SYSTEMATIC REVIEWS

The ultrasound gap in de-resuscitation trials: A systematic review of physiological assessment deficits

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ABSTRACT

Background: Fluid overload is associated with increased mortality in critically ill patients, yet de-resuscitation trials frequently report negative or inconclusive results. This systematic review examines the relationship between parameter objectivity, ultrasound utilization, and trial outcomes in de-resuscitation research.

Methods: We conducted a comprehensive systematic review of randomized controlled trials investigating de-resuscitation interventions in critically ill adults. Risk of bias was evaluated using the Cochrane Risk of Bias 2 tool. Statistical analysis included comparison of ultrasound versus non-ultrasound studies and pooled outcome analysis.

Results: 13 studies were identified which randomised 2495 patients. Of the included studies, 4 (30.8%) performed some form of ultrasound assessment. However, only 1 study (7.7%) explicitly used ultrasound to guide de-resuscitation interventions. However, it did not achieve significant fluid separation between the control and interventional arm. No studies achieved positive hard clinical outcomes (mortality reduction or major morbidity reduction) from de-resuscitation interventions. However, several studies successfully achieved their stated primary endpoints: fluid balance separation was achieved in 7 of 13 studies (53.8%), feasibility objectives were met in 3 studies, and improvements in secondary endpoints including ventilator-free days and time to extubation were demonstrated in select studies. These findings suggest that achieving targeted fluid balance changes does not necessarily translate to improved clinical outcomes.

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Conclusions: Current research is characterized by a significant 'ultrasound gap,' where the theoretical benefits of POCUS are not yet integrated into interventional trials. Future research must bridge this gap using standardized, physiology-driven protocols.

Key words: de-resuscitation, fluid overload, ultrasound, parameter objectivity, systematic review, critical care

Introduction

The management of fluid overload in critically ill patients represents one of the most challenging aspects of intensive care medicine, with profound implications for patient outcomes and healthcare resource utilization (1). Fluid accumulation occurs in the majority of critically ill patients due to aggressive initial resuscitation, ongoing fluid administration for medication delivery, nutritional support, and the pathophysiological changes associated with critical illness that impair fluid excretion (2,3). Observational studies consistently demonstrate a dose-dependent relationship between positive fluid balance and adverse outcomes, including increased mortality, prolonged mechanical ventilation, and extended intensive care unit (ICU) stays (4,5).

Despite this compelling observational evidence, randomized controlled trials (RCTs) investigating de-resuscitation strategies have yielded disappointing results, with many studies failing to demonstrate clear clinical benefits (6,7). This apparent paradox between observational evidence and interventional trial outcomes has generated considerable debate within the critical care community and has led to various hypotheses attempting to explain these discordant findings (8).

One prominent hypothesis suggests that the failure of de-resuscitation trials stems from the use of subjective assessment parameters that introduce variability, bias, and inconsistency in intervention delivery (7, 9). Proponents of this theory argue that objective, measurable parameters with specific numerical thresholds should yield more consistent and successful trial outcomes by reducing clinician variability and improving protocol adherence (10, 11). This perspective has influenced the design of recent de-resuscitation trials, with investigators increasingly incorporating objective hemodynamic targets, biomarker-guided approaches, and standardized assessment protocols (12, 13).

However, this hypothesis has never been systematically tested across the broader landscape of de-resuscitation research. Furthermore, the definition and classification of "objective" versus "subjective" parameters in de-resuscitation research remains poorly standardized, with different investigators applying varying criteria and thresholds.

Point-of-care ultrasound (POCUS) has emerged as a promising tool for objective, real-time assessment of fluid status and responsiveness in critically ill patients (14 – 16). Multiple studies have demonstrated the utility of ultrasound-derived parameters, including inferior vena cava (IVC) diameter and collapsibility, venous excess ultrasound (VExUS) score, and echocardiographic assessment of cardiac function, in guiding fluid management decisions (17, 18).

Although ultrasound assessment offers potential advantages for objective fluid status evaluation, its inclusion within deresuscitation protocols remains limited. This is partially because the VExUS and fluid tolerance are relatively new concepts (19 – 22). Previous studies have demonstrated the utility of ultrasound parameters in assessing fluid responsiveness in critically ill patients, yet the specific application of ultrasound guidance to active deresuscitation interventions has not been systematically evaluated. Some investigators have incorporated comprehensive ultrasound assessments into their protocols, while others have relied on traditional hemodynamic parameters or clinical judgment alone. This heterogeneity in approach provides an opportunity to examine whether ultrasound utilization is associated with improved trial outcomes or more successful achievement of fluid balance targets.

This systematic review aims to comprehensively evaluate the relationship between parameter objectivity, ultrasound utilization, and trial outcomes in de-resuscitation research. We hypothesized that studies incorporating explicit ultrasound guidance for de-resuscitation decisions would demonstrate superior fluid balance achievement and clinical outcomes compared to those relying on traditional assessment methods. Additionally, we sought to examine whether parameter objectivity (as classified across five assessment domains) would predict trial success rates.

Methods

Study design and protocol

We conducted a comprehensive systematic review of randomized controlled trials (RCTs) investigating de-resuscitation interventions in critically ill patients. The review was designed to examine the relationship between parameter objectivity, ultrasound utilization, and trial outcomes. Our methodology incorporated both quantitative parameter classification and qualitative assessment of trial characteristics to provide a comprehensive evaluation of factors influencing de-resuscitation trial success. The review protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (23). The review has also been registered on PROSPERO (CRD420251275295).

Search strategy and information sources

A comprehensive search of multiple electronic databases was conducted, including PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, from their inception to August 2025. The search strategy combined keywords and Medical Subject Headings (MeSH) terms related to "fluid overload," "de-resuscitation," "fluid removal," "diuretics," "ultrafiltration," "critical care," "intensive care," and "randomized controlled trial." No language restrictions were applied to maximize study inclusion.

The search strategy was developed in consultation with a medical librarian, and refined through iterative testing to ensure comprehensive coverage of relevant literature. Reference lists of included studies and relevant review articles were manually screened for additional eligible trials. Conference abstracts and grey literature were also searched to identify unpublished or recently completed studies.

