

Association between fluid overload and mortality in children with sepsis: a systematic review and meta-analysis

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ABSTRACT

Background Sepsis is one of the main causes of morbidity and mortality worldwide. Fluid resuscitation is among the most common interventions and is associated with fluid overload (FO) in some patients. The objective of this systematic review and meta-analysis was to summarise the available evidence on the association between FO and morbimortality in children with sepsis. **Methods** A systematic search was carried out in PubMed/Medline, Embase, Cochrane and Google Scholar up to December 2022 (PROSPERO 408148), including studies in children with sepsis which reported more than 10% FO 24 hours after admission to intensive care. The risk of bias was assessed using the Newcastle-Ottawa scale. Heterogeneity was assessed using I^2 , considering it absent if <25% and high if >75%. A sensitivity analysis was run to explore the impact of the methodological quality on the size of the effect. Mantel-Haenszel's model of random effects was used for the analysis. The primary outcome was to determine the risk of mortality associated with FO and the secondary outcomes were the need for mechanical ventilation (MV), multiple organ dysfunction syndrome (MODS) and length of hospital stay associated with FO. **Results** A total of 9 studies (2312 patients) were included, all of which were observational. Children with FO had a higher mortality than patients without overload (46% vs 26%; OR 5.06; 95% CI 1.77 to 14.48; $p<0.01$). We found no association between %FO and the risk of MODS (OR: 0.97; 95% CI 0.13 to 7.12; $p=0.98$). Children with FO required MV more often (83% vs 47%; OR: 4.78; 95% CI 2.51 to 9.11; $p<0.01$) and had a longer hospital stay (8 days (RIQ 6.5–13.2) vs 7 days (RIQ 6.1–11.5); $p<0.01$). **Conclusion** In children with sepsis, more than 10% FO 24 hours after intensive care admission is associated with higher mortality, the need for MV and length of hospital stay.

INTRODUCTION Fluid resuscitation is an essential part of the sepsis bundle of therapeutic measures aimed at improving outcomes.^{1 2} Reaching goals within the first hours using crystalloids optimises tissue perfusion and modifies the clinical course of the disease.^{3 4} However, fluid resuscitation may often be associated with

INTRODUCTION

fluid overload (FO) in some patients. The objective of this systematic review and meta-analysis was to summarise the available evidence on the association between FO and morbimortality in children with sepsis. A systematic search was carried out in PubMed/Medline, Embase, Cochrane and Google Scholar up to December 2022 (PROSPERO 408148), including studies in children with sepsis which reported more than 10% FO 24 hours after admission to intensive care. The risk of bias was assessed using the Newcastle-Ottawa scale. Heterogeneity was assessed using I^2 , considering it absent if <25% and high if >75%. A sensitivity analysis was run to explore the impact of the methodological quality on the size of the effect. Mantel-Haenszel's model of random effects was used for the analysis. The primary outcome was to determine the risk of mortality associated with FO and the secondary outcomes were the need for mechanical ventilation (MV), multiple organ dysfunction syndrome (MODS) and length of hospital stay associated with FO. A total of 9 studies (2312 patients) were included, all of which were observational. Children with FO had a higher mortality than patients without overload (46% vs 26%; OR 5.06; 95% CI 1.77 to 14.48; $p<0.01$). We found no association between %FO and the risk of MODS (OR: 0.97; 95% CI 0.13 to 7.12; $p=0.98$). Children with FO required MV more often (83% vs 47%; OR: 4.78; 95% CI 2.51 to 9.11; $p<0.01$) and had a longer hospital stay (8 days (RIQ 6.5–13.2) vs 7 days (RIQ 6.1–11.5); $p<0.01$). In children with sepsis, more than 10% FO 24 hours after intensive care admission is associated with higher mortality, the need for MV and length of hospital stay.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fluid overload (FO) in critically ill children has been associated with worse outcomes and higher mortality. Children with sepsis may have predisposing conditions favouring FO (excessive fluid resuscitation, increased vascular permeability, endothelial damage, kidney injury and inflammatory response, among others). FO in children with sepsis is increasingly reported in all care settings.

