American Journal of Emergency Medicine 55 (2022) 157–166

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Outcomes of CMS-mandated fluid administration among fluid-overloaded patients with sepsis: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 19 December 2021
Received in revised form 22 February 2022
Accepted 4 March 2022

Keywords:
Sepsis
Septic shock
Congestive heart failure
End stage renal disease
Volume overload

ABSTRACT

Introduction: The outcomes of large-volume IVF administration to septic shock patients with comorbid congestive heart failure (CHF) and/or end-stage renal disease (ESRD) are uncertain and widely debated in the existing literature. Despite this uncertainty, CMS continues to recommend that 30 ml/kg of an intravenous crystalloid solution be administered to patients in septic shock starting within 3 h of presentation. We performed a systematic review and meta-analysis to assess the relationship between adherence to this guideline and outcomes among patients whose underlying comorbidities present a risk of fluid overload.

Methods: Our search was conducted on PubMed and Scopus through November 5, 2021 to identify studies that evaluated clinical outcomes among septic patients with CHF/ESRD based on volume of fluid administered. The primary outcome measured was mortality at 30 days post-hospital discharge. Other outcomes included the rates of vasopressor requirements, invasive mechanical ventilation during hospitalization, as well as length of stay in the intensive care unit and/or hospital. We used random effects meta-analysis when two or more studies reported the same outcome.

Results: We included five studies in the final meta-analysis, which comprised 5804 patients, 5260 (91%) of whom received non-aggressive fluid resuscitation, as defined by the studies' authors. Random-effects meta-analysis for all-cause mortality showed that aggressive fluid resuscitation was associated with statistically non-significant increased odds of mortality (OR 1.42, 95% CI 0.88–2.3, $P = 0.15$, $I^2 = 35\%$). There was no statistical association between volume of IVF administration and other outcomes evaluated.

Conclusion: Among septic shock patients with CHF and/or ESRD, administration of greater than or equal to 30 ml/kg IVF was associated with a non-significant increase in odds of mortality. All other outcomes measured were found to be non-significant, although there was a trend toward better outcomes among patients in the restricted-volume compared to the standard-volume IVF groups. Since this meta-analysis only included five observational studies, more studies are needed to guide an optimal volume and rate of fluid administration in this patient population.

1. Introduction

Sepsis is a significant threat to health in the United States and worldwide. It is diagnosed in 1.7 million adults per year and is responsible for 1 in 3 hospital deaths annually in the U.S. [1]. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is characterized by profound circulatory, cellular, and metabolic abnormalities and is associated with a greater risk of mortality [2]. For the past two decades, guidelines for the treatment of severe sepsis and septic shock have been formulated by the Surviving Sepsis Campaign (SSC), a joint program of the Society for Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine. SCCM guidelines have been incorporated by the US Center for Medicare and Medicaid Services (CMS) into their Inpatient Quality Reporting (IQR) Program. US Hospitals routinely report their adherence to these guidelines, which can affect not only a hospital's reimbursement for the care of Medicare patients, but also its reputation, as the results of

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https://doi.org/10.1016/j.ajem.2022.03.004
0735-6757/

Systemic Inflammatory Response Syndrome (SIRS) criteria	Septic shock criteria
Two or more of the following:	*Two or more SIRS criteria plus BOTH of the following:*
Temp <38 °C or <36°C	Vasopressor required to maintain MAP ≥65 mm Hg
Heart rate >90/min	Serum lactate >2 mmol/L in the absence of hypovolemia
Respiratory rate >20/min or Paco2 <32 mm Hg	
White blood cell count >12000/mm3 or <4000/mm3 or >10% immature bands	

Fig. 1. Definitions of sepsis and septic shock by the Third International Consensus for Sepsis and Septic Shock (Sepsis-3) [2,3].

compliance with the IQR guidelines are reported on the CMS website. CMS IQR guideline adherence is an "all-or-nothing" measure; failure to meet a single one of the 100 elements included in the measure results in the case being recorded as a guideline failure.

The administration of intravenous fluids (IVF) is an important variable in the management of septic shock. Several iterations of SSC guidelines have recommended that a weight-based IV fluid bolus of 30 ml/kg of crystalloid fluids be administered to all patients meeting their definition of septic shock (Fig. 1) that should be started within 3 h of ED presentation [2,3]. In 2015, CMS then incorporated these guidelines into their SEP-1 quality measures, making no exclusions for patients with potential volume-overload comorbidities such as congestive heart failure (CHF) or end-stage renal disease (ESRD). Subsequent CMS guidelines excluded patients with implantable LV assist devices from the measure and clarified that the patient's Ideal Body Weight could be used to calculate the fluid bolus volume for patients with a BMI greater than 30. CMS also clarified that the fluid bolus had to be started (not completed) within 3 h of diagnosis and that the minimum fluid administration rate was 126 ml/h. The measure has been called into question given that it is supported by little physiologic and experimental evidence [4-6]. In 2021, the Surviving Sepsis SCCM guidelines downgraded this measure from a strong to weak recommendation because the practice is supported by low quality evidence [7], but it remains as part of the "all-or-nothing" CMS SEP-1 measures [8].

