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Fluid balance and mortality in adult ICU patients with sepsis or septic shock: a systematic review and meta-analysis of observational studies

Federico Fonda[1], Daniele Orso[1*], Irene Comisso[1], Eleonora De Crignis[1], Francesco Meroi[1], Bino Galioto[1], Tiziana Bove[3,4] and Giorgio Della Rocca[2]

Abstract

Background Fluid therapy is a cornerstone of sepsis management; however, excessive fluid accumulation might be associated with adverse outcomes. The association between fluid balance (FB) and mortality in critically ill patients with sepsis or septic shock remains uncertain.

Methods We conducted a systematic review and meta-analysis of observational studies assessing the association between FB and mortality in adult ICU patients with sepsis or septic shock (PubMed, Scopus, CINAHL; through May 2024). Random-effects models estimated pooled odds ratios (ORs) for all-cause mortality; meta-regression explored dose–response patterns and heterogeneity. Risk of bias was assessed with ROBINS-E; certainty of evidence with GRADE.

Results Twenty-six studies(64,755 patients) were included, most of which were retrospective with moderate-to-high risk of bias. Higher cumulative FB was associated with higher odds of mortality (OR 2.11, 95% CI 1.65–2.69). This association was consistent across different FB time windows and definitions; subgroup analyses did not identify study-level factors explaining heterogeneity. Meta-regression supported a linear dose–response relationship. No statistically significant association was observed between FB and the need for renal replacement therapy (OR 1.34, 95% CI 0.76–2.36). According to GRADE, the certainty of evidence was very low.

Conclusions Among critically ill adults with sepsis or septic shock, higher fluid balance was associated with higher mortality. These observational associations are vulnerable to confounding by illness severity, precluding causal inference. Given the very low certainty of evidence, standardised definitions of fluid balance and randomised trials are needed. Potential differences between sepsis and septic shock warrant shock-status stratification.

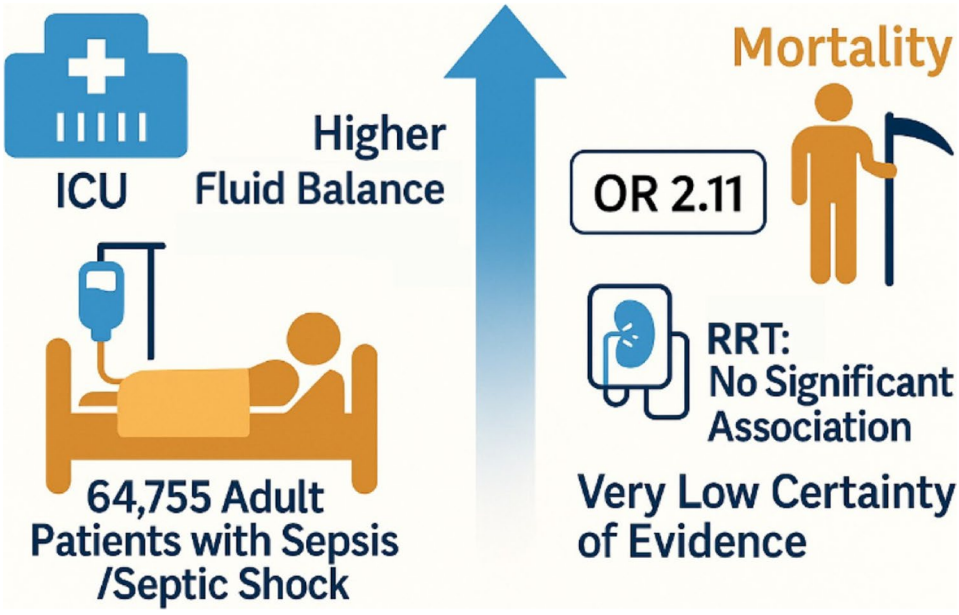
Trial registration PROSPERO CRD42024538393.

Keywords Fluid balance, Intensive care unit, Mortality, Nursing, Sepsis, Septic shock, Fluid overload, Fluid management

*Correspondence:
Daniele Orso
daniele.orso@asufc.sanita.fvg.it

Full list of author information is available at the end of the article

Graphical abstract



Introduction

Sepsis and septic shock are frequent causes of intensive care unit (ICU) admission and remain associated with substantial morbidity and mortality [1, 2]. Among potentially modifiable factors, the fluid balance (FB) accumulated during critical illness has been repeatedly examined as a marker of risk, yet its calculation and reporting vary widely across studies [3]. Observational analyses have reported that patients with higher cumulative FB tend to have higher mortality and organ dysfunction [4]; however, these associations are heterogeneous and sensitive to when and how FB is assessed (e.g., absolute values at fixed time points, cumulative sums over several days, or indices standardised to body weight). Clarifying these differences is important to interpret the literature and to inform future research.

This systematic review and meta-analysis synthesises clinical data on the relationship between FB and mortality in critically ill adults with sepsis or septic shock and explores the need for renal replacement therapy (RRT) as a secondary outcome. We prespecified eligibility criteria, extracted FB definitions, and evaluated risk of bias and certainty of evidence. Our primary aim was to quantify the association between higher FB and mortality, acknowledging the limitations inherent to nonrandomized designs. We also examined whether alternative FB metrics or assessment windows were associated with different effect estimates and between-study heterogeneity.

Because randomised trials of fluid strategies target treatment policies rather than achieved FB per se, they address a related but distinct question; therefore, we summarise trial evidence in the Discussion to contextualise our findings, without inferring causality from observational associations. By collating definitions, timing, and analytic choices across studies, this review aims to support more consistent FB measurement and reporting and to identify priorities for future trials.

Methods

A systematic review with meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5] (Table S1, Supplementary Data). The protocol was prospectively registered in PROSPERO (CRD42024538393). An initial scoping search was performed before registration to refine eligibility criteria and fluid balance (FB) definitions. The formal systematic search, conducted according to the registered protocol, covered PubMed, Scopus, and CINAHL from inception to 28th May 2024, supplemented by manual reference checks and screening of relevant meta-analyses. In line with best practice, an updated search was performed immediately prior to submission to capture any newly published studies, with additions reported in the PRISMA flow diagram.

Regarding the registration, two clarifications are required: (i) Study types: while the registry listed "interventional studies" as potentially eligible, we prespecified during full protocol development that the quantitative synthesis would focus on achieved FB as an exposure. Because RCTs of fluid strategies evaluate assigned interventions (and typically do not report a harmonized,

study-level achieved FB exposure), they were summarized narratively and excluded from pooling; (ii) Statistical analyses: the implemented analyses (random-effects pooling, influence diagnostics, meta-regressions – including a linear continuous model and an exploratory spline model – publication bias assessment with funnel plots and Egger's test) are consistent with the registered plan, with the spline model explicitly labeled as exploratory to address potential non-linearity.