WHAT THIS STUDY ADDS

⇒ We found that more than 10% FO in children with sepsis at any time during their PICU (Paediatric Intensive Care Unit) stay was related to higher mortality, a need for mechanical ventilation and a longer intensive care stay.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Children with sepsis should receive rational fluid resuscitation, be monitored daily for FO, and be assessed for patient phenotypes of fluid non-responders or those who require early fluid de-resuscitation strategies.

morbidity and mortality complications.^{5–16} In fact, for every 6% increase in positive fluid balance in critically ill children, the risk of dying is considered to increase 1%.¹⁶ Excessive fluid administration is often seen in sepsis, which in terms of content,^{17 18} and volume has been associated with unsatisfactory outcomes.^{19 20} In these children, the inflammatory response leads to endothelial barrier loss, glycocalyx degradation, increased vascular permeability and increased interstitial oedema.²⁰ Excessive fluids coupled with fluid extravasation from the intravascular space may affect all organs and be associated with serious complications.^{21 22}

An association has been found between fluid overload (FO) and a higher frequency of pulmonary oedema, significantly affecting respiratory function, which increases these



children's risk of needing mechanical ventilation (MV).¹² In addition, FO can increase intra-abdominal pressure and affect kidney, liver or gastrointestinal function.^{13 14} This organ involvement may be greater in postoperative patients and be related to more complications. Likewise, FO in sepsis can increase intracranial pressure which may lead to more cerebral oedema. Acid-base balance complications as well as hyponatraemia or hypokalaemia associated with excess fluids may worsen neurological function, further increasing the risk of serious complications.¹² FO can increase the production of inflammatory cytokines and endothelial activation, contributing to greater organ dysfunction and mortality.²¹

It is important to clearly define %FO to enable prevention or rapid intervention.²³ While several definitions have existed, the most accepted one is to consider %FO as fluid balances greater than 5% in the first 24 hours after admission to intensive care, or any figure greater than 10% after paediatric intensive care unit (PICU) admission including patients with acute kidney injury, prior to renal support therapy start.^{24 25} In general, most studies have included all children in critical care, including cardiovascular, renal and postoperative patients, as well as those with infectious complications.²⁵ However, since children with sepsis have a greater use and abuse of fluid resuscitation with crystalloids, and are more susceptible to FO due to increased vascular permeability or its associated myocardial dysfunction, we believe that this population has a different risk associated with the %FO.²⁶ Therefore, the objective of this study was to analyse and gather the

best available evidence for evaluating the impact of %FO on the mortality of children with sepsis.

METHODS

Search strategy and selection criteria

A systematic search of the main medical databases was performed, with no language restriction. This systematic review was prospectively registered on PROSPERO (408148, available at: <https://www.crd.york.ac.uk/PROSPERO>). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses and MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines were used to report the study's findings.^{27 28}

Children 1 month to 18 years old with sepsis of any aetiology and severity were included. Patients with septic shock were included. Studies with any methodological design which reported the impact of %FO on the mortality of paediatric patients with sepsis and septic shock in intensive care were included. In addition, studies with any methodological design, as well as grey literature (published abstracts from major conferences, OpenMD and OpenGrey) or peer-reviewed articles were included, along with those that also reported the %FO associated with other outcomes like duration of MV, hospital stay, or multiple organ failure associated with %FO. Studies in preclinical models, studies in pregnant women, studies in newborns (including premature infants),

Table 1 Studies included in the systematic review (n=9)

Author	Year Country	Design	Patients (n)	General mortality (%)	Percentage of fluid overload considered
Chen <i>et al</i> ¹⁴	2016 China	Prospective	202	30.2	FO≥5% or 10% in first 24 hours
Diaz <i>et al</i> ¹⁵	2017 USA	Prospective	224	15.6	FO≥10% LOS in UCIP
Márquez <i>et al</i> ⁵	2019 México	Prospective	242	33	FO≥10% in first 96 hours
Naveda <i>et al</i> ⁹	2017 Venezuela	Prospective	149	25.5	FO≥10% in first 72 hours
Rusmawatingtyas <i>et al</i> ¹⁰	2021 Indonesia	Prospective	665	57.9	FO≥10% between 24 hours at 7 days
Kong <i>et al</i> ¹⁶	2021 China	Retrospective	309	26.2	FO≥10% in first 72 hours
Abulebda <i>et al</i> ⁶	2014 USA	Retrospective	317	12.6	FO≥10% in first 24 hours
Bhaskar <i>et al</i> ²⁹	2015 USA	Case-control study	114	13	FO≥10% in first 72 hours
Martinez <i>et al</i> ¹¹	2017 México	Case-control study	90	50	FO>10% in first 72 hours

Mortality at 28 days.
FO, fluid overload.