Patients who are chronically fluid-overloaded and become septic present a challenge to providers. Clinicians are often reluctant to order a 30 ml/kg bolus if they judge the patient to be volume overloaded. This leads to guideline nonadherence [9] due to the concern that administering an excessive amount of fluid may precipitate pulmonary edema as infused fluids are diverted to interstitial space due to leaky capillaries and vasodilatory shock from infection [10].

Studies that have considered the correlation between large-volume fluid therapy and outcomes including mortality, number of ICU admissions, and intubation rates among these patients have found conflicting results. Several studies report that a higher cumulative fluid balance is associated with worse outcomes [11-16], while others have found that higher volumes of fluid have either a neutral or beneficial impact on such outcomes [17,18]. The goal of this systematic review and meta-analysis is to evaluate the quantity and quality of existing evidence as it pertains to the impact of fluid administration on clinical outcomes in septic patients with CHF and/or ESRD in order to better understand the safety and efficacy of the recommended 30 ml/kg fluid bolus administration in this patient population.

2. Methods

2.1. Search strategy and selection criteria

Our study followed the guidelines of the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [19]. We conducted a search of PubMed and Scopus databases from their beginnings through November 5, 2021. Studies were identified on PubMed using combinations of the following Medical Subject Heading (MeSH) search terms: *Sepsis; Fluid Therapy; Heart Failure; Heart Failure, Systolic; Heart Failure, Diastolic; Renal Insufficiency; Kidney Failure, Chronic; Emergency Medicine; Emergency Treatment; Evidence-Based Emergency Medicine; Critical* Care*; Critical Care Outcomes; Intensive Care Units; Intubation; Respiration, Artificial*. Studies were identified on SCOPUS by combinations of the search terms *sepsis, fluid therapy, fluid overload, volume overload, heart failure, renal insufficiency, renal failure, kidney failure, end stage renal disease,* and *chronic kidney disease*. We included all studies that investigated the outcomes of treatment with non-aggressive fluid therapy compared to aggressive fluid therapy in patients diagnosed with septic shock and fluid overload (FO). FO criteria were met if patients had a diagnosis of CHF or ESRD, or if there was provider documentation of concern for hypervolemia prior to diagnosis of septic shock. We included observational (retrospective, prospective) studies and randomized trials. We excluded studies published in non-English language, case reports, and non-full-text publications such as conference abstracts. We also excluded studies that involved patients <18 years of age, pregnant patients, and pre- or post-operative patients. We searched included studies' references for further eligible studies, but we did not contact authors for more data.

2.2. Outcome measures

We selected our primary outcome as patients' all-cause mortality up to 30 days post-hospital discharge. Other outcomes included the rates of vasopressor requirements, invasive mechanical ventilation during hospitalization, as well as length-of-stay in the intensive care unit (ICULOS) or hospital (HLOS). The need for use of vasopressors was reported by the authors, however, we defined "vasopressor use" as administration of norepinephrine (noradrenaline), epinephrine (adrenaline), phenylephrine, vasopressin, dopamine, terlipressin, and/or ephedrine.

2.3. Quality assessment and heterogeneity

We used the Newcastle – Ottawa Scale (NOS) to assess observational studies' quality [20]. The quality of each included study was independently assessed by two investigators. Any disagreement was adjudicated as a group, and we reported the results from the consensus reached. We assessed heterogeneity with Q-statistic and I^2 statistic. The Q-statistic tests for the null hypothesis that our pooled studies' effect size would be similar to the true effect size. If the *P*-value for the Q-statistic >0.05, we accept the null hypothesis that our study's results would be similar to the true effect size. The I^2 statistic reflects the variance between studies' effect sizes that were not due to chance. For example, an I^2 value of 10% would suggest that 10% of the variance between our study's effect size and the true effect size was from true heterogeneity between studies and not by chance.

2.4. Data extraction

Our investigators used a standardized Excel spreadsheet (Microsoft Corp, Redmond, WA, USA) to extract data from our included studies. Data being extracted included studies' demographic information (first author's name, year of publication, study design, study sample size) and patient characteristics (age, gender, comorbidities). Similarly, for assessment of studies' quality, two investigators independently extracted the necessary data. The group met and adjudicated any difference, and we reported the finalized results from the group's consensus.

2.5. Statistical analysis

We used descriptive analyses with mean (Standard Deviation [SD]) and percentages to present the extracted data when appropriate. When authors only reported median and interquartile, we converted those values to means (SD) as previously reported [21].