Eligibility criteria, information sources and search strategy

We included primary observational studies (prospective or retrospective, with or without propensity methods) that evaluated the association between achieved fluid balance (FB = total inputs − total outputs) and all-cause mortality in adults (≥ 18 years) with sepsis or septic shock admitted to the ICU. Eligible reports had to quantify FB as an exposure (absolute, indexed, cumulative or daily) and report mortality (ICU, in-hospital or 28-/90-day).

We excluded: qualitative studies, editorials, commentaries, letters, conference abstracts, case reports, guidelines, reviews (with/without meta-analysis), non-English publications, and studies reporting partial fluid metrics only (e.g., "fluid therapy", "infusion regimen", "IV fluids", "fluid strategy" without outputs) or fluid overload defined solely by clinical/radiologic criteria without quantitative FB.

Interventional studies (including RCTs) that compared fluid administration strategies (e.g., restrictive vs. usual care) were not pooled because they randomised assigned policies rather than standardising or directly analysing achieved FB as a common exposure. These trials are summarised narratively in the Discussion to contextualise our findings but were not eligible for a quantitative synthesis focused on achieved FB.

Study selection and data collection process

Search results were imported into the Covidence platform [6]. Study selection was subsequently conducted in two phases: (a) title/abstract screening and (b) full-text screening. Duplicate results were automatically removed by the platform, and the screening was performed independently and blindly by three researchers (FF, IC, DO). In case of disagreements about article eligibility, the team discussed the eligibility criteria with the involvement of an additional experienced researcher (TB).

An electronic data extraction form was implemented into the Covidence platform and piloted with three included articles to ensure its usefulness, appropriateness and feasibility [6, 7]. Three researchers (FF, IC, DO), with appropriate knowledge on the concept of FB extracted the data cooperatively. Any disagreement was resolved through a majority decision after a collective discussion. The following data were extracted: name of the author(s), year, country, study design, sample size(s), reported characteristics of the sample (i.e., age, gender, comorbidities etc.), fluid balance value(s), fluid balance determination method(s), and mortality outcomes. Duplicates were identified and removed using Covidence automated de-duplication. Title/abstract screening and full-text review were performed in duplicate by independent reviewers. Quality control of automation steps included manual spot-checks of de-duplicated records and reconciliation of discrepancies during full-text screening.

Fluid balance definitions

Across studies, fluid balance (FB) was reported using different metrics. Absolute FB denotes the net fluid volume (inputs minus outputs) over a specified window (mL). Indexed FB refers to absolute FB normalised to body weight (mL/Kg). Cumulative FB is the sum of daily net balances across the prespecified window; daily FB refers to the net balance within a single 24-h period. Categorical FB indicates exposure defined by thresholds or quantiles (e.g., higher vs. lower FB groups), whereas mixed models combine more than one of the above approaches within the same study. For exploratory dose–response analyses, we used the study-level proportion of patients allocated to the higher FB group as the predictor.

Risk of bias assessment

Two authors (DO and FF) independently assessed the risk of bias (RoB) using ROBINS-E (Risk Of Bias In Non-randomized Studies of Exposures) [8]. RoB was classified as low if it was not detected in any domain, allowing 'some concerns' only in the first domain. A study was classified as high risk if more than three concerns were present in any domain; very high risk was assigned when more than three domains were judged at high risk. Disagreements were resolved by discussion, with a third reviewer (IC) adjudicating as needed.

Data synthesis

Data were extracted from the Covidence platform and shared among the research team members (FF, DO, IC, EDC, FM, BG, TB) [6, 7]. Studies were aggregated by similarities, and emerging evidence was synthesised narratively according to the available guidance [9]. Textual descriptions, tables and figures were prepared to present the synthesised findings.

Statistical analysis

For binary outcomes, we fitted fixed- and random-effects models; random-effects estimates are emphasised given substantial between-study heterogeneity. Odds ratios (ORs) were pooled using inverse-variance methods; fixed-effect (including Peto) analyses were considered sensitivity checks. Heterogeneity was quantified with I^2

(and τ^2 where applicable). Influence analyses and meta-regressions were performed to explore potential sources of heterogeneity. Small-study effects were assessed with funnel plots and Egger's test where appropriate. We further explored heterogeneity using Graphical Display of Study Heterogeneity (GOSH) analyses with clustering to identify subgroups of studies exerting disproportionate influence on pooled effects.

In addition to the primary analyses, we performed exploratory dose–response assessments: (i) a continuous meta-regression using the study-level proportion of patients allocated to the higher FB group as predictor; and (ii) a categorical meta-regression stratifying studies into tertiles (Low, Medium, High) based on this proportion. Ranking plots were derived from model-based probabilities and presented descriptively.

Analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria; version 4.3.2; available at https://www.R-project.org) with meta, dmetar, metafor , splines, and related packages [10].

Certainty of evidence

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. This approach considers risk of bias, inconsistency, indirectness, imprecision, and publication bias across studies. As the included studies were observational in nature, the initial certainty was rated as low. It could be downgraded further based on methodological limitations or heterogeneity, or could be upgraded for large effects, dose–response, or when all plausible residual confounding would reduce the observed association (thereby increasing confidence in the association). The overall certainty of evidence for each outcome was summarized as high, moderate, low, or very low, according to standard GRADE methodology [11].

Results

Study selection and characteristics

The search retrieved 1,157 records in total. Of these, 858 were automatically removed as duplicates and 1 record was deemed ineligible by an automation tool. The remaining 298 records underwent title/abstract screening, with 69 full texts assessed for eligibility. Ultimately, 26 studies (n = 64,755) were included in the systematic review and quantitative synthesis (Fig. 1) [12–37]. Although the eligibility criteria encompassed forms of distributive shock beyond septic shock, all included studies enrolled patients with sepsis or septic shock.

Six studies were prospective [12–17] and twenty were retrospective [18–37] (Table 1). Fluid balance (FB) was assessed using heterogeneous time windows across studies (e.g., early fixed intervals such as 24–48 h, the first 3–7