Study selection and eligibility criteria

Studies were included if they met the following criteria: (1) RCT design investigating active fluid removal or conservative fluid management strategies; (2) adult critically ill patients (age ≥18 years) in ICUs; (3) intervention aimed at achieving negative fluid balance, preventing further fluid accumulation, or actively removing excess fluid; (4) comparison with usual care, placebo, or alternative fluid management strategy; and (5) reported clinical outcomes with sufficient methodological detail for parameter classification.

Studies were excluded if they: (1) focused solely on initial resuscitation without addressing subsequent fluid management; (2) involved paediatric populations (age <18 years); (3) were conducted in non-critically ill populations; (4) lacked sufficient methodological detail for parameter assessment; (5) were observational studies, case series, or non-randomized trials; or (6) investigated interventions not directly related to fluid balance management.

Two review authors independently screened titles and abstracts of all identified records. Full texts of potentially eligible articles were retrieved and assessed for final inclusion. Disagreements between reviewers were resolved through discussion and consensus, with a third author available for arbitration when necessary.

Data extraction and management

A standardized data extraction form was developed and pilot-tested on a subset of included studies. One author extracted data from all included studies, and a second author independently verified the extracted data for accuracy and completeness. Extracted data included study characteristics (design, setting, sample size), population demographics, intervention details, control group characteristics, outcome measures, and specific parameters required for our classification framework.

Particular attention was paid to extracting detailed information about ultrasound utilisation, including the specific ultrasound parameters used, frequency of assessment, operator training, and integration into clinical decision-making algorithms.

For the primary comparative analysis, studies were classified as ‘ultrasound-guided de-resuscitation’ only if ultrasound assessment (including inferior vena cava diameter/collapsibility, venous excess ultrasound score, echocardiography, or Doppler-derived parameters) was explicitly used to trigger or guide active fluid removal decisions. Studies where ultrasound was performed for baseline characterization, concurrent hemodynamic monitoring, or weaning assessment but not specifically to guide deresuscitation interventions were classified as ‘non-ultrasound-guided de-resuscitation’ for the primary analysis, though secondary classification tracked all ultrasound usage.

Risk of bias assessment

All included studies underwent comprehensive risk of bias assessment using the Cochrane Risk of Bias 2 (RoB 2) tool (24). This tool evaluates five domains of potential bias: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Each domain was assessed as “Low risk,” “Some concerns,” or “High risk” based on standardized criteria, with an overall judgment derived from the individual domain assessments.

The RoB 2 assessment was particularly important for this analysis given the inherent challenges in blinding fluid management interventions and the potential for implementation bias in complex clinical protocols. Special attention was paid to the impact of open-label designs on outcome measurement and the potential for differential implementation of interventions between study groups.

Statistical analysis

Descriptive statistics were used to summarize study characteristics and outcome data. Categorical variables describing study design, population, and methodology were presented as frequencies and percentages. Continuous variables including sample sizes and outcome percentages were presented as medians with interquartile ranges or means with standard deviations as appropriate.

The primary comparative analysis examined fluid balance achievement rates between ultrasound-guided and non-ultrasound-guided studies using descriptive comparison. Fisher’s exact test was used to compare proportions of studies achieving fluid balance separation between groups ($\alpha = 0.05$). For studies reporting fluid balance as continuous variables with between-group comparisons, achievement of ‘separation’ was defined as reported p-value <0.05 for the comparison.

No meta-analytic pooling was performed due to heterogeneity in patient populations, intervention protocols, timing of assessment, and outcome definitions. Exploratory assessment of temporal trends in ultrasound adoption across publication decades was performed using descriptive comparison.

Results

Study selection and characteristics

The systematic search identified 2,847 potentially relevant records after duplicate removal. Following title and abstract screening, thirteen RCTs met the inclusion criteria and were included in the final analysis (25 – 37). The study selection process is detailed in the PRISMA flow diagram (Figure 1).

The 13 included studies consisted of 2,495 participants and were published between 2004 and 2025, representing two decades of de-resuscitation research. Study sample sizes ranged from 23 to 1,001 participants (median 100, IQR 41-180).

The characteristics of the included trials are shown in Table 1.

The key outcomes and safety signals are shown in Table 2.

The included studies represented diverse critical care populations, including general ICU patients (n=3 studies), patients with acute kidney injury (n=5 studies), sepsis patients (n=2 studies), patients requiring mechanical ventilation weaning (n=2 studies), and