To assess outcomes, we used random-effects meta-analysis when 2 or more studies reported the same outcome. We reported dichotomous outcomes (mortality, need for intubation or vasopressors between treatment groups) as odds ratios (ORs) and 95% confidence intervals (95% CI). To compare continuous outcomes (ICULOS and HLOS), due to the heterogeneity in authors' methods of reporting the outcomes (median vs. mean), we expressed the effect size as the standardized difference of means (SDM) and 95% CI. An absolute SDM value ≥0.8 would be considered a large magnitude for effect size between treatment groups [22]. An SDM value of 0.5 was considered a medium magnitude, while an SDM value ≤0.2 was considered a small magnitude for differences between groups.

Moderator analyses were also performed to investigate potential sources of heterogeneity and to compare the primary outcome of all-cause mortality between subgroups. Studies' demographic information was divided into categorical variables of subgroups (goal of fluid resuscitation, type of FO condition) for analysis.

We assessed our meta-analysis' publication bias using both the Begg's and Egger's tests. If the *P*-value for either the Begg's or Egger's test is <0.05, this suggests low likelihood of publication bias. We also planned to assess further publication bias using the Orwin's Fail-safe N test, which suggests the necessary number of missing studies or future studies that would change our meta-analysis' overall effect size. The higher the number of the Orwin's Fail-safe N test, the less likelihood the publication bias. We did not perform the funnel plot due to the small number of included studies. For sensitivity analysis, we used random-effects with one-study-removed meta-analysis. In the one-study-removed meta-analysis, a random-effects meta-analysis was performed without the earliest study, while including all other studies. Subsequently, a second meta-analysis was performed without the second-earliest study, and so on. The one-study-removed meta-analysis indicates whether any single study would heavily affect the overall effect size of our meta-analysis. Our analysis was performed using the software Comprehensive Meta-Analysis [23].

3. Results

3.1. Summary of included studies

We identified 304 papers from our electronic searches (Fig. 2). We reviewed 15 full-text articles and included 5 studies in our meta-analysis. All 5 studies were retrospective observational studies [24-28]. One of the observational retrospective studies was a case-control study [24] while another utilized propensity score matching [27]. One study [28] that accounted for the majority of patients included in the meta-analysis, did not report patient age or gender. Therefore, we were not able to report data on the age or gender for our pooled population (Table 1A).

Two retrospective studies [26,27] were given a total score of 8/9 on the NOS scale, while three studies [24,25,28] achieved a total NOS score of 9/9 (Table 1A). As a result, all 5 included studies were graded as "high quality."

The meta-analysis included a total of 5804 patients. There were 5260 (91%) patients who received non-aggressive fluid resuscitation, as defined as by the studies' authors, for which the goal of fluid resuscitation was less than 30 ml/kg. There were 544 (9%) patients who received aggressive fluid resuscitation, that was defined as a goal resuscitation volume of at least 20 ml/kg or as defined by the studies' authors (Table 1B).

3.1.1. Primary outcome: All-cause mortality, up to 30 days after hospital discharge

All included studies reported in-hospital mortality. The unadjusted pooled mortality rate for the non-aggressive fluid group was 2% (110/5260) compared to 12% (67/544) in the aggressive fluid group. Random-effects meta-analysis for all-cause mortality showed that receiving aggressive fluid resuscitation was associated with non-statistically significant higher odds of mortality among patients with FO conditions (OR 1.42, 95% CI 0.88–2.3, $\boldsymbol{P} = 0.15$) (Fig. 3A). The *P*-value for the Q-statistic was 0.19, and the I^2 value was 35%. The sensitivity analysis using one-study-removed meta-analysis showed that the effect size ranged between 1.15 and 1.65, which was well within the 95% confidence interval of the pooled results. These results indicated that no single study influenced the overall effect size of our meta-analysis (Fig. 3B).

Additionally, the Begg rank test's *P*-value was 0.81, while the Egger test's *P*-value was 0.70, indicating that our meta-analysis for the primary outcome had low likelihood of publication bias. Furthermore, the Orwin's Fail-safe N test suggested that at least 18 missing studies or future studies, all having an odds ratio of 0.9 favoring aggressive fluid therapy (similar to the odds ratio reported by Rice et al. [26]), would be necessary to change the current odds ratio of mortality to 1.0.

From subgroup analysis comparing the goal of volume resuscitation (low volume [20–27 ml/kg] vs. high volume [at least 30 ml/kg]), studies involving a lower goal of volume resuscitation [25,26] did not report a statistically significant reduction in mortality (OR 0.88, 95% CI 0.44–1.75, $\boldsymbol{P} = 0.71$, $I^2 = 0$) (Table 2). For subgroup analysis comparing type of FO (kidney disease only vs. mixed types of FO), studies among patients with chronic kidney disease (CKD) [26] and ESRD [24,25] reported a non-significant risk of mortality favoring aggressive fluid therapy (OR 0.96, 95% CI 0.55–1.67, $\boldsymbol{P} = 0.89$, $I^2 = 0$). There was no difference of mortality odds ratio when studies with matching versus unmatched patients were compared (Table 2), although studies with matching patients [24,27] reported an I^2 value of 0.