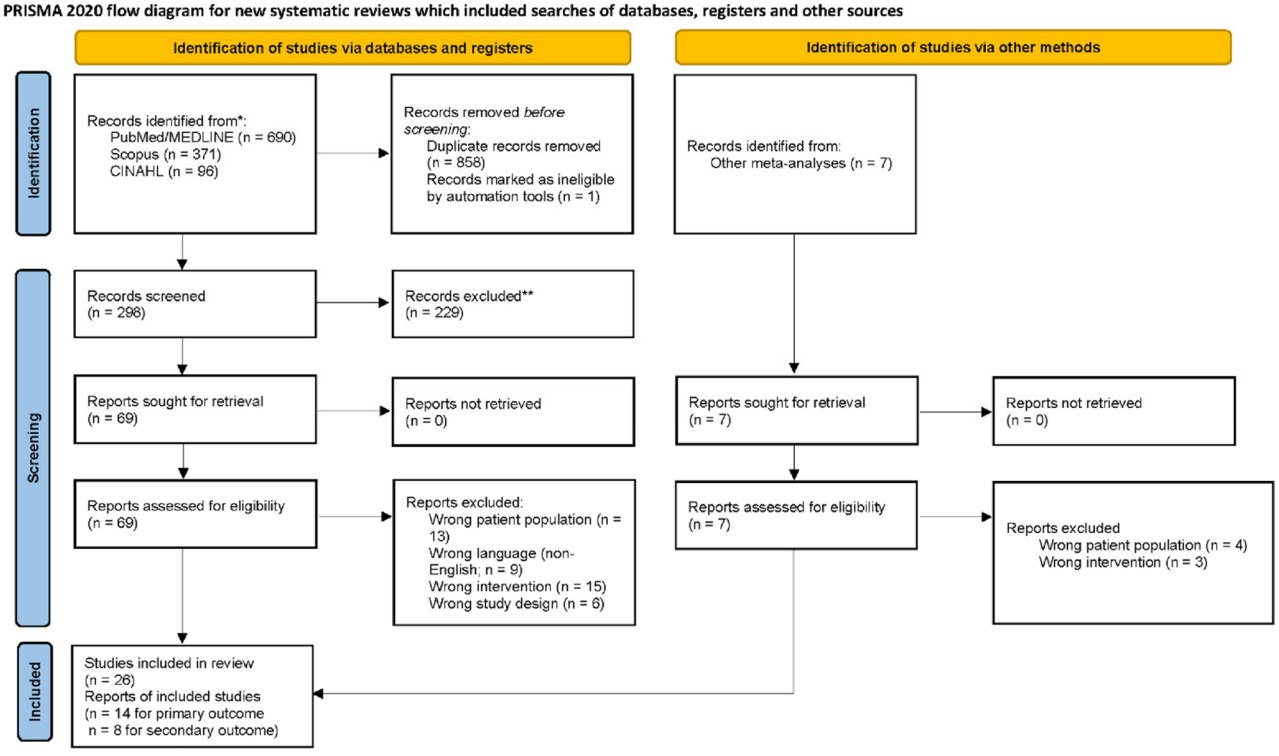


Fig. 1 PRISMA 2020 flow diagram for study selection. Of 1,157 records identified, 858 duplicates were removed automatically and 1 record was excluded by an automation tool as ineligible. After screening and eligibility assessment, 26 studies were included in the review

Table 1 Characteristics of the included studies evaluating the association between fluid balance and mortality in critically ill patients

Author, year	Design	*N*	Timeframe	Severity (APACHE II/III, SOFA)	Outcome	FB model	FB variable	Secondary outcomes
de Souza, 2024 [12]	Prospective	139	0–72 h from shock onset	SOFA 5 [3–8]	Mortality	Mixed	Continuous	Components of FB, nutrition
Hyun, 2023 [13]	Prospective	2516	Day 1–3	SOFA 7 [5–9]	28-day mortality	Indexed	Categorical	MV-free days, ICU discharge
Sakr, 2017 [14]	Prospective	1808	Day 1, 3, 7	SOFA 9.5 ± 3.8	28-day mortality	Absolute	Categorical	NR
Acheampong, 2015 [15]	Prospective	173	Day 1–7	SOFA 8.2 ± 3.4	ICU mortality	Absolute	Continuous	NR
Sirvent, 2015 [16]	Prospective	42	Day 1–4	SOFA 7.1 ± 3.4	28-day mortality	Cumulative	Continuous	NR
Cunha, 2015 [17]	Prospective	40	Shock + 7 days	SOFA 7.4 ± 3.5	LOS	Cumulative	Continuous	LOS (ICU/hospital)
Patel, 2023 [18]	Retrospective	17,480	NR	APACHE 67.6 ± 26.3	Mortality	Mixed	Categorical	Sepsis subtype outcomes
Tackaert, 2023 [19]	Retrospective	482	Day 1–3	SOFA 8.5 ± 4.4	30-day mortality	Indexed	Categorical	ICU/hosp mortality, AKI, CRRT, MV
Dash, 2023 [20]	Retrospective	710	Day 7	SOFA 8.5 ± 1.9	ICU mortality	Indexed	Categorical	28 d mortality, LOS
Wang, 2022 [21]	Retrospective	4610	Day 1–3 and 4–7	APACHE II 25.1 ± 7.5	1-year mortality	Cumulative	Continuous	NR
Kharadi, 2022 [22]	Retrospective	1048	Day 1–3	NR	ICU mortality	Mixed	Continuous	Hosp mortality, ICU LOS
Zhang, 2022 [23]	Retrospective	936	24 h	SOFA 5 [3–8]	In-hospital mortality	Indexed	Continuous	30 d mortality, ICU and hospital LOS
Zhang, 2021 [24]	Retrospective	19,557	Day 1–3	SOFA 7 [4–9]	In-hospital mortality	Cumulative	Categorical	MV duration
Wang, 2021a [25]	Retrospective	337	Day 1–7	SOFA 5 [4-8]	In-hospital mortality	Mixed	Categorical	Vasopressors, MV duration
Wang, 2021b [26]	Retrospective	986	Day 1–7	SOFA 8 [6–11]	28-day mortality	Indexed	Categorical	Organ dysfunction, MAKE
Dhondup, 2020 [27]	Retrospective	633	Full ICU stay	SOFA 7 [5–10]	ICU/in-hosp mortality	Cumulative	Continuous	ICU/hosp LOS
Huang, 2019 [28]	Retrospective	104	Day 1–3	SOFA 10.2 ± 3.1	MODS, 28-day mortality	Cumulative	Continuous	28 d mortality
Shen, 2018 [29]	Retrospective	8584	Day 1–2, 48 h	SOFA 5 [4–8]	In-hospital mortality	Indexed	Continuous	ICU/hosp LOS
Pittard, 2017 [30]	Retrospective	186	Day 1–7	SOFA 11 [9–13]	In-hospital mortality	Cumulative	Continuous	ICU/hosp LOS, RRT, MV
Cronhjort, 2016 [31]	Retrospective	841	Day 1–3	SOFA 10 ± 3.3	90-day mortality	Indexed	Continuous	Life support-free days
Brotfain, 2016 [32]	Retrospective	297	Day 1–3	SOFA 3.4 [3–4]	ICU/hosp mortality	Cumulative	Continuous	Organ dysfunction, ICU readmission
de Oliveira, 2015 [33]	Retrospective	116	24–48 h	APACHE II 17 [13–26]	60-day mortality	Cumulative	Categorical	AKI (RIFLE-F)
Neyra, 2015 [34]	Retrospective	2632	Day 1–3	SOFA 4.0 [2.0–7.0]	In-hospital mortality	Cumulative	Continuous	AKI incidence
Koonrangsesomboon, 2015 [35]	Retrospective	1048	Day 1–3	SOFA 10 [8–13]	ICU mortality	Cumulative	Continuous	ICU/hosp LOS
Sadaka, 2014 [36]	Retrospective	350	24 h	SOFA 10.2 ± 2.8	In-hospital mortality	Cumulative	Categorical	NR
Alsous, 2000 [37]	Retrospective	36	Day 1–3	SOFA 8.9 ± 1.0	3-day mortality	Categorical	Categorical	NR

