Fluid accumulation in critically ill children: a systematic review and meta-analysis

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Summary

Background Fluids are often administered for various purposes, such as resuscitation, replacement, maintenance, nutrition, or drug infusion. However, its use is not without risks. Critically ill patients are highly susceptible to fluid accumulation (FA), which is associated with poor outcomes, including organ dysfunction, prolonged mechanical ventilation, extended hospital stays, and increased mortality. This study aimed to assess the association between FA and poor outcomes in critically ill children.

Methods In this systematic review and meta-analysis, we searched PubMed, Embase, ClinicalTrials.gov, and Cochrane Library databases from inception to May 2024. Relevant publications were searched using the following terms: child, children, infant, infants, pediatric, pediatrics, critically ill children, critical illness, critical care, intensive care, pediatric intensive care, pediatric intensive care unit, fluid balance, fluid overload, fluid accumulation, fluid therapy, edema, respiratory failure, respiratory insufficiency, pulmonary edema, mechanical ventilation, hemodynamic instability, shock, sepsis, acute renal failure, acute kidney failure, acute kidney injury, renal replacement therapy, dialysis, mortality. Paediatric studies were considered eligible if they assessed the effect of FA on the outcomes of interest. The main outcome was all-cause mortality. Pooled analyses were performed by using random-effects models. This review was registered on PROSPERO (CRD42023432879).

Findings A total of 120 studies (44,682 children) were included. Thirty-five FA definitions were identified. In general, FA was significantly associated with increased mortality (odds ratio [OR] 4.36; 95% confidence interval [CI] 3.53–5.38), acute kidney injury (OR 1.98; 95% CI 1.60–2.44), prolonged mechanical ventilation (weighted mean difference [WMD] 38.1 h, 95% CI 19.35–56.84), and longer stay in the intensive care unit (WMD 2.29 days; 95% CI 1.19–3.38). The percentage of FA was lower in survivors when compared to non-survivors (WMD −4.95 [95% CI, −6.03 to −3.87]). When considering only studies that controlled for potential confounding variables, the pooled analysis revealed 6% increased odds of mortality associated with each 1% increase in the percentage of FA (adjusted OR = 1.06 [95% CI, 1.04–1.09).

Interpretation FA is significantly associated with poorer outcomes in critically ill children. Thus, clinicians should closely monitor fluid balance, especially when new-onset or worsening organ dysfunction occurs in oedematous patients, indicating potential FA syndrome. Future research should explore interventions like restrictive fluid therapy or de-resuscitation methods. Meanwhile, preventive measures should be prioritized to mitigate FA until further evidence is available.

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Keywords: Fluid accumulation; Fluid overload; Critically ill children; Pediatric intensive care unit

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Research in context

Evidence before this study

A meta-analysis published in 2018 revealed a significant association between fluid overload and worse clinical outcomes in children, including increased mortality, prolonged mechanical ventilation, and a higher occurrence of acute kidney injury. Since then, there has been a better understanding of the risks of fluid accumulation, and the term "fluid overload" is no longer recommended. Therefore, to provide updated evidence, we conducted a systematic review and meta-analysis of studies assessing the impact of fluid accumulation on clinical outcomes in children admitted to paediatric intensive care units. We searched PubMed, Embase, ClinicalTrials.gov, and Cochrane Library databases from inception to May 2024. Relevant publications were identified using terms such as child, children, infant, pediatric, critically ill children, critical illness, intensive care, pediatric intensive care unit, fluid balance, fluid overload, edema, respiratory failure, pulmonary edema, mechanical ventilation, hemodynamic instability, shock, sepsis, acute renal failure, acute kidney injury, renal replacement therapy, dialysis, and mortality. Pediatric studies were eligible if they assessed the impact of fluid accumulation on outcomes of interest, with the primary outcome being all-cause mortality.

Added value of this study

Our search identified more than twice the number of studies (120 studies) and over five times the cases compared to the previous meta-analysis (44,682 children), thereby strengthening our findings and facilitating a comprehensive sensitivity analysis across diverse definitions of fluid accumulation and specific populations. Our results confirmed that fluid accumulation remains highly prevalent among critically ill children and is significantly associated with poor outcomes. The significant heterogeneity in fluid accumulation definitions across studies underscores the challenge in defining this condition in children.

Implications of all the available evidence

Clinicians should closely monitor fluid balance in critically ill children, suspecting fluid accumulation syndrome in oedematous patients with new-onset or worsening organ dysfunction. Our findings underscore the urgent need to standardize diagnostic criteria for fluid accumulation in paediatric population. In addition, as fluid accumulation is also a marker of illness severity, future research should focus on evaluating the effectiveness of interventions, such as restrictive fluid therapy strategies or active fluid removal (de-resuscitation).