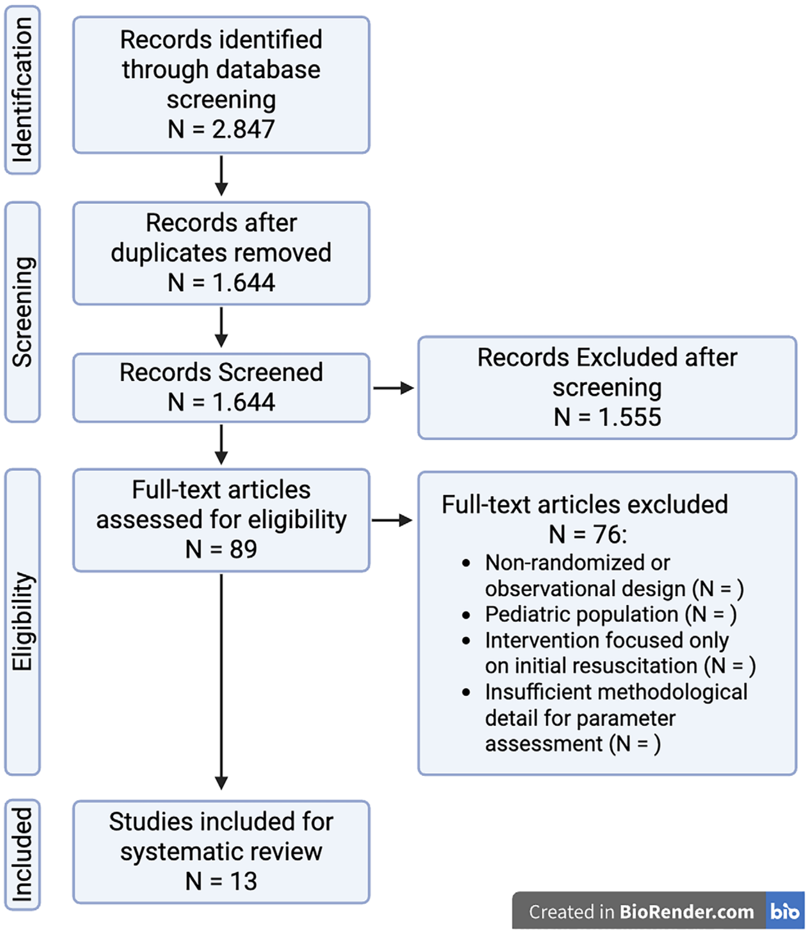

Figure 1. Prisma Flow Diagram.

patients with acute respiratory distress syndrome (n=1 study). This diversity provides a comprehensive view of de-resuscitation approaches across different clinical contexts.

Ultrasound utilization analysis

Four of 13 studies (30.8%) performed some form of ultrasound assessment, but only one study (7.7%) explicitly used ultrasound parameters to guide active de-resuscitation interventions.

Ultrasound utilization and fluid balance separation

Of the 13 studies, four (30.8%) [31, 32, 36, 37] utilized ultrasound in some capacity for patient assessment, while nine (69.2%) did not. A post-hoc analysis was conducted to evaluate the association between any ultrasound use and the achievement of significant fluid balance separation between study arms (Table 3). One of the four studies involving any ultrasound use (25.0%) achieved significant fluid balance separation, compared to six of the nine studies with no ultrasound involvement (66.7%). This difference was not statistically significant ($p = 0.27$, Fisher's exact test; OR 0.17, 95% CI [0.01, 2.45]).

A sub-analysis was performed to assess the impact of protocols that explicitly used ultrasound-derived parameters to guide the de-resuscitation strategy (Table 4). Only one study (7.7%) met this definition [36]; it did not achieve significant fluid balance separation (0/1, 0%). Among the 12 studies that did not use explicit ultrasound guidance, seven (58.3%) achieved significant separation. No significant association was

Table 1. Characteristics of included trials

Study (First author)	Design / Setting	Population (n analyzed)	Intervention	Comparator	Main inclusion criteria	Primary outcome(s)	Duration / Follow-up
Wichmann et al. [35]	**Multicentre**, double-blind RCT (3 ICUs, Denmark)	Clinically stable adult ICU patients with ≥5% fluid overload (**n=41**)	Goal-directed deresuscitation with continuous IV **furosemide** infusion targeting neutral cumulative fluid balance (±750 mL)	Placebo infusion with identical protocol	ICU adults with shock treated ≥4 h with vasopressors $\geq 0.1\ \mu g\ kg^{-1}\ min^{-1}$ and ≥1 marker of fluid overload	Days alive and out of hospital at 90 days	**90 days**
Semler et al. [31]	**Single-centre**, open-label, randomized pilot trial (Vanderbilt Univ. MICU, USA)	Adults with sepsis and cardiopulmonary dysfunction after initial resuscitation (**n=30**)	Conservative fluid management protocol: fluids restricted during shock; **furosemide** infusion ($3–24\ mg\ h^{-1}$) to achieve neutral daily balance	Usual care (clinician-directed fluid and diuretic use)	Sepsis with ≥2 SIRS + shock (MAP < 60 mm Hg or vasopressors) or respiratory failure (MV or SpO_2 < 97% on $FiO_2 \geq 0.3$)	Mean daily fluid balance (Phase II); ICU-free days (Phase III, not reached)	**14 days** (Phase II only)
Silversides et al. [34]	**Multicentre** open-label RCT (8 UK ICUs)	Mechanically ventilated adults > 24 h post-ICU admission (**n = 179**)	Two-stage strategy: conservative fluid administration + active deresuscitation (IV **furosemide** ± **indapamide** + **spironolactone** or **ultrafiltration**)	Usual care	Ventilated ICU pts 24–48 h after admission; expected > 1 day stay	24-h fluid balance (day 2–3)	**180 days**
Cinotti et al. [32]	**Multicentre** single-blind RCT (4 ICUs, France)	Adults on invasive MV with ≥3% weight gain after stabilization (**n=166** ITT)	Protocolised **furosemide** to return to reference weight; hold for predefined metabolic/renal limits	No diuretics (rescue only for pulmonary edema)	MV with FiO_2 ≤60%, PEEP ≤10; hemodynamic stabilization; weight gain ≥3%	Fluid balance (weight change to successful extubation)	**60 days**
Hamishehkar et al. [28]	**Multicentre** RCT (2 ICUs, Iran)	ICU adults with AKI (**n=100**)	**Furosemide** 40–80 mg IV bolus → 1–5 mg/hinfusion; titrate to UO > $0.5\ mL{\cdot}kg^{-1}{\cdot}h^{-1}$	Usual care (no diuretics)	AKI by RIFLE criteria	NGAL (plasma/urine) trends; kidney function (Cr, BUN)	Biomarkers to day 7; mortality to **day 28**.
Berthelsen et al. [30]	**Multicentre** pilot RCT (Denmark)	**n = 20** (7 forced; 13 usual care)	Forced deresuscitation: **furosemide** bolus→infusion (≤ 40 mg/h) ± **CRRT**; target −1 mL/kg IBW/h; safety stops (MAP < 50, mottling, lactate > 4)	Usual care; CRRT discouraged unless predefined indications	ICU adults with AKI (KDIGO), RRS < 60%, > 10 % fluid overload	Cumulative fluid balance at day 5	**90 days**.