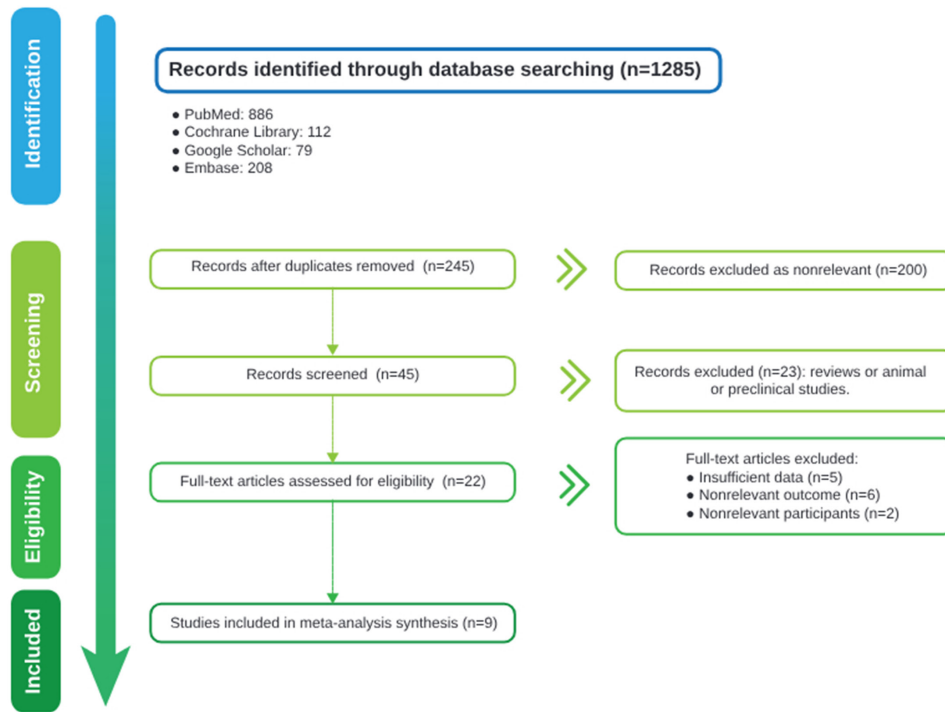


Figure 1 Article selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews and meta-analyses.

studies outside of paediatric critical care, letters to the editor, narrative reviews and studies which did not describe the clinical outcomes were excluded.

The definition of sepsis used for this study was taken from the campaign to improve sepsis survival in children and the Latin American consensus on paediatric sepsis.^{1 2} FO was any positive fluid balance greater than 10% at any time after admission to paediatric critical care.

The following formula was used to calculate overload.^{23 29}

$$\frac{[\text{Total fluid intake in litres} - \text{total fluid output in litres}]}{\text{admission weight in kilograms}} \times 100.$$

A systematic review of the literature was performed in the Cochrane library, PubMed/Medline, Embase, LILACS and Google Scholar from December 1990 to 31 December 2022. The following MESH terms were used: (“sepsis”[MeSH Terms] OR (“shock,

septic”[MeSH Terms] AND (“child”[MeSH Terms] OR “child”[All Fields] OR “children”[All Fields] AND (“fluid”[All Fields] OR “fluid s”[All Fields] OR “fluids”[All Fields]) AND (“overload”[All Fields] OR “overloaded”[All Fields] OR “overloading”[All Fields] OR “overloadings”[All Fields] AND (“mortality”[MeSH Terms] NOT (“adult”[MeSH Terms].

Study selection and data processing

The titles and abstracts were reviewed (JF-S, MFS-Z). The inclusion criteria were applied and those who met them underwent a full text review with data extraction. If there were questions about the eligibility criteria, a second investigator made the decision of whether to include the study (MPSG, NL, VSL). A standard data extraction form was designed. The data obtained are summarised in table 1.