Introduction

Fluid administration is a cornerstone intervention to improve microcirculatory perfusion of critically ill patients. However, its use is not without risks. Like any other drug, fluids have specific indications, contraindications, dose, duration, and potential adverse effects. Among the main harms of fluid therapy is fluid accumulation (FA), which can lead to interstitial oedema and progressive organ dysfunctions. When fluid accumulates, it results in compromised diffusion of oxygen and metabolites, altered tissue architecture, blocked capillary blood flow and lymphatic drainage, and disturbed cell-to-cell interactions.[1] Unfortunately, critically ill children are highly susceptible to FA, affecting approximately one-third of patients admitted to the paediatric intensive care unit (PICU).[2]

Several studies have reported an association between FA and increased morbidity and mortality in children.[3–8] Nonetheless, its causal relationship with organ dysfunction has not yet been established. FA is also a marker of severity, as more seriously ill patients often require greater amounts of fluids for resuscitation. Thus, it is still unclear how FA impacts clinical outcomes. Even the concept of FA has been changing in recent years. Traditionally, it was perceived as a binary concept, simplistically categorized based on fixed thresholds. However, current understanding acknowledges FA as a continuum, with varying individual thresholds.[9] Therefore, any degree FA may independently contribute to impairing end-organ function, leading to a condition called "FA syndrome".[1]

Understanding the clinical implications of FA is essential for clinicians to optimize fluid therapy strategies and guide the design of future studies aimed at preventing or minimizing FA. Since the last meta-analysis by Alobaidi et al., in 2018, numerous relevant publications have emerged on this topic.[2] Therefore, this systematic review and meta-analysis aimed to evaluate the impact of FA on outcomes in critically ill children and identify the definitions and methods used to measure FA in this population.

Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] The review protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews database (CRD42023432879).

Search strategy

The search was initiated in September 2023 and updated in May 2024. Searched literature databases included PubMed, Embase, ClinicalTrials.gov, and Cochrane Library. Relevant publications were searched using the following terms: child, children, infant, infants, pediatric, pediatrics, critically ill children, critical illness,

critical care, intensive care, pediatric intensive care, pediatric intensive care unit, fluid balance, fluid overload, fluid accumulation, fluid therapy, edema, respiratory failure, respiratory insufficiency, pulmonary edema, mechanical ventilation, hemodynamic instability, shock, sepsis, acute renal failure, acute kidney failure, acute kidney injury, renal replacement therapy, dialysis, mortality. Other pertinent studies were sought through a manual search of the reference lists. When necessary, additional information was requested from the corresponding authors via email. No language or date restrictions were applied. The complete search strategy is described in the Appendix (pages 2 and 3).

Study selection

Two authors (V.C.L. and R.A.V.) independently screened the titles and abstracts, then the full texts. Final eligibility was determined according to predefined standard criteria. Disagreements were resolved through discussion and consensus, and, if needed, a third author (T.H.dS.) was consulted.

Studies were included if they met the following criteria: (1) presented original data from interventional or observational studies that investigated patients admitted to a PICU; (2) provided a clear definition of FA, fluid balance, or fluid overload; and (3) reported at least one outcome of interest. The exclusion criteria were as follows: (1) investigated a population predominantly of neonates; (2) included subjects over 18 years old; (3) reported data from participants receiving extracorporeal membrane oxygenation; and (4) were conference abstracts, letters, editorials, case reports, case series, or review articles.

Outcome measures

The primary outcome was all-cause mortality, as defined in each study. Secondary outcomes included: duration of mechanical ventilation, hospital and PICU lengths of stay, organ dysfunction, haemodynamic instability, and respiratory support necessity.

Data extraction

Two authors (V.C.L. and T.H.dS.) independently extracted the following data from included studies: study design, sample size, participant characteristics, definition of FA, and outcomes of interest. Discrepancies were resolved through discussion, and if needed, a third author (I.dS.F.) was consulted. No simplifications or assumptions were made.

Statistics

Descriptive statistics were reported using proportions and means with standard deviations (SD) or median and interquartile range (IQR) unless otherwise noted. For the meta-analysis of skewed data, sample means and SD were estimated using a standard approach as described by Wan et al.[11]

Meta-analyses were performed using random effects models with inverse variance weighting in Review Manager software, version 5.3.5 (Cochrane Collaboration, 2014). Dichotomous outcomes were compared using the odds ratio (OR), while continuous outcomes were compared using weighted mean difference (WMD), both with their 95% confidence intervals (CI). A two-sided $p < 0.05$ was considered statistically significant. Meta-analysis is unfeasible when there is significant heterogeneity between exposures (i.e., FA definitions) or an insufficient number of studies for a specific outcome. In these cases, the results were presented descriptively in narrative form.