Study (First author)	Design / Setting	Population (n analyzed)	Intervention	Comparator	Main inclusion criteria	Primary outcome(s)	Duration / Follow-up
Wiedemann et al. [25]	**Multicentre** RCT, 2×2 (conservative vs liberal fluids; PAC vs CVC)	**n = 1000**	Conservative: CVP < 4 or PAOP < 8; **diuretic-driven**; pause during shock	Liberal: CVP 10–14 or PAOP 14–18; bolus-driven	MV adults with ALI/ARDS (PaO_2/FiO_2 < 300; bilateral infiltrates; no LA hypertension)	60-day mortality	Protocol ≤7 d; outcomes to **60 d**.
Mekontso Dessap et al. [27]	**Multicentre** RCT; AWS used in both arms	**n = 304** (152/arm)	BNP-guided: if BNP ≥200 pg/mL, restrict fluids; IV **furosemide** 10–30 mg q3h(target UO 4.5–9 $mL \cdot kg^{-1}$/3 h); ± **acetazolamide**	Usual care, BNP blinded	MV ≥24 h; FiO_2 ≤50%; PEEP ≤8; hemodynamic stability; sedation decreased/stopped	Time to successful extubation	**60 days**.
Chen & Kollef [36]	**Single-centre** pilot RCT (medical ICUs)	**n = 82** (41/41)	TFM with **daily fluid-responsiveness testing** (PPV, IVC index, SVI; ≥2 positive) → if non-responsive: restrict/stop fluids, concentrate infusions; consider diuretics/RRT	Usual care (no TFM recommendations)	Septic shock needing vasopressors ≥12 h after initial ≥30 mL/kgresuscitation	Study-fluid volumeand net balance by day 3 & day 5	Up to **5 days** (ICU stay)
Cantarovich et al. [26]	**Multicentre** double-blind RCT (France; ICUs & nephrology wards)	**n = 330** (166 / 164)	High-dose **furosemide**: 25 mg/kg/day IV (max 2 g) or 35 mg/kg/day PO (max 2.5 g) after a 15 mg/kg IV test; once daily post-RRT	Placebo(matched IV/PO)	Established ARF requiring RRT(BUN>180 mg/dL, oligo-anuria ≥48 h, or uremic syndrome)	Survival	Through dialysis phase or **7 days** post-RRT.
Vaara et al. [33]	**Multicentre** pilot RCT (7 ICUs, EU/AUS)	**n = 100** (49/51)	Restrictive fluid management bundle: minimize inputs, match outputs with unrestricted **diuretics**, consider **RRT** to achieve neutral/negative daily balance	Usual care	Adult ICU pts, AKI, not hypovolemic, 12–72 h in ICU	Cumulative fluid balance at 72 h	Intervention ≤7 d; exploratory outcomes to **90 d**.
Bagshaw et al. [29]	**Multicentre** blinded RCT (3 ICUs)	**n = 73** (37/36)	Low-dose **furosemide**: 0.4 mg/kg bolus → 0.05–0.40 mg/kg/h infusion to UO 1–2 mL/kg/h (≤7 d)	Placebosaline with identical algorithm	Early AKI (RIFLE–Risk), ≥2 SIRS, resuscitation goals achieved	Worsening AKI within 7 d	Drug ≤7 d; mortality to **90 d**.
Castro et al. [37]	**Single-centre** RCT (Chile); physiological trial with bioreactance & PLR	**n = 24** (12/12)	FR-guided deresuscitation (**UF/diuretics** per pathway) until PLR-positive, then stop	Empiric negative FB(same tools) until preset negative balance	MV >24 h & <7 d; >10% weight gain; stabilized, CRT<3 s, minimal/no vasopressors	*Primary objective:* cardiovascular/ hemodynamic outcomes	In-ICU; **48 h post-extubation.**

Table 2. Key outcomes and safety signals.

Study (First author)	Δ Fluid balance (Interv – Ctrl)	Mortality	Renal outcomes (AKI / RRT)	Other key outcomes	Ultrasound / Fluid responsiveness testing	Key message
Wichmann et al. [35]	~ **–3 L** by **day 5**; significant separation (p < 0.001)	40 % vs 29 % (NS)	AKI 35 % vs 24 %; RRT 4.8 % vs 0 %	No difference in DAOH-90 (50 vs 45 days, p = 0.94)	**No / No**	**Feasible** deresuscitation strategy; early-terminated (4 % of target sample); neutral balance hard to assess by charting alone
Semler et al. [31]	**–398 mL/da**y (95 % CI –1227 to +430; p = 0.33) – below –500 mL threshold	27 % vs 30 % (NS)	Stage III AKI 40 % vs 21 %; RRT 6.7 % vs 6.7 %	ICU-free days 9 vs 11 (NS); ventilator-free 13 vs 12	**No** (baseline IVC ultrasound only) / **No**	Protocol **feasibl**e; **no harm**; lower-than-expected fluid exposure **limited group separation**
Silversides et al. [34]	**–970 mL (24 h)**, –3.3 L by day 5 (p < 0.01)	21 % vs 16 % (NS)	AKI 5 % vs 6 % (NS) ; RRT ≈ 17 % baseline	ICU-free 13.8 vs 14.9 days (NS); non-serious AE ↑ (34 % vs 19 %) – mainly metabolic alkalosis	**No / No**	**Feasible** protocol; **safe** hemodynamics; reduced fluid balance; **no clinical benefit**; needs large RCT.
Cinotti et al. [32]	≈ **–5 kg** (primary & sensitivity analyses; **p<0.001** in main analyses)	ICU **14% vs 18%**, Day-60 **17% vs 23%** (NS)	**Worsening AKI 60% vs 75% (p=0.03)**; RRT **8% vs 5%**(NS)	VFD D60 **54 vs 51**(NS); MV **12 vs 14 d**(NS)	Yes / Yes (Echo/PPV for resuscitation protocols; not triggers)	Diuretic-guided deresuscitation **reduces fluid accumulation**with acceptable safety; no proven effect on hard outcomes.
Hamishehkar et al. [28]	**No separation** in fluid balance; **urine output** ↑ with furosemide (≈ +2 L/day)	**20% vs 28%**(NS, 28-day)	CRRT **no difference**; NGAL decreased in **both** groups	Early lower pNGAL/Cr with furosemide; differences fade by day 7	**No / No**	Furosemide increased diuresis but **did not change fluid balance or outcomes**; biomarker-centric RCT, not deresuscitation-triggered.
Berthelsen et al. [30]	**–5.8 L** at day 5 (p = 0.003); strong separation	**29 % vs 46 %**(NS, 90 d)	CRRT use similar; AF fewer with intervention	Neutral balance 86 % vs 30 % (p = 0.06); no hemodynamic harm signal	**No / No**	**Feasible** forced removal protocol with **clear fluid-balance reduction**; trial **underpowered** for clinical outcomes.
Wiedemann et al. [25]	≈ **–7.1 L** over **7 days** (p<0.001)	**25.5% vs 28.4%**(NS)	Dialysis **10% vs 14%**(p=0.06)	**VFDs 14.6 vs 12.1; ICU-free 13.4 vs 11.2** (both p<0.001)	**No / No** (CVP/PAOP-guided)	Conservative strategy **improves VFDs/ICU-free days** with large fluid-balance separation, **no mortality difference**.
Mekontso Dessap et al. [27]	≈ **–2.1 L** more negative during **weaning** (p < 0.0001)	ICU **11.8% vs 12.5%**, D60 **13.8% vs 18.4%**(NS)	Renal failure rates **similar**; no difference in shocks/electrolytes	**Faster extubation** (42.4 vs 58.6 h, **p=0.034**); ↑ **VFDs** (D14/D28/D60); ↓ **VAP** and ↓ **need for fluid loading**	**No / No**	BNP-guided protocol **safely reduces fluid balance** and **shortens weaning**, especially with **LVD**; no LOS/mortality effect.