This table summarizes 26 studies – both prospective and retrospective – investigating the impact of fluid balance (FB) on mortality and secondary outcomes. Studies varied in sample size, timing of FB assessment (from initial 24 h to full ICU stay), and in the modelling of fluid balance (absolute, indexed, cumulative, or mixed). FB was reported as a continuous or categorical variable, and outcomes included ICU and hospital mortality, organ dysfunction, mechanical ventilation duration, and renal replacement therapy. Heterogeneity in definitions and timeframes highlights the lack of standardization in fluid balance quantification across studies

Abbreviations: *AKI* acute kidney injury, *CRRT* continuous renal replacement therapy, *FB* fluid balance, *ICU* intensive care unit, *LOS* length of stay, *MAKE* major adverse kidney events, *MODS* multiple organ dysfunction syndrome, *MV* mechanical ventilation, *NR* not reported, *RRT* renal replacement therapy

ICU days, or the entire ICU stay) and with varying metrics (absolute values, cumulative sums, indexed values, or mixed approaches). In most studies, FB was defined as the net difference between inputs and outputs (absolute FB, mL). Several studies indexed this value to body weight (indexed FB, mL/kg). Severity of illness among enrolled patients was consistently high, with reported median SOFA scores ranging from approximately 5 to 11 and APACHE II scores from 17 to 25 across studies, indicating populations with moderate-to-severe critical illness. Mortality endpoints also varied (e.g., 28-day, ICU, or in-hospital mortality), and in a minority of studies the time frame was not specified.

Substantial heterogeneity was observed in how FB was calculated and accounted, with studies including a variable number of input and output elements. Most considered intravenous fluids and urine output, whereas insensible losses and complex outputs (e.g., gastrointestinal/drain outputs) were infrequently reported. This variability may introduce measurement bias and limit comparability across studies (Table 2).

Risk of bias

The risk of bias (RoB) across included studies ranged from some concerns to high risk (Fig. 2). Patient selection was inherently prone to bias because all studies were observational, with most being retrospective. Additional unmeasured confounders may also have introduced bias. Among retrospective studies, only one employed methods to balance groups (e.g., propensity score matching). Several studies reported secondary outcomes, and many stratified patients by survival status rather than by fluid balance exposure, which we considered an additional potential source of bias.

All-cause mortality

A quantitative synthesis of 14 studies including 32,004 patients was feasible for the primary outcome of all-cause mortality. Owing to the substantial between-study heterogeneity (I^2 = 85%), we applied a random-effects model. The pooled odds ratio (OR) for higher versus lower fluid balance was 2.11 (95% CI 1.65–2.69; Fig. 3A).

When stratified by study design, retrospective studies yielded an OR of 2.10 (95% CI 1.48–2.97; I^2 = 88%), while prospective studies showed an OR of 2.35 (95% CI 2.03–2.74; I^2 = 0%) (Figure S1, Supplementary Data). Three studies [20, 24, 27] were identified as outliers; excluding these, the pooled OR was 2.21 (95% CI 1.76–2.78) with reduced heterogeneity (I^2 = 63%). When stratified by the time frame of FB assessment (Figure S3, Supplementary Data), the association between higher FB and mortality was not statistically significant in studies evaluating FB within the first 1–2 days (OR 2.03; 95% CI 0.80–5.15; I^2 = 0%), whereas a consistent and significant association was observed in studies with longer evaluation windows (>2 days: OR 2.03; 95% CI 1.24–3.34; I^2 = 83.2%).

At the meta-regression, neither the year of publication (residual heterogeneity I^2 = 85%), study design (I^2 = 87%), mortality definition (I^2 = 90%), nor the time window used for fluid balance assessment (I^2 = 80%) explained a significant proportion of the between-study heterogeneity. The Egger's test did not indicate funnel plot asymmetry (p = 0.06) (Fig. 4A).

Influence diagnostics (GOSH analysis) identified three distinct study clusters with different effect–heterogeneity profiles (Supplementary Figure S5, Table S3). These patterns suggest that subsets of studies exert differential influence on the pooled estimates.

Beyond the standard meta-regression, we conducted exploratory dose–response analyses. A continuous meta-regression indicated that a higher study-level proportion of patients assigned to the higher fluid balance group was associated with higher log-odds of mortality (p for trend < 0.01; Fig. 5), and this association persisted after adjusting for the method used to calculate FB (indexed vs. absolute). In contrast, a spline-based model did not identify a significant non-linear relationship (QM = 2.32; p = 0.51; Supplementary Figure S6). When studies were stratified by tertiles of patients in the higher FB group, the estimated risk peaked in the medium tertile, with a slightly lower estimate in the highest tertile (Supplementary Figure S7). Ranking probabilities further suggested that the 'Low' FB category was most likely to be favorable (72%), while the 'High' category most often ranked least favorable (SUCRA, Table S4, Supplementary Figure S8).

Need for RRT/CRRT

The secondary outcome of requiring RRT/CRRT was evaluated in a quantitative synthesis of 8 studies including 12,204 patients. The random-effects model yielded an OR of 1.34 (95% CI 0.76–2.36; I^2 = 86%) for higher versus lower FB (Fig. 3B). As the confidence interval crossed 1, the association was not statistically significant.

When stratified by study design, retrospective studies showed an OR of 1.27 (95% CI 0.65–2.49; I^2 = 85%), while prospective studies showed an OR of 1.89 (95% CI 1.55–2.29) (Figure S2, Supplementary Data). No outliers were identified relative to the random-effects model. Similarly, when stratified by the time frame of FB assessment (Figure S4, Supplementary Data), the association between higher FB and the need for RRT/CRRT did not reach statistical significance in any subgroup. Meta-regression suggested that the time window of FB assessment contributed to heterogeneity (residual I^2 = 88%; R^2 = 12%). Given the limited number of studies, Egger's test was considered unreliable (Fig. 4B).