To assess clinical heterogeneity, the studies were analysed in subgroups stratified by exposure (i.e. main measure of FA) and population characteristics. Statistical heterogeneity among studies was assessed using both Cochran's Q statistic and I^2 statistic. Heterogeneity was considered to be statistically significant when $p < 0.05$ or $I^2 \geq 50\%$.[10] The potential for publication bias was assessed through the visual examination of funnel plots and by employing statistical tests, including Begg and Mazumdar's adjusted rank correlation test and Egger et al.'s regression asymmetry test.[12,13]

The risk of bias (ROB) assessment was independently conducted using the Newcastle–Ottawa Scale (NOS), by the authors responsible for data extraction. Studies with NOS star scores ranging from zero to four, five to six, and seven to nine were classified as having high, moderate, and low ROB, respectively.

Role of the funding source

This research did not receive any funding.

Results

Literature search

The search found 66,980 studies. After removing 13,229 duplicates, 53,751 studies were screened by title and abstract. Out of the 124 selected for full-text analysis, 120 met the inclusion criteria. Further details on the selection process are available in Fig. 1.

Characteristics of the included studies

This review included a total of 44,682 participants from 80 retrospective studies, 37 prospective studies, 2 case–control studies, and 1 secondary analysis of a randomised clinical trial. Participant's median age ranged between four months and 11 years. Among the selected studies, 15 (12.5%) focused on patients with sepsis, 16 (13.3%) on children undergoing cardiac surgery, 31 (25.8%) on patients with acute kidney injury (AKI) receiving renal replacement therapy, 20 (16.6%) on mixed clinical-surgical cases, and 7 (5.8%) on paediatric acute respiratory distress syndrome (PARDS). The main characteristics of the studies are shown in Supplementary Table S1 (Appendix pages 4–12).

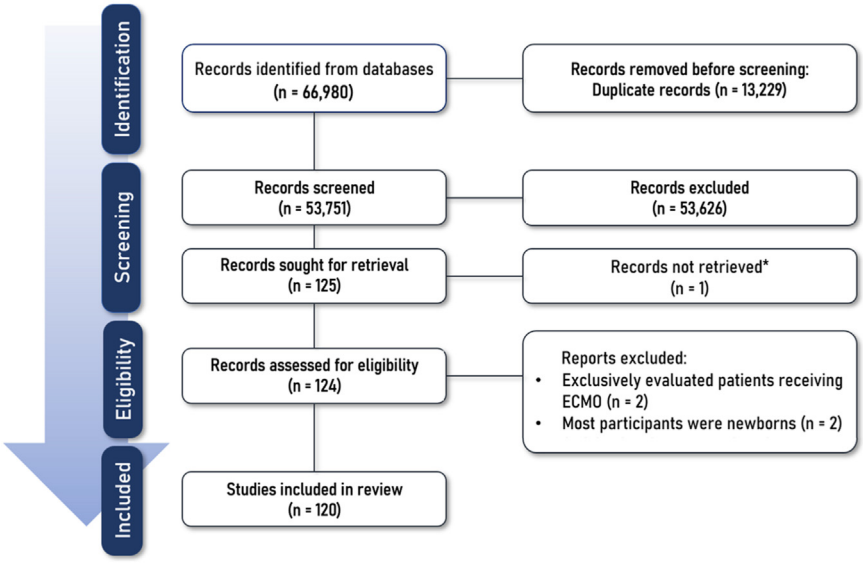

Fig. 1: **Flow chart of study selection and inclusion.**[14]

Fluid balance metrics

The most common metric used to evaluate fluid balance was the percentage of FA (%FA), which was employed in 106 studies and defined by the following formula: $\textit{Percentage of fluid accumulation}\ (\%) = \left(\frac{\textit{total fluid intake}\ (L) - \textit{total fluid output}\ (L)}{\textit{admission weight}\ (\text{kg})}\right) \times 100.$ Eighty-seven studies reported the cumulative %FA, 11 the highest % FA during a specific evaluation period (referred to as peak FA%), and eight both metrics. Additional fluid balance metrics included net fluid balance in relation to weight (ml/kg), used in 14 studies; liquid fluid balance in relation to body surface area (ml/m^2), in one study; and the percentage of weight change, in four studies and calculated as follows: $\textit{Percentage of weight change}\ (\%) = \left(\frac{(\textit{current weight} - \textit{admission weight})}{\textit{admission weight}}\right) \times 100.$

In fluid balance formulas, the denominator for "admission weight" varied across studies, with PICU admission weight used most commonly (51 studies), followed by hospital admission weight (13 studies). Further details are provided in Supplementary Table S2 (Appendix page 13).