Study (First author)	Δ Fluid balance (Interv – Ctrl)	Mortality	Renal outcomes (AKI / RRT)	Other key outcomes	Ultrasound / Fluid responsiveness testing	Key message
Chen & Kollef [36]	**No significant separation**: Day 3 median +1.95 L vs +3.12 L (P = .20); Day 5 +2.64 L vs +3.62 L (P = .40)	**56.1% vs 48.8%**(NS)	**RRT 41.5% vs 39.0%**(NS)	Ventilator days **8.0 vs 5.0** (NS); vasopressor days **4 vs 4**(NS)	**Yes / Yes** (IVC index, SVI; PPV)	**Feasible** TFM with daily responsiveness testing, but **advisory design** yielded **no significant fluid-balance or outcome differences**; mandates likely needed in future RCTs.
Cantarovich et al. [26]	**Not addressed**; diuresis endpoints favored furosemide	**No difference**	**No difference** in RRT sessions/time; Cr<2.26 mg/dL **NS**	Faster to ≥2 L/day (**5.7 vs 7.8 d, p=0.004**); more pts reached ≥2 L/day (**57% vs 33%, p<0.001**); polyuria ↑	**No / No**	High-dose furosemide **increases diuresis** but **does not improve survival or renal recovery** in established ARF needing RRT.
Vaara et al. [33]	**−1.15 L at 72 h** ($p = 0.033$); **−0.82 L at 24 h** ($p = 0.004$); **−1.53 L by day 7/ICU discharge** ($p = 0.046$)	90-day mortality **19.6% vs 26.5%** (NS, exploratory)	**RRT ≤14 d: 13% vs 30%** (RR 0.42, $p = 0.043$)	**AEs** 22% vs 49% ($p = 0.001$); **SAEs** 12% vs 31% ($p = 0.031$); duration of AKI trend (−1 d, $p = 0.071$)	**No / No**	RFM **safely lowers fluid balance** and **reduces RRT use** vs usual care in AKI; feasibility demonstrated; larger trials warranted.
Bagshaw et al. [29]	**−1.08 L** (NS) overall; UO ↑ at 6 h & 24 h	**Hospital 8.1% vs 14.3%** (NS); **90-day 21.6% vs 30.5%** (NS)	**Worsening AKI 43% vs 37%** (NS); **RRT 27% vs 29%** (NS)	**AEs incidence higher** with furosemide (mostly electrolytes/alkalosis)	**No / No**	Low-dose furosemide **did not reduce AKI progression** or improve outcomes; **protocol deviations & supplementary diuretics** likely blunted separation.
Castro et al. [37]	**No between-group FB difference** reported; FR at endpoint 100% vs 58% (p = 0.012)	Not reported (physio trial)	Not reported	**SBT 14 h vs 36 h** (p = 0.031); **Extubation 26 h vs 57 h** (p = 0.007); MV 49 h vs 62 h (p = 0.065); **pH 7.43 vs 7.47** (p = 0.028)	**No** (echo performed but not used to guide fluid removal) / **Yes** (PLR-bioreactance)	**Targeting fluid responsiveness** (not fixed negative FB) **sped weaning and avoided alkalosis**, with **preserved perfusion and stable hemodynamics**.

AE, adverse event; AF, atrial fibrillation; AKI, acute kidney injury; ARF, acute renal failure; CI, confidence interval; Ctrl, control; Cr, creatinine; DAOH-90, days alive and out of hospital at day 90; d, days; Δ (delta), between-group difference (Interv – Ctrl); FB, fluid balance; FR, fluid responsiveness; ICU, intensive care unit; Interv, intervention; IVC, inferior vena cava; LOS, length of stay; LVD, left ventricular systolic dysfunction; MV, mechanical ventilation; NGAL, neutrophil gelatinase–associated lipocalin; pNGAL, plasma NGAL; NS, not significant; PAOP, pulmonary artery occlusion pressure; PLR, passive leg raise; PPV, pulse-pressure variation; RCT, randomized controlled trial; RFM, restrictive fluid management; RR, risk ratio; RRT, renal replacement therapy; SAE, serious adverse event; SBT, spontaneous breathing trial; SVI, stroke volume index; TFM, targeted fluid minimization; UO, urine output; VAP, ventilator-associated pneumonia; VFD(s), ventilator-free day(s)

Table 3. Comparison of Fluid Balance Separation by Any Ultrasound Involvement.