3.1.2. Secondary outcome: Need for invasive mechanical ventilation during hospital stay

The unadjusted rate of invasive mechanical ventilation during hospitalization for the non-aggressive fluid resuscitation group was 4% (221/5209), compared with 12% (60/492) among the aggressive fluid group. Our random-effects meta-analysis demonstrated that non-aggressive fluid resuscitation was not associated with lower risk of invasive mechanical ventilation between groups (OR 0.69, 95% CI 0.42–1.15, $\boldsymbol{P} = 0.15$) (Fig. 4A). The *P*-value for the Q-statistic was 0.21, and the I^2 statistic value was 33%.

3.1.3. Secondary outcome: Need for vasopressor administration during hospital stay

Among the included studies, Khan et al. [27] reported whether there was a vasopressor requirement within 72 h of admission, while all other studies reported vasopressor requirement during entire hospital stay. The pooled rate of vasopressor requirement for the non-aggressive fluid group was 47% (135/286), compared to 55% (130/189) (31%) in the aggressive fluid group. Random-effects meta-analysis showed that

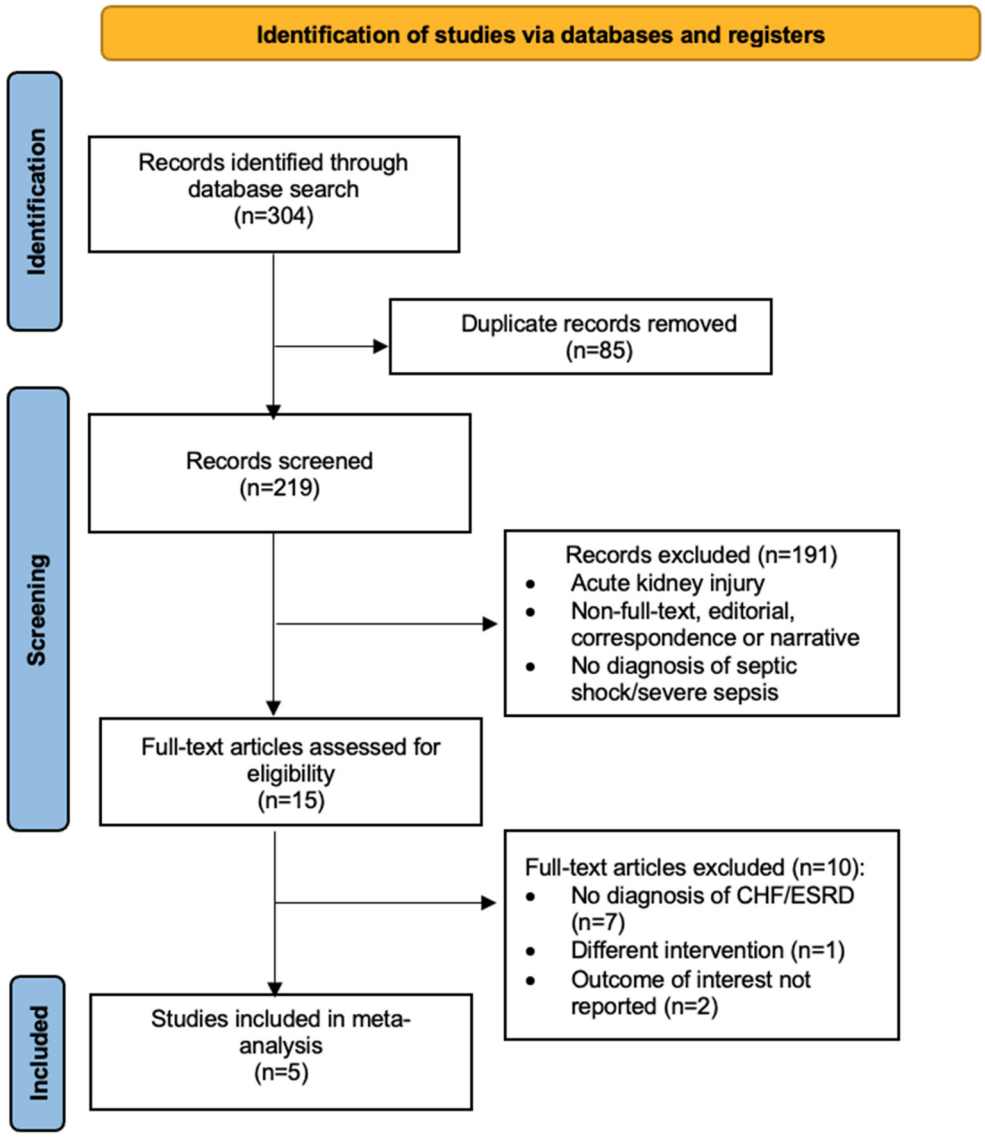

Fig. 2. PRISMA flow chart for including databases.

receiving non-aggressive fluid resuscitation was not associated with a higher likelihood of vasopressor administration (OR 0.85, 95% CI 0.57–1.26, $\boldsymbol{P} = 0.42$) (Fig. 4B). The *P*-value for the Q-statistic was 0.67, and the I^2 statistic was 0.