Fluid accumulation definitions

Definitions of FA varied widely across the included studies. Authors often arbitrarily defined FA and tested its association with outcomes of interest. Threshold values ranged between 3% and 20%, and evaluation periods varied from 24 h to the entire PICU stay. The comprehensive descriptions of the FA definitions found are available in Supplementary Table S3 (Appendix pages 14–16).

Outcomes

Mortality

Fifty-seven studies assessed mortality by categorizing % FA as a dichotomous exposure, utilizing 35 different FA definitions and encompassing a total of 69,155 cases. Regardless of the varied definitions employed in studies, FA was associated with increased mortality [OR = 4.36 (95% CI, 3.53–5.38; $p < 0.001$], with significant clinical and statistical heterogeneity observed among studies ($I^2 = 86\%$) (Supplementary Figure S1 in the Appendix, pages 17–19). When considering only the 15 studies that controlled confounding variables, the meta-analysis showed an adjusted OR of 3.90 (95% CI, 2.54–5.97; $p < 0.001$; $I^2 = 56\%$; n = 6323) (Supplementary Figure S3 in the Appendix, pages 22 and 23).

A sensitivity analysis was conducted by grouping studies sharing similar FA definitions (i.e. using the same FA threshold and assessment period). FA within 24 h of PICU admission showed a significant association with increased mortality, with a pooled OR of 7.93 (95% CI, 2.81–22.39; $p < 0.001$; $I^2 = 87\%$; n = 5597) for %FA > 5% and 8.77 (95% CI, 2.42–31.77; $p < 0.001$; $I^2 = 88\%$; n = 5168) for %FA > 10% (Fig. 2). When considering 72 h following admission to the PICU, the pooled OR was 3.80 (95% CI, 2.06–7.01; $p < 0.001$; $I^2 = 88\%$; n = 16,448) for %FA > 10% and 3.60 (95% CI, 2.20–5.88; $p < 0.001$; $I^2 = 60\%$; n = 15,818) for % FA > 20% (Fig. 3). At the onset of renal replacement therapy (RRT), FA also demonstrated a notable association with mortality, presenting a pooled OR of 2.96 (95% CI, 1.85–4.73; $p < 0.001$; $I^2 = 80\%$; n = 2488) for % FA > 10% and 2.91 (95% CI, 1.82–4.63; $p < 0.001$; $I^2 = 68\%$; n = 1991) for %FA > 20% (Fig. 4).

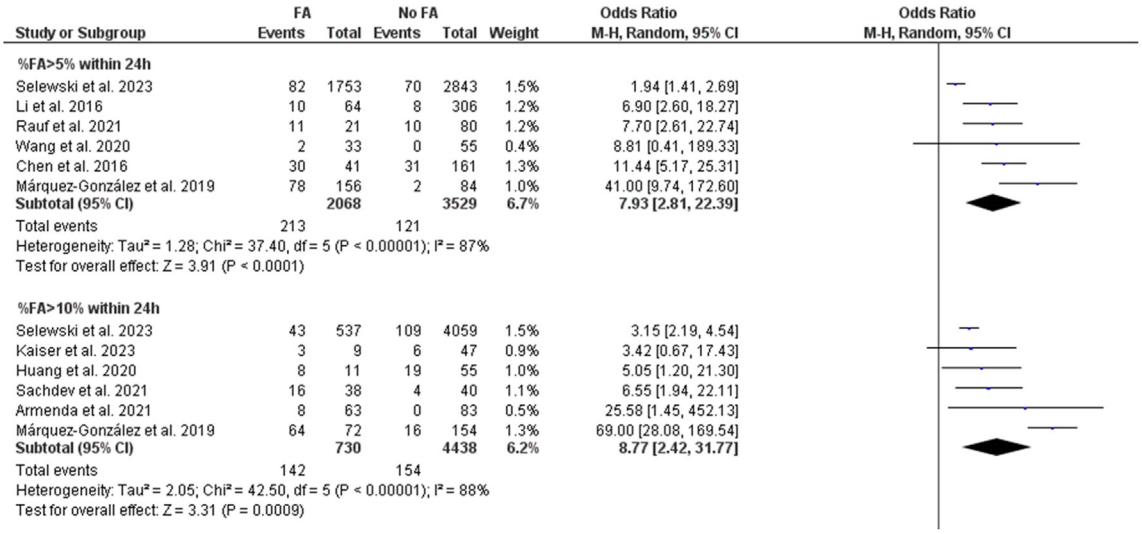

Fig. 2: Association between mortality and the percentages of fluid accumulation (%FA) higher than 5% and 10% within 24 h.