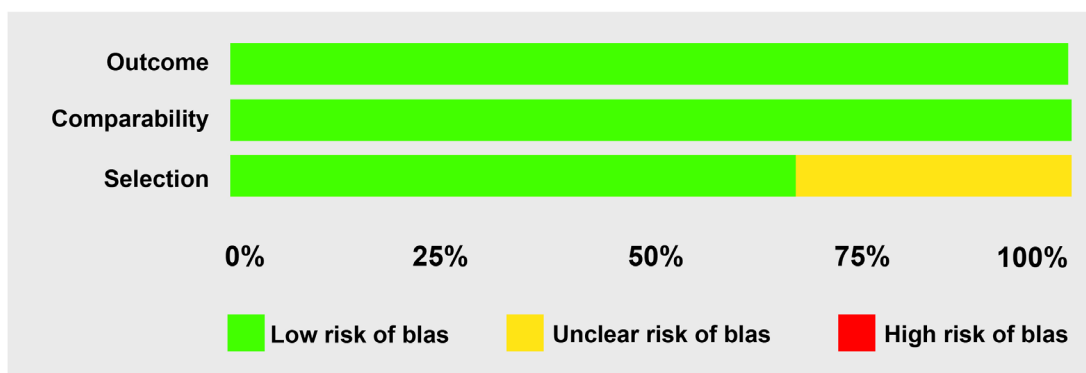


Figure 2 Evaluation of the risk of bias in the included studies on patients with sepsis.

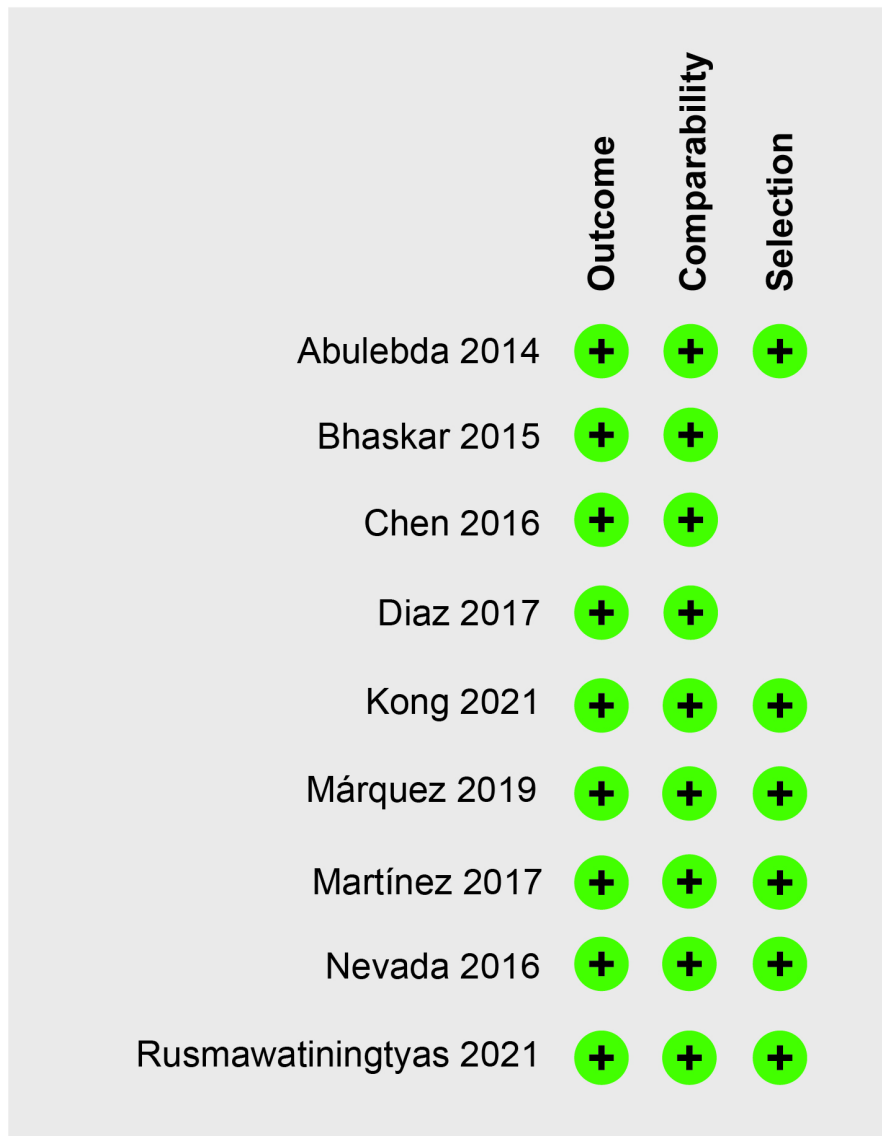


Figure 3 Risk of bias in the included studies, determined by the Newcastle-Ottawa Scale.