Table 2 Components of fluid balance assessment across included studies

Author(s), year^	Sample size (*n*)	Input variables			Output variables									Number of variables considered		
		Intravenous fluids	Oral fluids	Enteral fluids	Urine	Stool	Drains	Thoracentesis/Paracentesis	Emesis	Blood losses	Ultrafiltrate/dialysis	Gastrointestinal losses	Insensible fluid losses	Input (*n*)	Output (*n*)	Total (*n*)
Zhang, 2021 [24]	19,557	+	+		+	+	+	+	+	+	+		-	2	7	9
Hyun, 2023 [13]	2516	+		+	+		+				+		-	2	3	5
Acheampong, 2020* [15]	173	+	+		+	+	+				+	+	-	2	5	7
Zhang, 2022 [23]	936	+			+	+	+							1	3	4
Wang YM, 2021 [25]	337	+	+	+	+		+				+			3	3	6
Shen, 2018 [29]	8584	+												1	0	1
Wang MP, 2021 [26]	986	+	+	+	+		+				+	+	-	3	4	7
Wang, 2022 [21]	4610	+		+	+	+	+		+		+			2	5	7
Huang, 2019 [28]	104	+	+		+		+				+	+		2	4	6
Tackaert, 2023 [19]	482	+	+	+	+		+				+	+		3	6	9
Cronhjort, 2016§ [31]	841	+			+		+				+		-	1	3	4
Koonrangsesomboon, 2015 [35]	1048	+	+		+		+	+			+			2	4	6
Pittard, 2017 [30]	186	+	+	+	+	+	+		+		+		-	3	5	8
de Souza, 2024** [12]	139	+	+	+	+		+				+	+	-	3	4	7
Sakr, 2017 [14]	1808	+		+	+		+				+		-	2	3	5
Brotfain, 2016 [32]	297	+		+	+	+								2	3	5
Dash, 2023 [20]	710	+	+	+	+	+	+			+	+		-	3	5	8
de Oliveira, 2014 [33]	116	+	+	+	+		+						-	3	2	5
Cunha, 2015 [17]	40	+		+	+		+				+		+	2	5	8
Number of studies considering each variable(n/N)		19/19	11/19	12/19	18/19	7/19	17/19	2/19	3/19	2/19	14/19	5/19	2/19			

This table summarizes the input and output variables used to calculate fluid balance in 19 studies. Intravenous fluids and urine output were the most commonly considered variables (included in 19/19 and 18/19 studies, respectively), while elements such as stool losses, gastrointestinal outputs, and insensible losses were rarely reported. The number of fluid components included in fluid balance calculations varied widely across studies (range: 1–9), underscoring substantial heterogeneity in fluid accounting practices and the lack of standardization in fluid balance determination

Footnotes:

^ Only studies reporting fluid balance variables are displayed ($n = 19$). The remaining 7 studies did not specify components and were excluded.

* In Acheampong, 2020 [15], stools were considered only in the presence of profound diarrhea.

** In de Souza, 2024 [12], gastrointestinal losses were included only in case of severe diarrhea (> 3 episodes/day).

§ In Cronhjort, 2016 [31], the authors did not specifically indicate "intravenous fluids," but reported "administered fluid volume," which was counted as intravenous fluids.

Certainty of evidence

Using the GRADE framework, the certainty of evidence for both mortality and RRT/CRRT was rated as very low (Table 3). This reflects the predominance of observational data with serious risk of bias, substantial between-study heterogeneity, imprecision of estimates, and potential publication bias. Although exploratory analyses suggested a possible dose–response relationship, these signals were inconsistent and hypothesis-generating only.

Discussion

This review summarizes evidence on the association between fluid balance (FB) and all-cause mortality in critically ill adults with sepsis or septic shock, and on the need for RRT/CRRT. In synthesis, patients with higher FB had approximately twice the odds of death compared with those with lower FB, whereas the association with RRT/CRRT was not statistically significant. Among studies evaluating RRT/CRRT, only one prospective study reported a significant association between higher FB and the need for renal support [14]. This isolated finding warrants cautious interpretation in the context of predominantly retrospective evidence. Substantial between-study heterogeneity was observed for both outcomes, and meta-regression did not identify study-level characteristics that explained a meaningful proportion of this heterogeneity.

This variability extends to both how and how much fluid is administered, as documented by the European Society of Intensive Care Medicine (ESICM) FENICE global cohort, which reported wide differences in the indications, volumes, rates, and monitoring of fluid challenges – with dynamic predictors and safety limits infrequently used [38].

Higher FB may reflect a marker of underlying illness severity rather than a direct treatment effect. Given the observational design of the included studies and incomplete adjustment for severity domains in several cohorts, residual confounding by severity is likely [14, 15]. Accordingly, the association between higher FB and mortality should be regarded as hypothesis-generating rather than causal. Randomised trials of fluid strategies in sepsis (e.g., CLASSIC and CLOVERS) have not, to date, shown a consistent mortality benefit of more restrictive approaches [39, 40]. Notably, these trials evaluate assigned strategies rather than standardising achieved FB as a common exposure. Two further trials (ARISE FLUIDS, NCT04569942; EVIS, NCT05179499) are ongoing [41, 42].

FB is clinically relevant in fluid therapy and shock support to maintain organ perfusion and oxygen delivery [43]. The clinical motivation for calculating FB includes avoiding potential adverse effects related to fluid overload (e.g., lung/brain/other organ oedema) and those associated with fluid depletion that may compromise oxygen delivery and cellular processes [44]. One retrospective study reported an association between negative FB and improved survival [37]. A hypothesis is that more frequent FB calculation early after sepsis or septic shock might facilitate earlier identification of deterioration and supportive interventions; however, this remains hypothesis-generating and is not established by our data [45]. Severe critical illness may coexist with capillary leak/third-space shifts that are difficult to quantify directly [46, 47]. Such shifts may be inferred from indirect signs (e.g., ultrasound findings or intra-abdominal pressure monitoring) [48] and can produce misleading signs of hypovolemia, prompting additional fluid administration [15], potentially creating a vicious circle with concurrent renal dysfunction [49].

Our influence diagnostics (GOSH clustering) indicated that between-study heterogeneity stems from subgroups of studies with distinct effect–variance profiles. In exploratory dose–response analyses, a continuous meta-regression showed that a larger study-level proportion of patients assigned to the higher fluid-balance group was associated with higher log-odds of mortality. By contrast, a spline-based model did not identify a significant non-linear relationship. Consistent with the tertile and ranking analyses, the overall pattern suggested a possible peak in risk at intermediate proportions, while lower fluid-balance categories more often ranked as most favorable [44, 48–50]. These findings are hypothesis-generating and do not establish causality. When studies were stratified by the time window used for FB assessment, the association with mortality was not statistically significant within the first 1–2 days, whereas it was consistent and significant with longer windows (>2 days), suggesting the importance of timing in FB evaluation.

Currently, there is no standardized, validated method for FB determination [51]. Potential inaccuracies in FB charting have been reported but cannot be quantified in our synthesis [52]. Several factors complicate precise accounting: arterial line flushing after blood sampling [53]; insensible and complex losses (respiratory secretions, stool water, fever, open abdomen) [54]; large pleural/abdominal effusions that accumulate over days yet are subtracted only on the day of drainage [48]. In our set, insensible losses were not calculated in many studies, and stool water was rarely considered. Such issues may be relevant in sepsis, where fever and gastrointestinal failure are frequent [55]. Without overt clinical signs or malfunctioning drains/tubes, third-space losses can be difficult to detect [56]. Weight change correlates only weakly with FB and may reflect changes in body composition during critical illness, limiting its value as a surrogate [57].