Group	Achieved Separation	Did Not Achieve Separation	Total Studies
Any Ultrasound Use	1 (25.0%)	3 (75.0%)	4
No Ultrasound Use	6 (66.7%)	3 (33.3%)	9
Total	7	6	13

Table 4. Comparison of Fluid Balance Separation by Explicit Ultrasound Guidance for De-resuscitation

Group	Achieved Separation	Did Not Achieve Separation	Total Studies
Explicit US Guidance	0 (0.0%)	1 (100.0%)	1
No Explicit US Guidance	7 (58.3%)	5 (41.7%)	12
Total	7	6	13

found between explicit ultrasound guidance and fluid balance separation (p = 1.00, Fisher's exact test).

Studies using ultrasound to guide de-resuscitation

Chen & Kollef (36) implemented the most comprehensive ultrasound approach for guiding de-resuscitation, utilizing IVC distension index, PPV monitoring, and stroke volume index measurements for daily fluid responsiveness testing. However, the authors noted that recommendations were advisory rather than mandated, which likely attenuated the intervention effect. Despite comprehensive ultrasound assessment, this study failed to achieve significant fluid balance separation (Day 3: +1.95 L vs +3.12 L, p=0.20; Day 5: +2.64 L vs +3.62 L, p=0.40).

Studies performing ultrasound assessment but not for de-resuscitation guidance

Cinotti et al. (32) used echocardiography and PPV assessment within their ICU protocols, but these parameters were specifically used to guide fluid resuscitation during the initial stabilization phase, not to guide de-resuscitation decisions. During the de-resuscitation phase, Cinotti employed a protocolized diuretic strategy, although this was without ultrasound guidance. Therefore, Cinotti is appropriately classified as a non-ultrasound-guided de-resuscitation trial.

Semler et al. (31) performed baseline IVC ultrasound measurement at enrolment for initial volume status characterisation but did not incorporate ultrasound guidance into the conservative fluid management protocol. The IVC measurements were recorded but not used to trigger or guide fluid removal decisions.

Castro et al. (37) performed transthoracic echocardiography at baseline and before spontaneous breathing trials. However, fluid removal decisions were guided by thoracic bioreactance-based passive leg raise testing (an impedance-based technology distinct from POCUS), not by ultrasound parameters. Echocardiography was used for descriptive hemodynamic characterization, not intervention guidance.

Pooled outcome analysis

Pooled analysis across all 13 studies revealed patterns in de-resuscitation trial outcomes. Seven studies (53.8%) achieved significant fluid balance separation between intervention and control groups, indicating that only these trials achieved their intended outcome. However, this success in achieving fluid balance did not translate into positive clinical outcomes.

Mortality outcomes: None of the studies demonstrated significant mortality benefits from de-resuscitation interventions. Several reported numerical trends toward improved mortality in intervention groups, although none achieved statistical significance. The largest study (FACTT trial, n=1000) showed no mortality difference between conservative and liberal fluid strategies (25).

Secondary outcomes: While most studies achieved their intended fluid balance targets, secondary outcomes such as ventilator-free days, ICU length of stay, and organ dysfunction scores showed inconsistent patterns. Some studies reported modest improvements in secondary endpoints; however these were generally not sustained or clinically meaningful.

Risk of bias assessment

Complete Risk of Bias 2 (RoB 2) assessments were conducted for all 13 included studies using standardized Cochrane criteria (Figure 2).

Comprehensive assessment using the Cochrane RoB 2 tool found significant methodological challenges across the included studies. No studies achieved an overall assessment of "Low Risk", highlighting the inherent difficulties in conducting high quality de-resuscitation research.

Overall risk distribution: Twelve studies (92.3%) were assessed as having "Some Concerns," while one study was classified as "High Risk." The absence of low-risk studies likely reflects the challenges of blinding fluid management interventions and the complexity of implementing standardized protocols in diverse ICU settings.

Cochrane Risk of Bias 2 (RoB 2) Assessment Summary

Study	**D1: Rand**	**D2: Deviate**	**D3: Missing**	**D4: Measure**	**D5: Select**	**Overall**
Wichmann et al. (2023)	🟢	🟡	🟢	🟢	🟢	🟡
Chen & Kollef (2015)	🟢	🔴	🟢	🟡	🟢	🔴
Silversides et al. (2021)	🟢	🟡	🟢	🟢	🟢	🟡
Wiedemann et al. (2006)	🟢	🟡	🟢	🟢	🟢	🟡
Cinotti et al. (2021)	🟢	🟡	🟢	🟢	🟢	🟡
Hamishehkar et al. (2017)	🟡	🟡	🟡	🟢	🟡	🟡
Dessap et al. (2012)	🟢	🟡	🟢	🟢	🟢	🟡
Semler et al. (2019)	🟢	🟡	🟢	🟢	🟢	🟡
Berthelsen et al. (2018)	🟢	🟡	🟢	🟢	🟢	🟡
Cantarovich et al. (2004)	🟡	🟡	🟡	🟢	🟡	🟡
Vaara et al. (2021)	🟢	🟡	🟢	🟢	🟢	🟡
Bagshaw et al. (2017)	🟢	🟡	🟢	🟢	🟢	🟡
Castro et al. (2024)	🟢	🟡	🟢	🟢	🟢	🟡

Legend:
- 🟢 Low Risk of Bias
- 🟡 Some Concerns
- 🔴 High Risk of Bias

Domains:
- **D1: Rand:** Bias arising from the randomisation process
- **D2: Deviate:** Bias due to deviations from intended interventions
- **D3: Missing:** Bias due to missing outcome data
- **D4: Measure:** Bias in measurement of the outcome
- **D5: Select:** Bias in selection of the reported result

Figure 2. RoB2 Summary.

Domain-specific findings: All 13 studies (100%) showed either "Some Concerns" or "High Risk" for the domain of "Deviations from Intended Interventions" (Domain 2).

The strongest domain was "Outcome Measurement" (Domain 4), with 12 studies (92.3%) achieving "Low Risk" assessment.

Domain 1 showed generally good performance, with 11 studies (84.6%) achieving "Low Risk" assessment, suggesting that most studies employed appropriate randomization methods and allocation concealment.