3.1.4. Secondary outcome: ICULOS

Three studies reported ICULOS [24-26]. The standardized difference of mean (SDM) for ICULOS was −0.002 (95% CI -0.35, 0.34, 0.38, $\boldsymbol{P} = 0.99$), indicating no difference in ICULOS between non-aggressive vs. aggressive fluid therapy groups (Fig. 4C).

3.1.5. Secondary outcome: HLOS

The SDM for HLOS was −0.11 (95% CI -0.60, 0.38, $\boldsymbol{P} = 0.67$), again indicating a very small, non-significant magnitude in difference between patients receiving restrictive fluid resuscitation compared to those receiving standard fluid volumes (Fig. 4D).

4. Discussion

This systematic review and meta-analysis of the limited body of evidence that exists suggests that there is not a significant difference in hospital mortality associated with restricted-volume fluid resuscitation compared to current CMS guidelines among patients who have a comorbidity of FO such as CHF and/or ESRD. There were also no statistically significant differences in other important clinical outcomes, including vasopressor use, need for mechanical ventilation, ICULOS and HLOS between groups.

Due to differences in patient selection and the various definitions of fluid therapy among the included studies, our meta-analysis demonstrated relatively low heterogeneity between our included studies' overall effect. A low I^2 value (35%) implied that most of the included studies in our meta-analysis agreed upon the final effect size that there was a trend toward higher odds of mortality associated with aggressive fluid therapy. This trend toward higher mortality was also observed in the subgroup of studies that defined their goal of fluid resuscitation as ≥30 ml/kg or when studies included more than one comorbidity of FO. Since these subgroups reported no heterogeneity ($I^2 = 0$), their effect size is expected to be similar to the true effect size. Similarly, studies using matched patients also reported low heterogeneity. While this result is intuitive, it highlights the need for more standardized methodology for future studies on this topic.

Table 1A
Characteristics of included studies

Author (Year)	Study design	Study type	Patients total, n	Bedside determination of volume "overload" included?	Type of "fluid overload"	Time to fluid admin (hours)	Age, years, mean		Number of pts	Age, mean (years)	Female, n	ICU admission, n	ICULOS, days, mean	HLOS, days, mean	Intubated, n	Vasopressor required, n	All-Cause, In-Hospital Mortality, n
Rice (2020)	Retrospective	Cohort	106	No	Chronic kidney disease	3	71.8	**<27 mL/kg**	51	71.2	23		2.6	5.1		18	4
								≥27 mL/kg	55	72.5	28		3.5	7.7		21	4
Rajdev (2020)	Retrospective	Case-control	104	Yes	ESRD	6	70.2	**<30 mL/kg**	80	69.2	24	52	4.3	7.2	4	41	31
								≥30 mL/kg	24	73.79	8	17	4	7	3	15	10
Khan (2020)	Retrospective	Propensity matching	208	No	CHF, ESRD, Cirrhosis	6	62.5	**<30 mL/kg**	104	62	44				36	57	19
								≥30 mL/kg	104	63	45				33	57	26
Akhter (2021)	Retrospective	Cohort	5282	No	CHF and ESRD	Not specified		**<30 mL/kg**	4974						179		35
								≥30 mL/kg	308						19		7
Rajdev (2021)	Retrospective	Cohort	104	No	ESRD	6		**<20 mL/kg**	51	69.5	13	30	6	7.2	2	19	21
								≥20 mL/kg	53	70.9	19	39	5	6.5	5	37	20

CHF, congestive heart failure; ESRD, end-stage renal disease; ICU, intensive care unit; ICULOS, intensive care unit length-of-stay; HLOS, hospital length-of-stay; ml/kg, milliliter per kilogram.

Table 1B
Study Quality Assessment Of Observational Studies Included In the Meta-Analysis Using The Newcastle-Ottawa Scale

Study (Year)	Newcastle-Ottawa Quality Assessment Scale				
	Selection (4)	Comparability (2)	Outcome (3)	Total	Grade
Khan RA (2020)	4	1	3	8	Good
Rajdev K (2020)	4	2	3	9	Good
Rice DM (2020)	4	1	3	8	Good
Akhter M (2021)	4	2	3	9	Good
Rajdev K (2021)	4	2	3	9	Good

In addition to variability in methodology, the included studies' authors proposed different definitions for aggressive fluid therapy. Rajdev et al. [25] defined aggressive fluid therapy resuscitation volume as ≥20 ml/kg, while all other studies defined aggressive fluid therapy as ≥30 ml/kg. In our sensitivity analysis, using one-study-removed meta-analysis, when the Rajdev 2021 study was not included, receiving aggressive fluid therapy defined as ≥30 ml/kg was associated with an odds ratio for mortality of 1.65 (95%CI 0.98–2.77, $P = 0.06$) (Fig. 3B). This result confirmed that, after removing the study with a lower threshold for "aggressive fluid therapy," receiving larger-volume fluid therapy was indeed associated with an increased likelihood of mortality, although this finding was still statistically non-significant. Further studies will be needed to confirm our findings and whether this difference is clinically significant.