Forty-four studies reported FA as continuous data (n = 19,125 cases). Overall, a significantly reduced %FA was observed in survivors compared to non-survivors (WMD, −4.95% [95% CI, −6.03 to −3.87]; $p < 0.001$; $I^2 = 93\%$). A total of 20 distinct evaluation periods were identified, with most studies assessing the period spanning from PICU admission to the RRT initiation. Within this timeframe, survivors exhibited a WMD in % FA of −6.69% (95% CI, −8.98 to −4.40; $p < 0.001$; $I^2 = 83\%$; n = 2710) (Supplementary Figure S2 in the Appendix, pages 20 and 21).

Twenty-three identified studies provided adjusted effect estimates for confounding variables such as mortality risk scores, organ dysfunction scores, use of vasoactive drugs, among others. Details on the confounding variables can be found in the Appendix (pages 24–25). In these studies, the pooled analysis revealed a 6% increase in the odds of mortality associated with

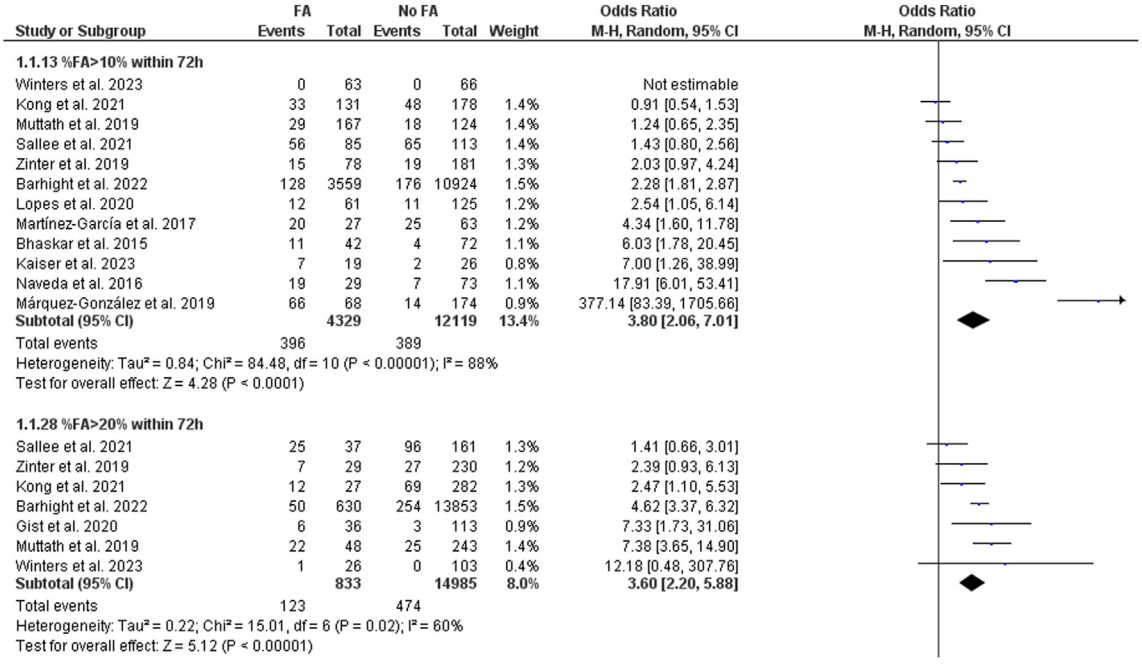

Fig. 3: Association between mortality and the percentages of fluid accumulation (%FA) higher than 10% and 20% within 72 h.