Methodological quality assessment

The quality of the studies was assessed through their external and internal validity. The first considered the target population, generalisability and random error. For internal validity, probable information, selection and confounding biases were determined. The risk of bias for observational studies (cohorts and cases-controls studies) was evaluated with the

Newcastle-Ottawa scale³⁰ (online supplemental material 1).

Outcomes

The primary outcome was to evaluate the impact of %FO on mortality in paediatric patients with sepsis or septic shock at any time after PICU admission. The secondary outcomes included the need for

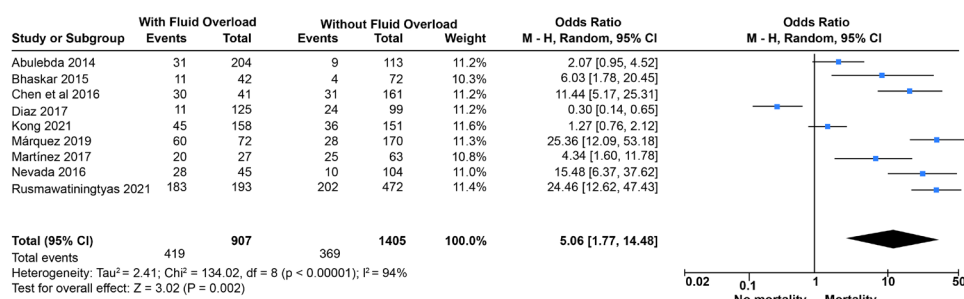


Figure 4 Forest plot of the risk of death in patients with fluid overload >10%.

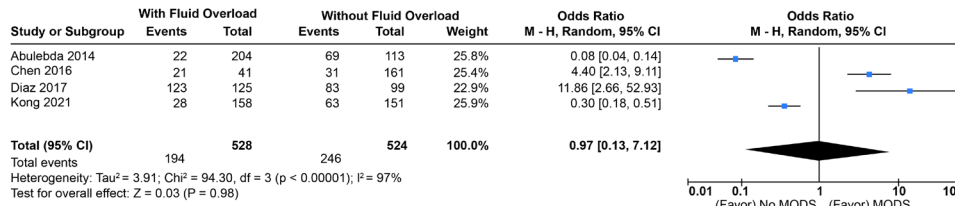


Figure 5 Forest plot of the risk of multiple organ dysfunction syndrome (MODS) in patients with fluid overload.

invasive MV, the presence or absence of multiple organ dysfunction syndrome (MODS) and PICU stay.

Data analysis

A descriptive analysis of the data obtained was performed. In order to compare the studies, when medians, ranges or IQR were reported, these were converted to means and SDs using the method proposed by Wan *et al.*³¹ For dichotomous variables, the OR was obtained with its respective 95% CI. The difference in means was calculated for continuous variables (95% CI). Heterogeneity was evaluated through visual inspection of the forest plots and with the I² statistic. An I² of 25%, 50% or 75% was assumed to indicate low, moderate and high heterogeneity, respectively. Subgroup and sensitivity analyses were conducted with the following variables to investigate which of these could potentially explain the heterogeneity: the statistical model (fixed vs random effects), methodological quality (high vs low) and each study's sample size. Potential publication bias was evaluated with a funnel plot and Egger test. A p<0.05 was considered to be statistically significant. The statistical analyses were done using Review Manager V.5.4 (ReVman V.5.4—Cochrane IMS, Cochrane Library, Oxford, United Kingdom) software.

Patient and public involvement

Patients and/or the public were not involved in this research's design, conduct, reporting or dissemination plans.

RESULTS

A total of 1285 studies were found (figure 1). After excluding duplicate and non-relevant studies, reviews and preclinical or animal studies, 9 studies were included which evaluated % FO in 2312 children with sepsis or septic shock hospitalised in intensive care.^{5 6 9-11 14-16 29} All of the studies had an observational design. No clinical trials were found which included a comparison of

the percentage of FO with the outcomes of interest. Two were designed as case-control studies.^{11 29} Seven were cohort studies. Of these, two were retrospective,^{6 16} and five were prospective.^{5 9 10 14 15} Table 1 summarises the characteristics of the included studies and the overall mortality reported.

All of the studies had a low risk of bias (figures 2 and 3). The Newcastle-Ottawa scale was used to evaluate the three groups: selection, comparability and outcomes. We found no publication bias in the analysed studies (online supplemental material 1).