The evidence for the development of a guideline for fluid administration to septic shock patients with FO is still inconclusive. Kuttab et al. [29] showed that achieving higher fluid volumes by 3 h was associated with decreased mortality in patients with septic shock. On the other hand, the findings by Akhter et al. [28] suggested that administration of larger fluid volumes was associated with higher odds of mortality among patients with FO. Although both studies were retrospective, Akhter et al. involved patients with conditions of potential volume overload (CHF and ESRD) exclusively, while Kuttab et al. also included patients who were deemed volume-overloaded based on physician assessment. Additionally, the primary outcome in Kuttab et al. was the barrier to achieve 30 ml/kg fluid resuscitation within 3 h of diagnosis of sepsis. The authors did not specifically report data for patients with FO. As a result, this study was not included in our meta-analysis.

The findings of our meta-analysis are similar to those of a systematic review conducted by Meyhoff et al. [30] that compared low- and high-volume IVF in initial management of sepsis. This study did not find a statistically significant difference in all-cause mortality between fluid groups and concluded that there was a very low quality of evidence across all outcomes. A systematic review on the topic published in 2020 by Messmer et al. found that fluid overload in critically ill patients was associated with a greater risk of mortality, but also noted that data on outcomes such as secondary infections, time on vasopressors, and length-of-stay were lacking [14].

Results of recent controlled trials and retrospective cohort studies on the issue are conflicting, which is further complicated by varying definitions of the measured outcomes used by authors. To highlight this issue, a study of fluid balance in septic patients by Shen et al. [31] found that a more negative fluid balance was associated with decreased mortality only in the second day of ICU admission, but not within the first 24 h. Similarly, a large observational cohort study by Sakr et al. [15] found that a higher fluid balance on day 3 of ICU admission was associated with mortality in septic patients, but this association was not seen with a higher fluid balance in the first 24 h of admission. This finding suggests that the impact of IVF volume on mortality in septic patients may be time-dependent. It should be emphasized that these studies did not focus exclusively on patients with FO at baseline; there remains a paucity of research on the subject as it applies to patients with CHF and ESRD.

While several studies have found that earlier administration of IVF to patients with severe sepsis is associated with reduced mortality [17,18], the applicability of these findings to patients with chronic FO is

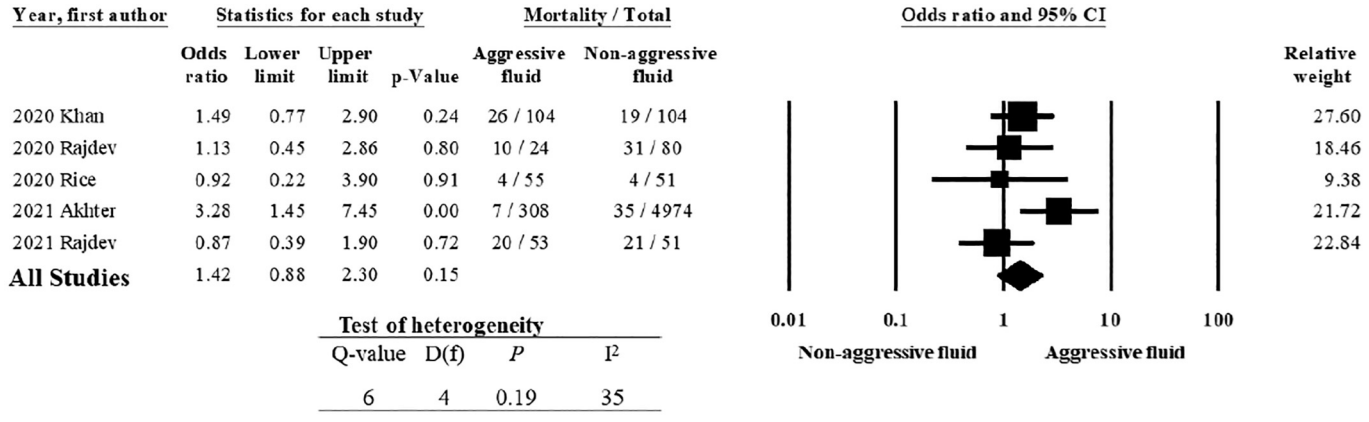

Fig. 3. Results from random-effects meta-analysis for all-cause mortality for patients who received aggressive fluid resuscitation vs. those who did not receive aggressive fluid therapy.
3A. Forest plot of random-effects meta-analysis for mortality.
3B. Sensitivity analysis of mortality, using one-study-removed random effects meta-analysis.