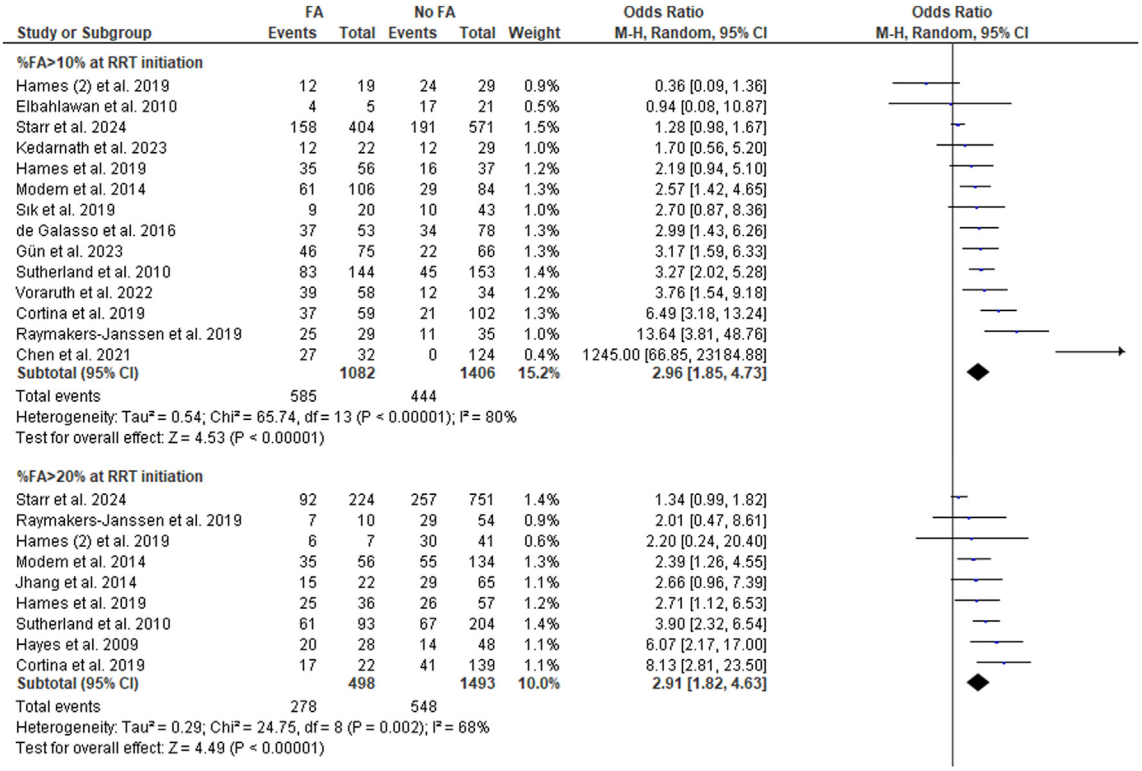

Fig. 4: Association between mortality and the percentages of fluid accumulation (%FA) higher than 10% and 20% at the initiation of renal replacement therapy (RRT).

each 1% increase in %FA (adjusted OR = 1.06 [95% CI, 1.04–1.09; $p < 0.001$; $I^2 = 79\%$; n = 11,331). Furthermore, a significant association between %FA and mortality was observed among patients receiving RRT (adjusted OR = 1.04 [95% CI, 1.02–1.06; $p < 0.001$; $I^2 = 16\%$; n = 884) and those with sepsis or septic shock (adjusted OR = 1.09 [95% CI, 1.04–1.14; $p < 0.001$; $I^2 = 69\%$; n = 723) (Supplementary Figure S4 in the Appendix, pages 24 and 25).

Additional sensitivity analyses were conducted, examining only studies published in the last 5 years (Supplementary Table S5 in the Appendix, page 38). Additionally, subgroups with more than 3 studies were analysed by removing the studies that had the greatest impact on the effect estimates (Supplementary Tables S6 and S7 in the Appendix, page 38).

Potential publication biases were observed in the analysis of studies reporting FA as dichotomous variables ($p < 0.001$ for both Egger's test and Begg's test) or as continuous variable (Egger's test, $p = 0.021$; Begg's test, $p = 0.687$). However, no publication biases were found considering only studies that used a FA threshold of 10% (Egger's test, $p = 0.052$; Begg's test, $p = 0.956$) or 20% (Egger's test, $p = 0.077$; Begg's test, $p = 0.835$) at the RRT initiation.

Funnel plots can be found in the Appendix (pages 32 and 33), as well as the forest plots of all dichotomous and continuous data analyses, categorized by %FA threshold and assessment period.

The ROB assessment was conducted for the primary outcome (mortality), with 112 studies meeting the criteria for good quality, while 8 were categorized as fair quality. The median ROB score was 8, ranging from 6 to 9. Potential ROB was observed in the items "representativeness of cohort" and "comparability of cohorts". The comprehensive ROB analysis can be found in Supplementary Table S4 (Appendix pages 34–37).

Acute kidney injury

Twenty-four studies explored the relationship between FA and AKI, reporting the exposure as either dichotomous (21 studies) or continuous data (four studies). There was a broad spectrum of FA thresholds and assessment periods across studies, as well as different criteria for diagnosing AKI. Overall, FA was associated with increased risk of AKI (OR = 1.98 [95% CI, 1.60–2.44]; $p < 0.001$; $I^2 = 76\%$; n = 47,577). The meta-analysis of four studies reporting FA as continuous data did not identify a significant distinction in the %FA between individuals who experienced AKI and those

who did not (WMD = 1.03 [95% CI, –0.39 to 2.46]; $p = 0.16$; $I^2 = 93\%$; n = 528). Forest plots depicting these analyses are provided in Supplementary Figures S5 and S6 (Appendix pages 26–28).

Duration of mechanical ventilation

Pooled data from 12 studies reporting FA as continuous exposure showed its association with a prolonged duration of mechanical ventilation (WMD = 38.1 h [95% CI, 19.35–56.84]; $p < 0.001$; $I^2 = 84\%$; n = 1819). Conversely, the meta-analysis of data from three studies, which defined prolonged mechanical ventilation as lasting over 7 days, revealed no association between this outcome and FA (OR = 2.11 [95% CI, 0.77–5.77]; $p = 0.15$; n = 736). Forest plots for these analyses are available in Supplementary Figures S7 and S8 (Appendix pages 29 and 30).