Discussion

Compared to fluid resuscitation, fluid de-resuscitation lags in terms of clinical and research guidelines (9,38,39). This systematic review of 13 randomized controlled trials (2,402 participants) identified several patterns relevant to de-resuscitation research methodology:

1. Ultrasound adoption: Only 2 of 13 studies (15.4%) explicitly used ultrasound parameters to guide de-resuscitation interventions, representing limited, albeit increasing, adoption. When including all ultrasound assessment (any form), 4 of 13 studies (30.8%) performed ultrasound evaluation.
2. Fluid balance achievement: Despite heterogeneous approaches to de-resuscitation, 7-8 of 13 studies (53.8-61.5%) successfully achieved statistically significant fluid balance separation between intervention and control groups, indicating that protocol-driven de-resuscitation is feasible and implementable.
3. Clinical outcomes disconnect: Despite achieving negative fluid balance targets in >50% of trials, no study demonstrated significant improvements in hard clinical outcomes (mortality, major morbidity). Several studies achieved secondary endpoints including improved ventilator-free days, faster extubation, or reduced organ dysfunction, however these did not translate to survival benefit.
4. Parameter heterogeneity: Substantial heterogeneity existed across studies in triggers for de-resuscitation, intervention protocols, fluid responsiveness assessment methods, and tolerance monitoring. This heterogeneity limits comparability across trials but does not appear to predict success or failure of individual interventions.

A key finding is the limited integration of ultrasound as a guiding tool for active fluid removal. While ultrasound is a powerful, non-invasive modality offering real-time insights into cardiac function, intravascular volume, and organ congestion, its proactive inclusion within de-resuscitation guidance protocols is notably lacking in the reviewed literature. This might be due to several factors, including varying levels of expertise in critical care ultrasound, the absence of clear algorithms for ultrasound-guided de-resuscitation, and a historical reliance on static, less dynamic measures of fluid status.

Ultrasound-based assessment offers theoretical advantages for de-resuscitation by providing:

- Dynamic fluid responsiveness assessment: Passive leg raise testing or respiratory variation in IVC diameter can identify patients who will respond to further fluid removal, potentially preventing futile or harmful interventions in non-responsive patients.
- Direct visualization of congestion: Lung ultrasound B-line assessment, hepatic vein distension, and VExUS grading can provide organ-specific evidence of fluid overload, potentially enabling more personalized de-resuscitation targeting.
- Serial monitoring capability: Real-time ultrasound reassessment during de-resuscitation can guide adjustments to the intensity of intervention based on actual physiological response rather than fixed protocols.

However, current evidence and guideline provide limited support for these theoretical advantages:

Only two studies explicitly tested ultrasound-guided de-resuscitation in this review. Chen & Kollef

(36) employed comprehensive ultrasound assessment (IVC, PPV, stroke volume) but failed to achieve fluid balance separation, potentially due to advisory (rather than mandated) recommendations. Cinotti et al. (32) achieved fluid balance separation but used ultrasound primarily to guide resuscitation rather than de-resuscitation specifically.

Given the limited empirical evidence, recommendations for ultrasound-guided de-resuscitation protocols should be considered preliminary and hypothesis-generating rather than definitive. Prospective, well-designed RCTs specifically testing standardized ultrasound-guided de-resuscitation protocols are needed before firm recommendations can be made.

Standardization in de-resuscitation research

Our analysis reveals substantial lack of standardization (de-standardization) across multiple domains of de-resuscitation research. This heterogeneity manifests in three critical areas:

- Fluid responsiveness assessment: 84.6% of studies (11/13) did not assess fluid responsiveness at all before or during fluid removal. Only 2 studies used dynamic responsiveness testing. This represents a critical gap given established evidence supporting fluid responsiveness-guided fluid administration.
- Tolerance monitoring: While most studies employed operational tolerance protocols, these were universally study-specific and locally developed. No studies employed standardized, validated tolerance assessment scoring systems (e.g., SOFA-based organ dysfunction assessment, VExUS grading for congestion assessment). This limits reproducibility and comparability.
- Parameter definitions: There was marked heterogeneity in what constituted 'fluid overload' (ranging from 2L positive balance to >5% weight gain to >10% weight gain), triggers for intervention timing, and targets for negative balance (from neutral to −1 mL/kg/h).

These standardization gaps may contribute to poor trial performance through several mechanisms:

- Inadequate patient selection may result in inclusion of patients not suitable for fluid removal
- Poor fluid responsiveness assessment may lead to inappropriate interventions in non-responders
- Heterogeneous tolerance thresholds may cause premature intervention termination when thresholds vary
- Lack of standardized protocols limits ability to identify and implement best practices.

Addressing these gaps should be a priority for future de-resuscitation research.

Proposed conceptual framework for physiologically guided de-resuscitation

To address the current paucity of physiologically guided de-resuscitation protocols and translate the findings of this review into actionable research directions, we propose a hypothesis-generating conceptual framework (Figure 3).

A common misconception in fluid management is equating fluid responsiveness (likelihood of stroke volume increase with further fluid) with fluid tolerance (absence of harm from congestion or organ dysfunction). Responsiveness testing (e.g. passive leg raise, IVC collapsibility) identifies candidates for resuscitation, but de-resuscitation requires separate assessment of tolerance to fluid removal and downstream congestion. This distinction is critical to avoid inappropriate interventions in non-responders or premature cessation in responsive patients with good tolerance.

The framework differentiates left-sided vs right-sided congestion, as pathophysiology, assessment, and de-resuscitation implications differ:

- Left-sided congestion (pulmonary oedema, impaired gas exchange): Prioritise lung ultrasound (B-lines), left ventricular filling pressures (E/e'), IVC size/distensibility. Moderate findings support continuation; severe findings warrant acceleration.