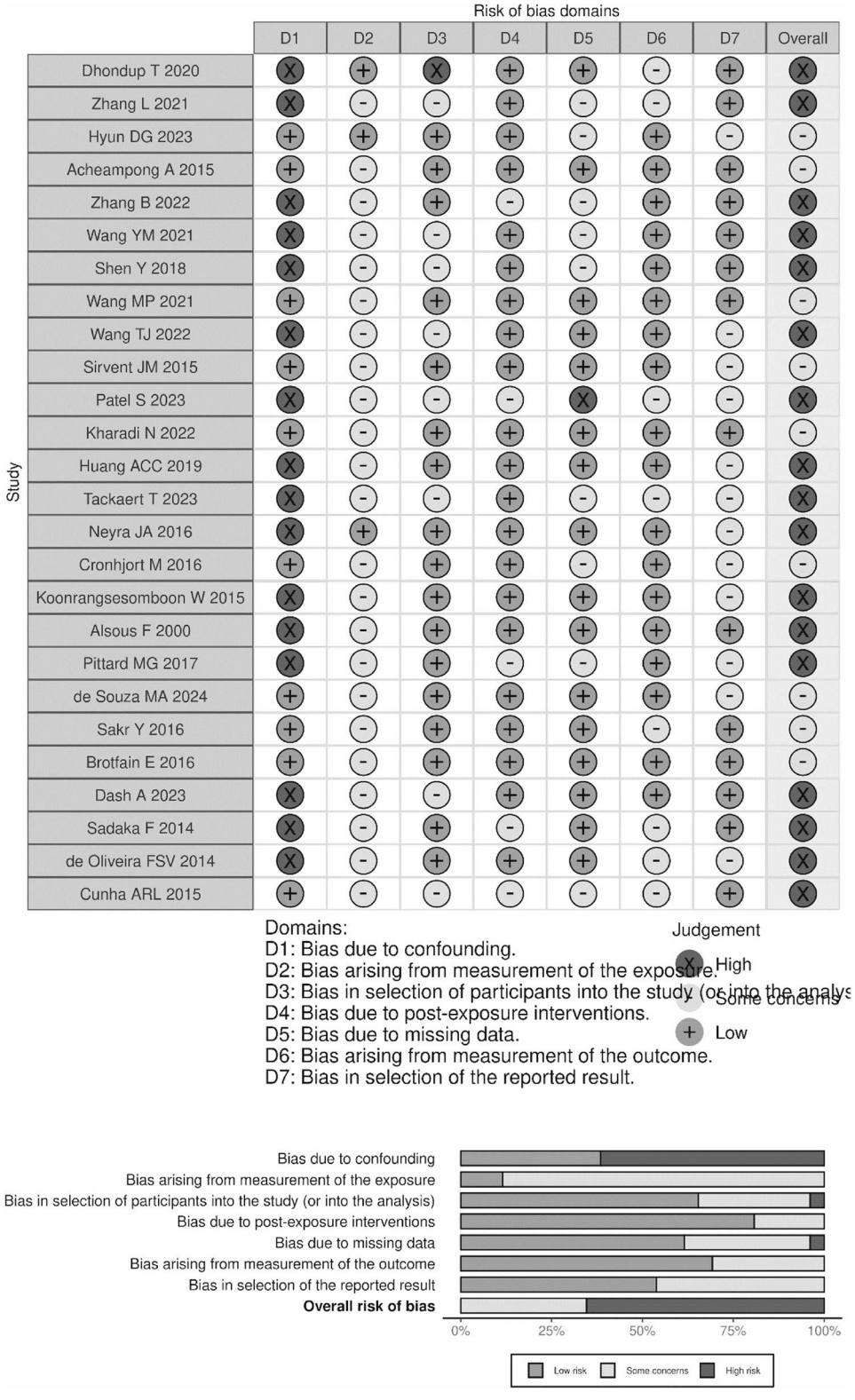


Fig. 2 Risk of bias assessment across included studies using the ROBINS-E tool. The figure summarizes risk of bias judgments across the seven ROBINS-E domains for the 26 included studies. Confounding (D1) was the most frequent source of high risk, whereas exposure measurement (D2) and participant selection (D3) were commonly rated as presenting some concerns. Other domains – including classification of exposure, deviations from intended exposures, missing data, and outcome measurement – showed mixed ratings across studies. Only a minority of studies were judged at low risk across all domains. Overall, the risk of bias was rated as high in most studies, reflecting the methodological limitations inherent to observational research on fluid balance

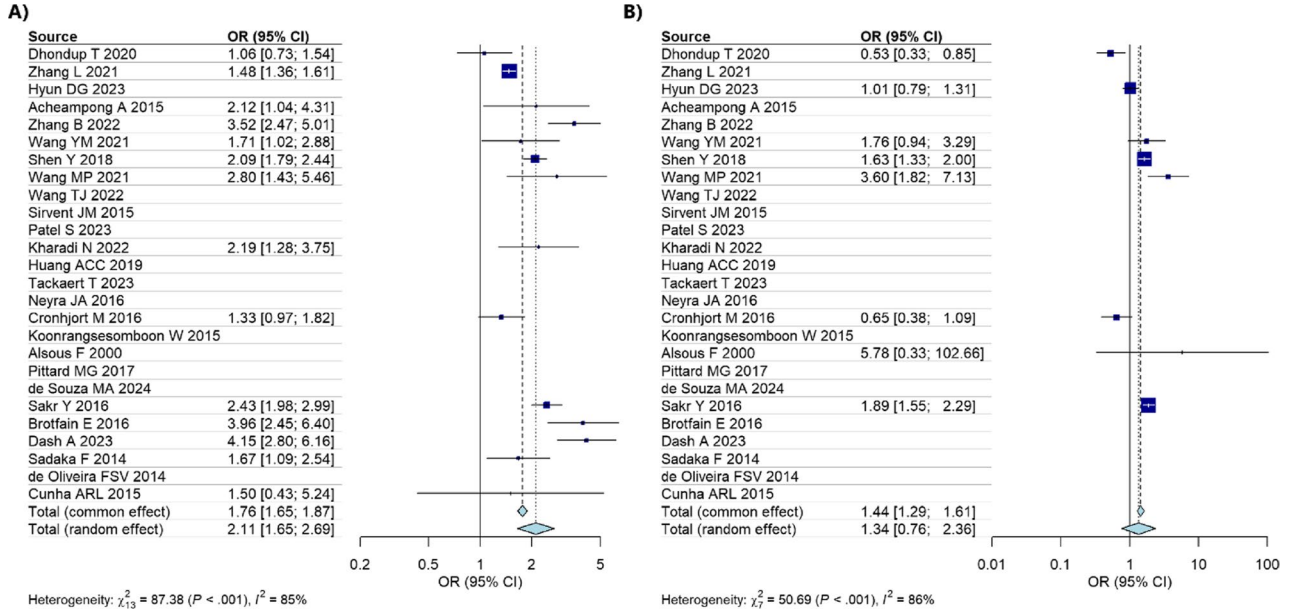


Fig. 3 Forest plots of the association between higher fluid balance and clinical outcomes. **A** Association between higher fluid balance and all-cause short-term mortality. Pooled analysis of 14 studies ($n = 32,004$) showed that higher fluid balance was associated with a higher risk of death (random-effects OR 2.11, 95% CI 1.65–2.69; $I^2 = 85\%$). **B** Association between higher fluid balance and the need for continuous renal replacement therapy (CRRT). Meta-analysis of 8 studies ($n = 12,204$) showed no statistically significant association (random-effects OR 1.34, 95% CI 0.76–2.36; $I^2 = 86\%$). Both outcomes demonstrated substantial heterogeneity, reflecting variability in study populations, definitions, and methods of fluid balance assessment

In this review, higher FB was associated with higher mortality, while the association with RRT/CRRT was not statistically significant. Given the observational nature of the evidence and substantial heterogeneity, these results should be interpreted with caution. Priorities include standardisation of FB measurement/reporting and additional high-quality studies to clarify relationships with patient-important outcomes.