PICU length of stay

Pooled data from 15 studies showed that FA was associated with a longer PICU stay (WMD = 2.29 days [95% CI, 1.19, 3.38]; $p < 0.001$; $I^2 = 75\%$; n = 2034) (Supplementary Figure S9, Appendix page 31).

Additional outcomes

In addition to the previously described outcomes, some studies observed a significant association with worse clinical outcomes, including the need for both non-invasive and invasive ventilatory support, multiple organ dysfunction, use of inotropic and vasoactive drugs, and low cardiac output syndrome, among various others. Details regarding the methods and outcomes extracted from the included studies are provided in Supplementary Table S1 (Appendix pages 4–12).

Discussion

This systematic review and meta-analysis revealed that FA is highly prevalent among critically ill children and is significantly associated with worse clinical outcomes, including increased mortality, occurrence of AKI, prolonged mechanical ventilation, and PICU stay. The substantial amount of data bolstered the robustness of our findings and facilitated a comprehensive sensitivity analysis, enabling the evaluation of numerous subgroups based on %FA thresholds and assessment periods. Furthermore, this meta-analysis is notable for choosing the term "fluid accumulation" rather than the commonly used "fluid overload". The latter, although widely employed, is frequently inappropriate, and this distinction is not merely a matter of semantics.[9,15]

The term "fluid overload" is often used interchangeably with "hypervolaemia", which may lead to confusion, potentially resulting in misguided therapeutic decisions. It is well known that intravascular volume may not be related to the amount of total body water, especially in critically ill patients with altered capillary permeability. While hypervolaemia is typically associated with interstitial oedema, the converse is not necessarily true, as FA can occur in situations of hypervolaemia, normovolaemia, or hypovolaemia. Incorrect terminology usage can contribute to misunderstandings, ultimately impacting therapeutic interventions.

Unfortunately, measuring and quantifying FA is not a straightforward task. Daily recording of intake and output is the method most studies used to estimate fluid balance, followed by serial body weight measurement, used by a few studies. However, both methods have limitations that can substantially compromise their accuracy.[16] Daily intake and output are typically monitored manually by the use of fluid balance charts. This process is prone to registration errors and does not account for insensible fluid losses. Serial weight measurement, in turn, is performed infrequently due to technical challenges, clinical instability, and difficulties in accounting for the weight of medical equipment. Although bioelectrical impedance and point-of-care ultrasound show promise for objective assessment of fluid status, their clinical utility remains unexplored in the PICU setting. Among the approaches to quantifying FA, the calculation of %FA, as suggested by Goldstein and colleagues, was the method most commonly used in the included studies.[17] While some authors have found an acceptable correlation between the %FA and the percentage of weight change, the concurrent application of both methods is most likely to provide a more effective estimation of body fluid status than relying on a singular approach.[16,18,19]

Although accurately estimating the %FA may present challenges, establishing a specific cut-off value that will determine FA syndrome is considerably more complex. The threshold of FA can vary substantially among individuals, depending on age, comorbidity, and phase of illness.[1,20] Therefore, there is no one-size-fits-all value. Definitions of FA varied substantially among studies. A total of 35 diverse definitions were included in the meta-analysis to appraise the primary outcome. The broad spectrum of definitions plays a major role in the observed substantial clinical and statistical heterogeneity. Accordingly, the overall pooled analyses should be interpreted with caution. Still, some subgroup analyses produced results that may be valuable for further evidence-based guidelines. Interestingly, the meta-analysis of studies controlling for potential confounding factors revealed that for each 1% increase in the % FA, there was a corresponding 6% increase in the OR of mortality. It is quite clear that FA, with its various definitions, is associated with negative outcomes. Thus, it is urgent to establish criteria for FA syndrome that are applicable to a broad spectrum of paediatric critical illnesses.[15] Subsequent research can then assess its accuracy.

Early FA was significantly associated with increased mortality, as evidenced by substantial OR of 7.93 and 8.77 for cut-off values of 5% and 10% within the initial 24 h. Similar results were found for cut-off values of 10% and 20% within 72 h, although with lower OR values (3.80 and 3.60, respectively). However, these analyses were not adjusted for disease severity. Although there is a well-established cause-and-effect relationship between FA and end-organ dysfunction, FA is also a marker of illness severity. More severely ill patients are likely to develop greater FA, especially in the early stages of the disease. Therefore, it was not surprising that the OR found for FA within 24 h were higher than those found for later periods. Even so, when meta-analysis included only studies adjusting for confounding variables, FA remained significantly associated with increased mortality. For a more comprehensive understanding of the impact of FA on clinical outcomes, upcoming studies should consider potential confounding variables, including age, comorbidities, specific pathologies, and the phase and severity of the disease. Furthermore, it is important to evaluate the impact of the type of fluid and the amount of non-resuscitation fluid exceeding the estimated hydration requirements on clinical outcomes.