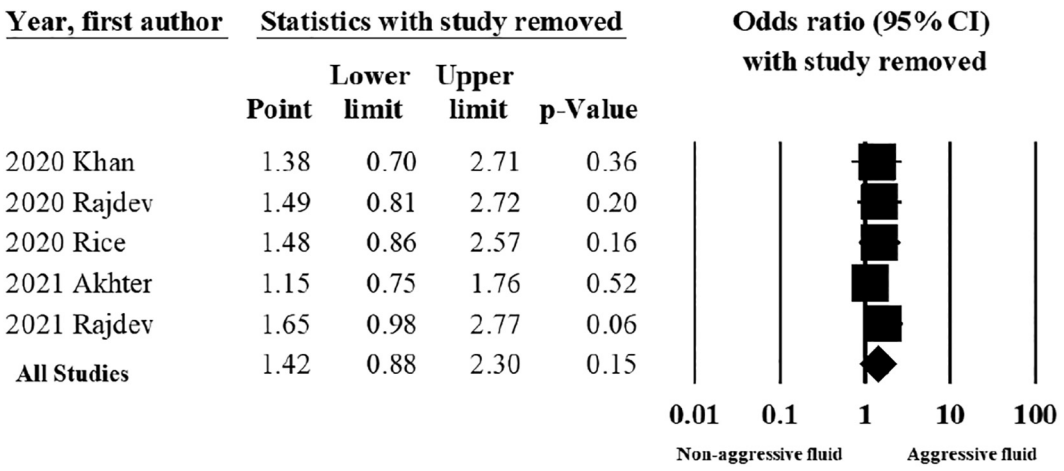

Fig. 3 (*continued*).

contested and unclear. Leisman et al. [18] found that there was a significant delay in time to IVF administration in septic patients with CHF and ESRD, and Franco Palacios et al. [32] found that a history of CHF was associated with a lower volume of IVF administration in the first 24 h of admission for sepsis. In both studies these findings were not associated with an increased risk of mortality but these findings highlight that despite CMS guidelines, clinicians are still very uncertain about the proper fluid volume and timing in this subgroup. These discrepancies between patients with sepsis with and without FO suggest that guidelines for IVF administration in patients with baseline, chronic FO should be different from those for septic patients without FO.. Physicians should be encouraged to clinically assess the fluid-responsiveness of patients with potential FO prior to aggressive fluid administration.

4.1. Limitations

Our meta-analysis has several limitations. It includes a small number of studies, most of which are observational which did not allow us to draw any definitive conclusions. Reporting of clinical outcomes was not consistent across the included studies, thus limiting the number of clinically relevant outcomes we could assess. Most studies did not report laboratory values (lactate or serum creatinine on hospital arrival or during ICU stay), baseline clinical measurements (BMI, temperature, heart rate and respiratory rate, other disease severity scores such as SOFA score or APACHE), or details related to other important interventions that typically occur in the care of patients with septic shock (such as time interval to administration of broad-spectrum antibiotics). Thus, the applicability of our findings to clinical practice is limited as it only examines IVF administration when sepsis is a multi-factorial condition. More cohort studies and randomized controlled trials looking specifically at critically ill patients with CHF and ESRD are needed in order to draw more reliable conclusions on the effects of fluid administration in these patients who experience septic shock.

None of the five studies included in this meta-analysis reported the volume of fluid administered beyond 3 h of patient presentation. This 3-h period represents the acute phase of sepsis treatment, and goal-directed treatment recommendations emphasize this initial phase. However, volume and rate of fluid administered during a patient's hospital stay is also likely to impact their clinical course and outcome. To this point, Jones et al. postulates that clinician discretion and more conservative fluid administration may be warranted after the acute phase [33].

Another limitation of this review is that outcomes based on crystalloid versus colloid fluids cannot be assessed. The total volume of all fluids administered was not not reported in most studies, which may have an effect on the findings in our analysis. This is an important consideration in the treatment of sepsis, as some studies suggest that use of colloids may reduce the volume of crystalloid fluids needed to achieve hemodynamic stability and may have an impact on organ function in septic patients [34,35]. Additionally, the definition of "aggressive fluid resuscitation volume" differed in the included studies which may create a challenge in external validity [25].

4.2. Implications for practice and policy

There are a few implications for clinical practice and policy from our study. We observed that approximately 90% of the patient population included in our study did not achieve the minimum amount of fluid resuscitation as required by the CMS. This would adversely affect the hospitals' IQR scores.

Our study also suggests that it may not be beneficial to apply a standardized resuscitation protocol to all patients with septic shock.

