline, balanced/buffered crystalloids, or standard care without protocolised albumin. Control arms in which clinician-directed albumin use was permitted but not mandated were eligible, provided contamination rates were extracted and reported.

Outcomes: Primary: All-cause mortality at the longest available follow-up, up to 90 days post-randomisation. Secondary: 28-day mortality; organ-support-free days (composite, ventilator, vasopressor, and renal-replacement-therapy-free days to day 28).

Study designs: Randomised controlled trials (individual or cluster). Non-randomised studies excluded.

Synthesis Methods

Frequentist analysis: Random-effects inverse-variance model with between-study variance (τ^2) estimated by restricted maximum likelihood (REML). Effect sizes pooled on the log risk ratio scale.

Bayesian analysis: Hierarchical meta-analysis using arm-level binomial–logit models in R (brms with cmdstanr). Four prior families for the pooled treatment effect (log-OR): (i) weakly informative Normal(0, 1.5); (ii) sceptical Normal(0, 0.354); (iii) optimistic Normal(−0.15, 0.28); (iv) pessimistic Normal(+0.15, 0.28). Heterogeneity prior: half-Student-t(3, 0, 1). HMC with 4 chains, 4,000 iterations per chain, adapt_delta ≥0.999.

Prespecified Subgroup Analyses

If ≥2 studies were available in each category:

- Albumin concentration (primary effect modifier): Hyperoncotic 20–25% versus iso-oncotic 4–5%.
- Dosing strategy: Serum-albumin-targeted versus fixed-dose or volume-replacement.
- Baseline hypoalbuminaemia: Enrolled population baseline albumin ≤25 g/L versus >25 g/L.

Prespecified Sensitivity Analyses

- Exclude trials at high risk of bias (including abstract-only reports).

- Exclude trials with control-arm albumin contamination >20%.
- 28-day mortality (or closest ≤30 days) instead of longest follow-up.
- Fixed-effect (inverse-variance, common-effect) model.
- Leave-one-out analysis (Bayesian).

Trial Sequential Analysis

TSA was conducted using MetaAnalysisOnline.com (Fekete and Győrffy, 2025), with the RTSA R package (Soerensen et al., 2025). Primary TSA assumed RRR = 15% (RR = 0.85), two-sided $\alpha = 0.05$, $\beta = 0.20$ (80% power), control-arm event rate derived from included trials. Sensitivity TSAs at RRR 10% and RRR 20%.

Certainty of Evidence

The certainty of evidence for the primary outcome was assessed using the GRADE framework (risk of bias, inconsistency, indirectness, imprecision, and publication bias).