Limitations

This study has several limitations. First, the number of available publications addressing mortality in relation to positive FB was limited, and most included studies were observational (retrospective or prospective) with relatively small sample sizes. Importantly, although randomised controlled trials on fluid resuscitation versus restriction in sepsis exist (e.g., CLASSIC, CLOVERS), they address treatment strategies rather than directly evaluating achieved FB and were therefore not included in our pooled analyses. This distinction should be made explicitly in interpreting our findings. A key limitation is potential confounding by illness severity. Patients with greater hemodynamic instability or organ dysfunction are more likely to receive larger fluid volumes; hence, higher FB may serve as a proxy for baseline severity. Because severity adjustment was heterogeneous and often incomplete across studies, residual confounding cannot be excluded.

A major limitation lies in the heterogeneity of methods used to calculate and report FB. Studies varied in the input and output variables considered, in the timing of FB determination after sepsis onset, and in whether FB was expressed as absolute, indexed, cumulative, or daily values. We attempted to address this variability through subgroup and meta-regression analyses, but residual heterogeneity remained high.

A further major limitation of this systematic review and meta-analysis is the lack of standardised, time-based data on fluid balance. The included studies varied widely in the timing of fluid balance assessment, and most reported only cumulative fluid balance across several days or for the entire ICU stay. As a result, our findings primarily reflect overall fluid accumulation during the index hospitalisation and do not provide direct evidence on fluid administration strategies in the early resuscitation phase of sepsis. Furthermore, we could not ascertain whether pre-hospital/EMS-administered fluids were consistently captured across studies, which may have introduced exposure misclassification of achieved FB at early time points.

Moreover, many included studies did not distinguish sepsis without shock from septic shock or combined these populations without shock-status stratification. Because shock status and hemodynamic phase likely modify fluid requirements and tolerance, the absence of stratification may obscure differential associations between achieved fluid balance and outcomes. Future

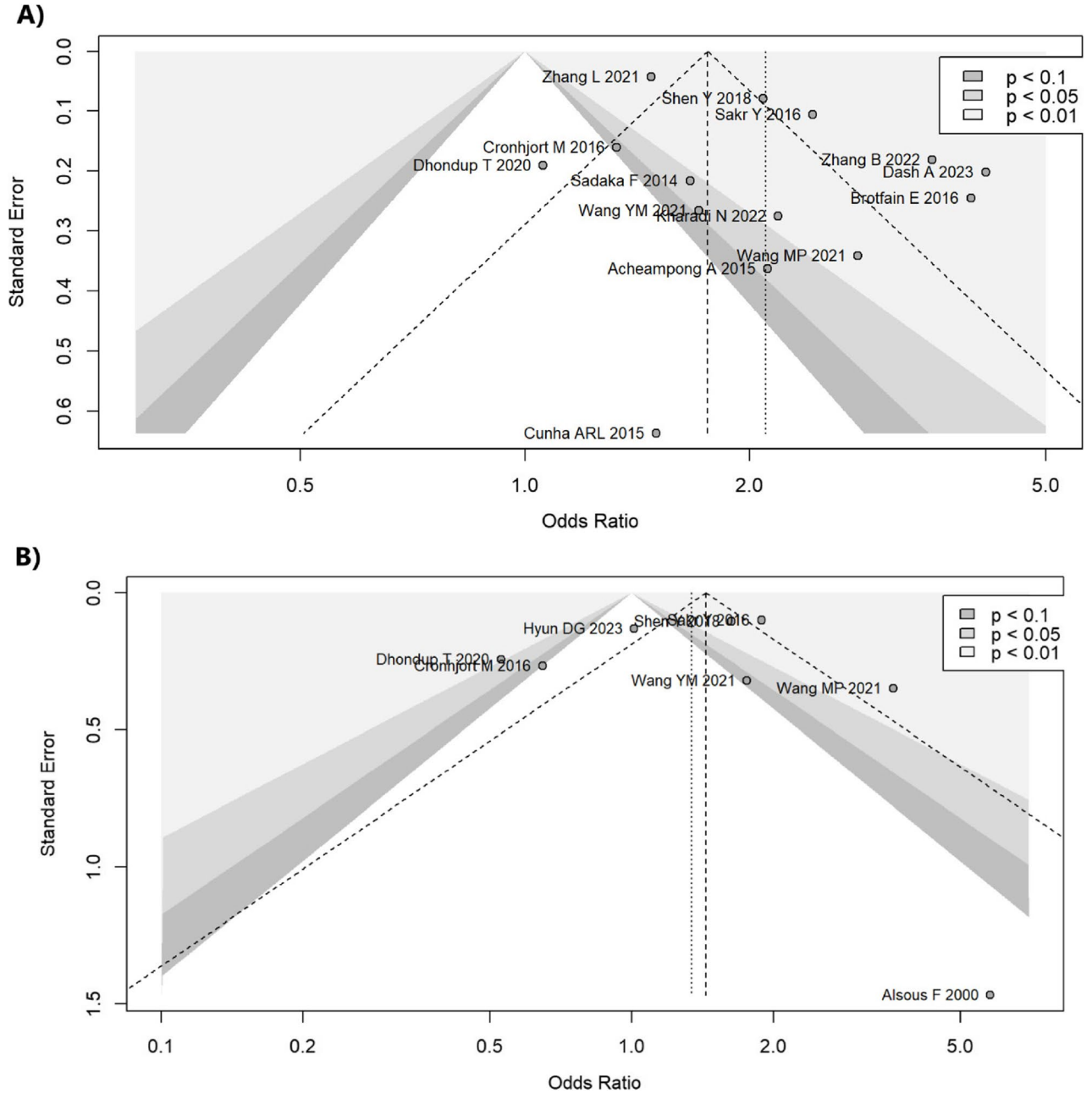


Fig. 4 Contour-enhanced funnel plots assessing publication bias. **A** Funnel plot for the outcome of all-cause short-term mortality. The plot shows a relatively symmetric distribution of studies. The Egger's test did not indicate significant asymmetry ($p = 0.06$). **B** Funnel plot for the outcome of need for RRT/CRRT. The plot shows fewer studies with an apparently symmetric distribution; however, given the limited number of studies, statistical tests for asymmetry were not considered reliable. Shaded areas indicate significance contours ($p < 0.1$, $p < 0.05$, and $p < 0.01$), aiding interpretation of whether potentially missing studies would be expected in regions of non-significant results

studies should prespecify shock-status strata and phase-specific time windows to assess potential effect modification.