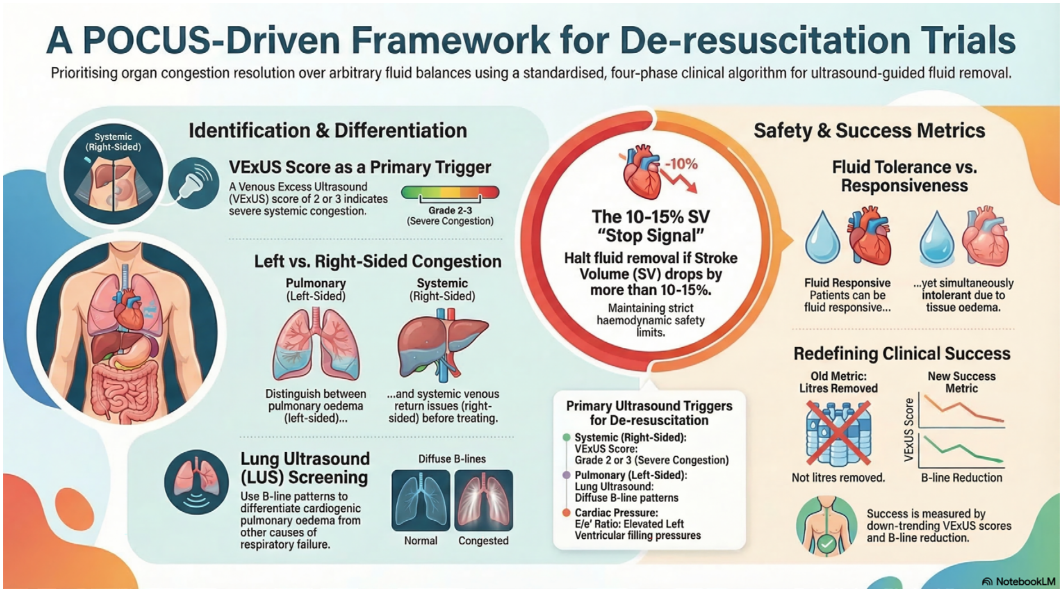

Figure 3. POCUS-driven framework for prioritising de-resuscitation over fluid balance using a standardised four-phase algorithm in ultrasound-guided trials. The diagram illustrates: (1) Identification & Differentiation of left-sided (lung ultrasound [LUS] B-lines, mitral/tricuspid inflow, differential cardiac function) vs right-sided congestion (VExUS grading, hepatic/renal vein Doppler); (2) Safety & Fluid Tolerance Metrics integrating 10-15% SV variation monitoring; (3) Fluid Responsiveness assessment (e.g. volume status triggers); and (4) Clinical Success outcomes (renal/hepatic function, lactate clearance). Primary ultrasound triggers include LUS, IVC, cardiac pressures. Hypothesis-generating conceptual tool for future de-resuscitation RCTs produced by NotebookLM using findings of systematic review findings.

- Right-sided congestion (venous/organ oedema): Use VExUS grading, hepatic/renal vein Doppler, right ventricular strain.

This algorithm is not prescriptive but serves as a scaffold for future RCTs to standardise and test ultrasound-integrated de-resuscitation, addressing the gaps identified in this review. Serial reassessment (daily or more frequent) allows dynamic adjustment.

Implications for future research

Based on the findings of this systematic review, future de-resuscitation research should prioritize several key areas. Of primary importance is the clarification of patient selection by determining the specific populations that would most benefit from active de-resuscitation, such as stratifying by underlying condition (e.g., sepsis vs. ARDS vs. general ICU), timing of intervention (early vs. late), and the presence or absence of acute kidney injury (AKI).

Then there is an urgent need to develop and validate standardized tolerance assessment protocols to establish reliable scoring systems or parameter combinations that can safely guide continued fluid removal and reduce clinician variability. Trials should be designed to explicitly test fluid responsiveness-guided de-resuscitation, comparing the impact of dynamic responsiveness assessment on outcomes against fixed-target approaches.

In addition, for ultrasound-guided de-resuscitation to be successfully pursued, standardized protocols must be established to specify the guiding parameters, assessment frequency, and concrete decision thresholds, moving beyond advisory recommendations. Following on from this, research should examine timing optimization, testing whether earlier or later intervention influences outcomes and whether patient stratification by timing improves overall results.

Finally, the focus on outcome selection must shift, with future trials prospectively determining which outcomes are most responsive to de-resuscitation interventions, such as ventilator-free days, ICU-free days, and organ dysfunction markers, rather than solely assuming mortality reduction.

Limitations

The interpretation of these findings must consider several limitations. First, methodological heterogeneity exists due to diverse patient populations, interventions (diuretics, ultrafiltration, fluid restriction), timing, and outcome measures across the 13 included studies, which limits meta-analytic pooling and the identification of best practices. Also, there are limited ultrasound-guided studies, as only two studies explicitly tested this approach, and one used advisory rather than mandated recommendations (36), limiting robust conclusions.

Publication bias is a concern since the review only included published RCTs, potentially excluding unpublished negative trials, ongoing studies, and observational research. Furthermore, none of the studies achieved a low overall risk of bias (Cochrane RoB 2); all showed concerns regarding deviations from intended interventions due to the inherent difficulty of blinding fluid management research.

The consistent finding of fluid balance achievement without clinical benefit may stem from inadequate power for hard outcomes, inappropriate outcome selection, or fundamental limitations of the de-resuscitation approach— it has not been possible to distinguish between these. Finally, temporal aspects are limited, as the longest follow-up was 28–90 days, meaning longer-term outcomes and potential delayed benefits or harms were not assessed.

Conclusions

This systematic review highlights the substantial variability in both the triggers and guiding parameters employed for active fluid removal in critically ill patients. A critical observation is the notable underutilization of ultrasound-based parameters in explicitly guiding de-resuscitation strategies. Despite this, protocol-driven fluid removal interventions effectively achieve negative fluid balances. The limited integration of ultrasound in guiding this crucial phase of fluid management represents a significant gap in current research.

Future well-designed RCTs are warranted to rigorously evaluate the impact of ultrasound-guided de-resuscitation on fluid balance, patient outcomes, and the incidence of complications associated with fluid overload. Evidence-based fluid management in the ICU is crucial to improve patient care.

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