Outcomes

Percentage FO and mortality

The association between the percentage of FO and mortality was described in all 2312 included patients. In all studies, the overall mortality for sepsis and septic shock was 32.6% (95% CI 26.5% to 37.6%). We found a higher risk of mortality at any time after PICU admission in patients with FO versus those with fluid balances without overload (46% vs 26%; OR 5.06; 95% CI 1.77 to 14.48; p<0.01) (figure 4).

Percentage of FO and MODS

Multiple organ failure in patients with septic shock was described in 4 studies with a total of 1052 patients.^{6 14 16} Altogether, 41.8% of the patients with septic shock had MODS. Of these, 100% of the cases were evaluated for MODS using the PELOD scale. A total of 36.7% of the patients with FO had MODS, compared with 47% of the children without FO. We found no association between %FO and the risk of MODS (OR: 0.97; 95% CI 0.13 to 7.12; p=0.98). However, the heterogeneity between studies was high (I² = 97%) (figure 5).

Percentage of FO and MV

Respiratory dysfunction and FO were described in 2 studies included for analysis, with a total of 316 patients.^{14 29} The overall need for MV support was 57%, which was more frequent in the group of patients with

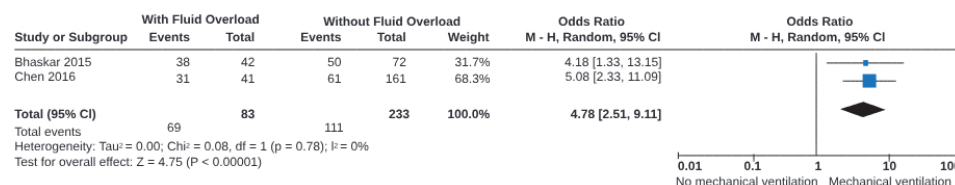


Figure 6 Forest plot of the risk of mechanical ventilation in patients with fluid overload.

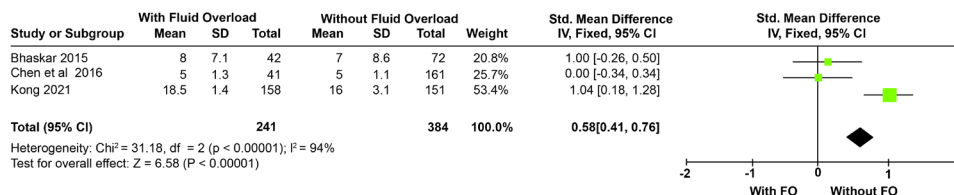


Figure 7 Forest plot of the paediatric intensive care unit stay in patients with fluid overload (FO).

FO (83% vs 47%; OR: 4.78; 95% CI 2.51 to 9.11; p<0.01) (figure 6).

Percentage of FO and PICU stay

Three studies were included for the analysis of PICU stay, with a total of 625 patients.^{14 16 29} The median PICU stay in these studies was 9.6 days (IQR 3–14). Children with FO had a longer PICU stay (8 days (RIQ 6.5–13.2) vs 7 days (RIQ 6.1–11.5); p<0.01) compared with patients with normal fluid balances (figure 7).

A sensitivity analysis was run for the primary outcome, evaluating the studies with low and high risk of bias, the sample size effect and the type of analysis employed (online supplemental material 2).

DISCUSSION

In this systematic review and meta-analysis that included 2312 children with sepsis, FO was found to be associated with greater mortality when it occurred at any time after PICU admission. We found no relationship between FO and a higher frequency of MODS, although the included studies had high heterogeneity. We found that children with sepsis and FO needed MV more often and had a longer PICU stay.

Fluid therapy is ubiquitous in the care of critically ill children.^{1 3 8} Often, excess fluid in children with sepsis arises from excessive maintenance fluid, medication, nutrition and crystalloid boluses for fluid resuscitation.¹ The first multicentre study to alert to increased mortality in children with the use of fluid resuscitation was the fluid expansion as supportive therapy study.³² The results showed that, while fluid resuscitation improved tissue perfusion in the children, it also significantly increased mortality compared with the control group. The findings of this study have led to a review of current clinical practice. It is suggested that the use of crystalloid boluses be tailored, with adequate monitoring of %FO. In addition, a fluid deresuscitation phase should be included in all children with septic shock to avoid the complications associated with excessive fluid administration.