The relatively small number of eligible studies further limited our ability to examine non-linear dose–response patterns or perform granular subgroup stratifications (e.g., by timing of balance assessment or septic phenotype). Although we performed exploratory meta-regressions using FB as a continuous predictor, these analyses should be interpreted cautiously given the potential for ecological bias and limited statistical power. Future harmonised prospective studies and, ideally, patient-level meta-analyses are needed to clarify the dose–response relationship between cumulative FB and mortality in sepsis.

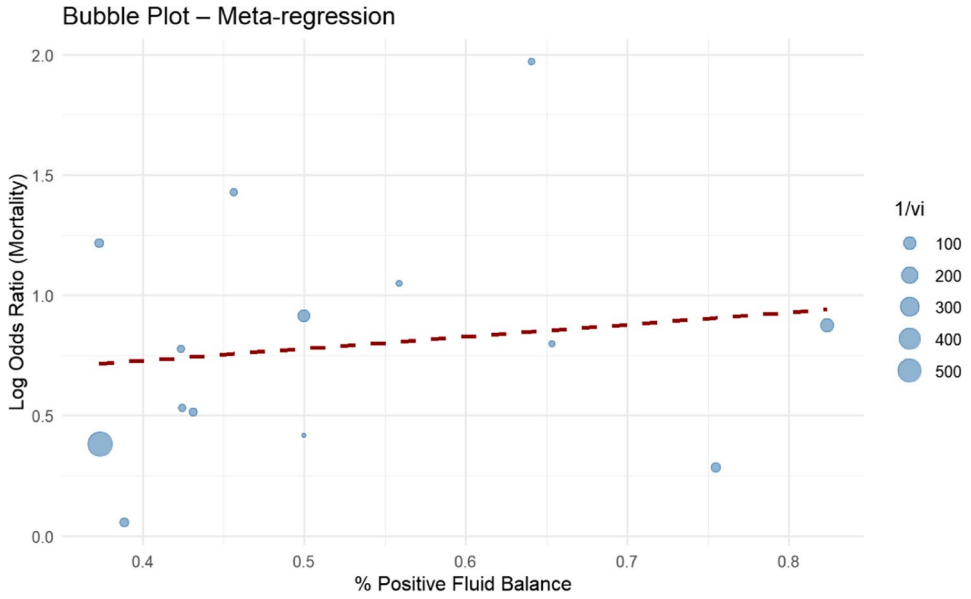


Fig. 5 Bubble plot – meta-regression of mortality on the study-level proportion of patients assigned to the higher fluid balance group. Each bubble represents one study; the x-axis shows the proportion of patients in the higher fluid balance group (%), the y-axis the log odds ratio for mortality, and bubble size is proportional to precision (1/vi). The dashed line depicts the fitted meta-regression trend (estimate 0.787, SE 0.134), indicating that studies with a larger proportion of patients in the higher fluid balance group were associated with higher log-odds of mortality ($z = 5.89$, $p < 0.0001$; 95% CI 0.525–1.049). Between-study heterogeneity was substantial ($\tau^2 = 0.188$; $I^2 = 89.3\%$)

Table 3 Summary of findings and GRADE assessment

Patient or population: patients with sepsis and septic shock
Settings: ICU/hospital
Intervention: a higher fluid balance
Comparison: a lower fluid balance

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	A lower fluid balance	A higher fluid balance				
All-cause short-term mortality	**136 per 1000**	**250 per 1000** (207 to 298)	**OR 2.11** (1.65 to 2.69)	32,004 (14 studies)	⊕⊖⊖⊖ **very low**	
Need for RRT/CRRT	**161 per 1000**	**205 per 1000** (127 to 312)	**OR 1.34** (0.76 to 2.36)	12,204 (8 studies)	⊕⊖⊖⊖ **very low**	

GRADE Working Group grades of evidenceHigh quality: Further research is very unlikely to change our confidence in the estimate of effect.Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.Very low quality: We are very uncertain about the estimate.

Comparison between higher versus lower fluid balance in critically ill patients with sepsis or septic shock. Outcomes include all-cause short-term mortality and the need for renal replacement therapy/continuous renal replacement therapy (RRT/CRRT). For each outcome, the assumed risk in the lower fluid balance group, the corresponding risk in the higher fluid balance group, relative effects (odds ratios with 95% confidence intervals), number of participants and studies, and the quality of the evidence (GRADE) are reported. Both outcomes were graded as very low certainty, reflecting methodological limitations, heterogeneity, and imprecision.

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*CI* Confidence interval, *OR* Odds ratio

Finally, we acknowledge that the initial database searches were performed before registration of the review protocol in PROSPERO. This temporal sequence represents a methodological limitation. An updated search was conducted prior to submission to ensure inclusion of the most recent evidence.

Conclusions

This meta-analysis suggests that, among ICU patients with sepsis or septic shock, a higher fluid balance was associated with higher mortality. The certainty of evidence was rated as very low, but the association appeared consistent across multiple analyses. No statistically significant association was observed between fluid balance and the need for renal replacement therapy. Sepsis without shock and septic shock may represent distinct clinical states with different fluid management implications;

consequently, future studies should prespecify shock-status strata and assess potential effect modification. These findings suggest the need for standardised methods of fluid balance assessment and for additional high-quality randomised evidence to clarify the clinical implications of fluid management strategies in sepsis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03518-9.

Supplementary Material 1.

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The authors declare that no part of the manuscript text was generated using artificial intelligence (AI). AI assistance (ChatGPT, OpenAI) was used only to generate an initial version of the graphical abstract, which was subsequently reviewed, edited, and finalised by the authors.We thank all investigators of the original studies included in the review for their contributions to the field.

Author contributions
FF, DO and IC conceived the study and designed the protocol. FF, DO, IC performed the literature search. FF, DO, IC, EDC, FM, BG, TB performed the data extraction. DO conducted statistical analysis and created the figures. FF, TB and GDR contributed to data interpretation and critical revision of the manuscript. All authors read and approved the final manuscript.

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Data availability
All data generated or analysed during this study are included in this published article and its supplementary information files. The dataset used for analysis is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable. This study is a systematic review and meta-analysis of previously published data.

Consent for publication
Not applicable.

Competing interests
Daniele Orso is an associated editor of BMC Anesthesiology.

Author details
[1]Department of Emergency, Udine University Hospital, Azienda Sanitaria Universitaria Friuli Centrale (ASU FC), Piazzale Santa Maria della Misericordia 15, Udine 33100, Italy
[2]Department of Medicine (DMED), University of Udine, Via Colugna 50, Udine 33100, Italy
[3]Department of Basic Biotechnological Sciences, Intensive Care Peri-Operative Clinics, Università Cattolica del Sacro Cuore, 00168 Rome, Italy
[4]Department of Emergency, Anesthesiological and Reanimation Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, 00168 Rome, Italy

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