AKI was the second most reported outcome. Along with the varied FA definitions, several criteria for AKI diagnosis were employed. Nonetheless, despite high clinical and statistical heterogeneity, FA was significantly associated with an increased risk of AKI. Similar results were found in a recent meta-analysis involving neonates.[21] Critically ill patients often experience AKI, which is clearly associated with adverse outcomes, including increased mortality.[13] Since there is no specific treatment for AKI, identifying modifiable risk factors is essential for better outcomes. Encapsulated organs, such as the kidneys and liver, are particularly vulnerable to the adverse effects of FA.[22] These organs cannot manage additional volume without a concurrent rise in interstitial pressure, leading to compromised blood flow. Moreover, FA is often associated with increased central venous pressure and/or intra-abdominal pressure, which can cause further impairment of renal perfusion. Deciphering the complex causal relationship between FA and AKI is challenging, and there is still debate about whether the former is a cause or a consequence of the latter.[23] Nevertheless, there is no doubt that patients with AKI are at a higher risk of developing FA and experiencing its serious adverse effects. Importantly, the current meta-analysis showed that FA greater than 10% and 20% at the RRT initiation was associated with increased mortality. Therefore, while certain patients might derive benefits from lower thresholds, clinicians should contemplate commencing RRT at these specific cut-off values.

Despite the harm of FA, the effectiveness of restrictive fluid therapies or active fluid removal strategies (deresuscitation) is still debated.[22] There is a notable scarcity of paediatric evidence on this topic. The FEAST trial, published in 2011, remains the sole randomised clinical trial comparing fluid bolus versus no-bolus therapy in children.[24] Maitland et al. enrolled 3141 children with severe febrile illness and impaired perfusion in resource-limited sub-Saharan African settings without PICU access. Participants who received fluid boluses had higher 48-h mortality than the control group. The study did not report data on FA. However, fluid bolus administered for resuscitation may not be the main driver of FA in critically ill patients. A large cohort study involving 14,483 patients found that 52% of participants received non-resuscitative fluids in excess of hydration requirements, with nutrition and fluid maintenance being the main sources of fluid burden.[25] Excessive non-resuscitative fluids were associated with increased mortality and fewer ventilation-free days. In adults, the unintentional volume administered as a vehicle for medication or electrolytes, known as fluid creep, constitutes a significant portion of the mean daily total fluid volume (32.6%).[26] This insidious and often forgotten volume could represent a promising target for intervention in further studies.

Some limitations of the present meta-analysis need to be addressed. First, since FA cannot be randomised, its assessment is predominantly based on observational research, leading to inherent biases. Consequently, most of the studies included in this systematic review were observational, many of which were retrospective and not adequately controlled for confounding variables. Given the complex cause-and-effect relationship between FA and mortality, our results do not allow us to infer that decreasing FA reduces mortality. Second, as previously discussed, this meta-analysis demonstrates considerable clinical and statistical heterogeneity. Despite our efforts to classify studies based on similar FA definitions, some studies grouped in the same stratum may exhibit slight methodological differences. Third, most authors did not consider FA occurred before the inclusion of participants, which may have underestimated the %FA in their analyses. Fourth, many data were reported as medians and IQR and thus needed to be converted to means and SD, which may have caused imprecisions in effect estimates. Finally, certain individuals were enrolled in more than one study or evaluated with diverse FA definitions, leading to their multiple inclusions in the meta-analyses.

In conclusion, FA is significantly associated with adverse outcomes, including increased mortality, AKI, prolonged mechanical ventilation, and extended PICU stays. As FA is a marker of disease severity, further studies are needed to evaluate the impact of restrictive fluid therapy strategies and active fluid removal on clinical outcomes in the paediatric population. Until high-quality evidence is available, clinicians should emphasize preventive measures to mitigate FA in critically ill patients.

Contributors

VCL, RAV, and IdSF conceived and designed the study. VCL and RAV conducted the investigation and were responsible for the resources and data curation. FdLC contributed to the investigation and data curation. HMS assisted with data curation. AMCV, DCdS, MBB, and RJNN provided critical input for the writing and editing of the manuscript. THdS was involved in conceptualization, investigation, original draft writing, formal analysis, and supervision of the study.

All authors reviewed and approved the final version before submission. All authors had access to all data used in this study, approved the final version of the manuscript, and accepted the responsibility for the decision to submit the manuscript for publication.

Data sharing statement

All data are included in the manuscript and appendix.

Declaration of interests

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102714.

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