In this regard, a recent systematic review and meta-analysis that included 44 observational studies and data from more than 7000 critically ill children concluded that FO was common in critical care, occurring in approximately 30% of the patients.¹² FO was found to be strongly associated with greater morbidity and mortality. However, studies have been published on children with sepsis which have found no relationship between the degree of FO and mortality.³³ Nevertheless, these studies

share significant limitations with regard to design and a heterogeneous metric in the definition and variables used to evaluate the outcomes related to fluid accumulation. With the recent definitions of FO, more unified criteria have been used to perform studies and evaluate the impact of excess fluids on the paediatric population.²³

Children with sepsis are more susceptible to fluid accumulation. Increased vascular permeability related to the associated inflammatory response, endothelial activation and glycocalyx degradation, among others, make them more prone to fluid accumulation outside of the intravascular space.^{17 18 20 21} Among the most important consequences of this overload and the inflammatory response are the progressive macrocirculation (cardiac output, heart rate, arterial pressure, etc) and microcirculation disturbances.²⁶ In sepsis, excessive fluid accumulation in the interstitial space makes oxygen diffusion towards the tissues more difficult, facilitating tissue hypoperfusion and the resulting tissue hypoxia and dysoxia.^{34 35} This tissue oxygenation problem could be the final common pathway which would at least partially explain the higher FO-associated mortality found in our study in children with sepsis.

In addition, we found that patients with greater FO had more frequent respiratory failure requiring MV. Alobaidi *et al*¹² found a greater association between FO and the need for prolonged MV. In fact, Acute Respiratory Distress Syndrome (ARDS) studies and the recent consensus recommendations suggest that a conservative fluid strategy and neutral or negative balances can improve pulmonary function and shorten the PICU stay.^{36 37} Valentine *et al* found that only 29% of patients with Acute Lung Injury (ALI) received restrictive fluid management in clinical treatment.³⁸ The Fluid And Catheter Treatment Trial in adults found that a conservative fluid management strategy in the first 7 days of intensive care was associated with less time on MV and a shorter length of stay in intensive care than a liberal fluid management.³⁹ These results should be studied in the future in the context of children with sepsis, since comorbidities, complications and organ dysfunction.

Interestingly, we found no association between FO and multiple organ dysfunction in the included studies. However, it seems that prolonged FO during intensive care is what is related to the onset of MODS. Recently, Chapalain *et al* found, in adults with sepsis, that MODS evaluated with the SOFA score was twice as high in the group without FO compared with the group with FO 24 hours after ICU admission.⁴⁰ However, the cumulative

fluid balance on the fifth day was three times higher in the group with FO, which was associated with an 85% rise in the SOFA score (delta). That is, a prolonged duration of FO during the ICU stay was the main factor associated with developing MODS. Active maintenance fluid control and a potential fluid deresuscitation phase are strategies increasingly used in both adults and children. These measures could limit the development of late-onset MODS associated in some studies with FO.

We consider that our study has several limitations. Only observational studies were included, describing an association between FO and mortality, which does not necessarily indicate causality. Unfortunately, we found no clinical trials in the literature which evaluated this outcome. Furthermore, some special patient subgroups (burns, trauma) were not described in the studies, which could limit the generalisation of our findings to these specific groups of children with sepsis. In this regard, a greater than 10% FO was taken as a dichotomous rather than continuous variable. This aspect should be kept in mind when interpreting the results in each application setting. Finally, the presence of FO was not consistently described throughout the PICU stay in most of the included studies. This limited our analysis because, as described in the MODS group, lack of fluid balance monitoring throughout the critical care stay can lead to an under-reporting of later-onset FO which can be associated with organ dysfunction and mortality.

CONCLUSIONS

In children with sepsis hospitalised in critical care, a greater than 10% FO 24 hours after intensive care admission has been associated with higher mortality, a greater need for MV and a longer intensive care stay. We were unable to show an association between FO and MODS due to insufficient reporting and daily fluid balance monitoring throughout the whole intensive care stay of children with sepsis.

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Contributors All authors conceptualised and designed the literature search. JF-S and MFS-Z initiated the search and the first draft. All authors contributed to subsequent drafts. JF-S, as group leader, supervised and moderated the search, initial drafts, the overall collation of the figures and tables and final manuscript. JFS(the guarantor) accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Competing interests No, there are no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the ethic and research committee at Fundación Cardioinfantil (DDI-351-2019). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. <http://creativecommons.org/licenses/by-nc/4.0/>

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