Table 2
Moderator analysis to compare the all-cause mortality between different subgroups of patients

Moderator Variables		Meta-analysis			Test of heterogeneity				Between group comparison
		Number of studies within subgroup	OR (95% CI)	*P*	Q-value	D(f)	*P*	I^2	*P*
Study type	Matching patients	2	1.32 (0.56–3.1)	0.52	0.3	1	0.63	0	0.85
	Unmatched patients	3	1.47 (0.79–2.48)	0.24	6	2	0.055	65	
Goal of volume resuscitation	20–27 ml/kg	2	0.88 (0.44–1.75)	0.71	0.06	1	0.94	0	0.13
	30 ml/kg	3	1.78 (0.98–3.22)	0.05	3	2	0.19	40	
Type of fluid overload	ESRD only	3	0.96 (0.55–1.67)	0.89	0.2	2	0.91	0	0.1
	Mixed	2	2.13 (0.99–4.6)	0.05	2	1	0.14	53	

ml/kg, milliliter per kilogram; D(f), degree of freedom; ESRD, end stage renal disease; OR, odds ratio; 95%CI, 95% confidence interval.

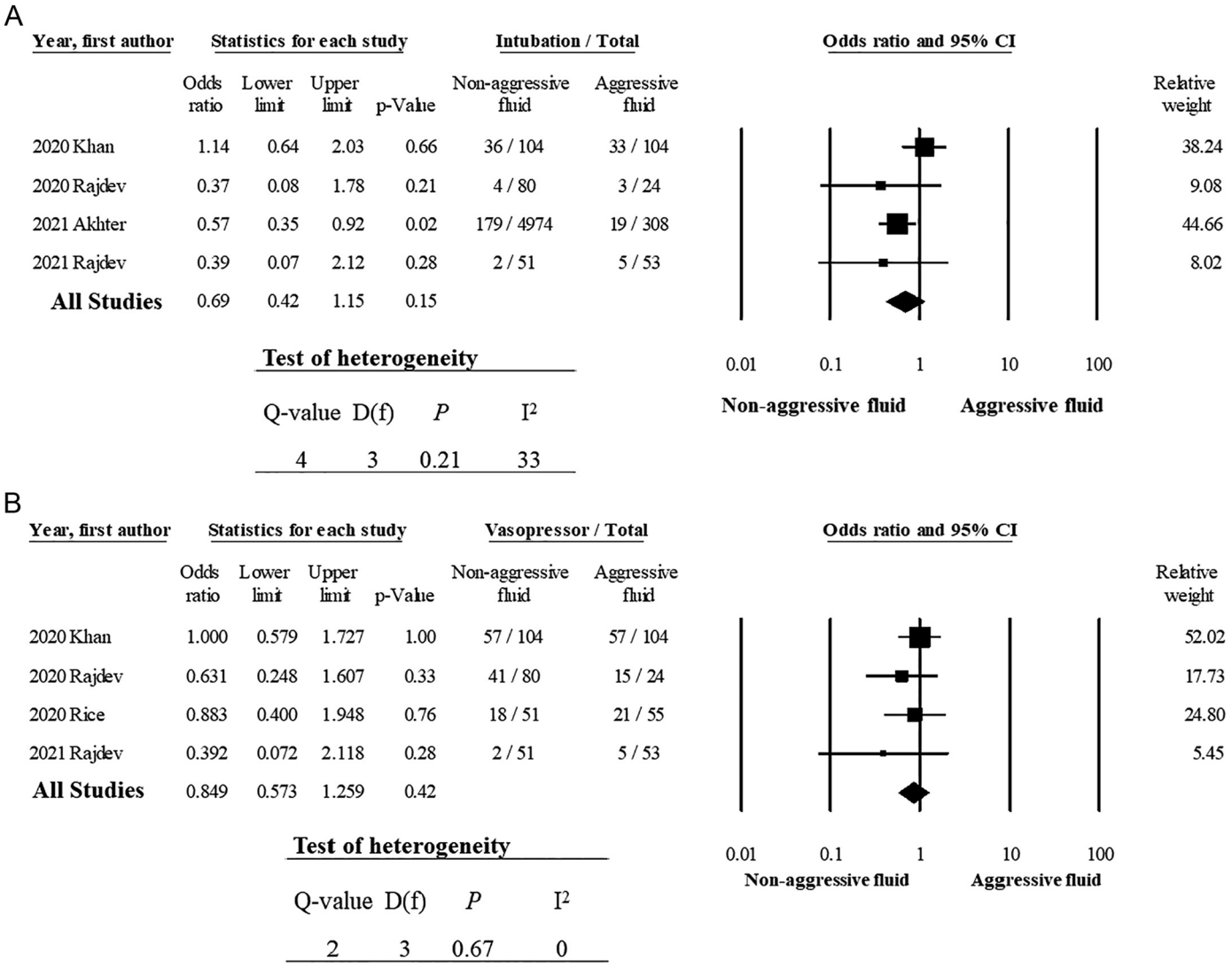

Fig. 4. Results from random-effects meta-analysis for secondary outcomes (the need for intubation, vasopressors, length of stay in the ICU and hospital) for patients who received aggressive fluid resuscitation vs. those who did not receive aggressive fluid therapy.
4A. Meta-analysis comparing the need for intubation.
4B. Meta-analysis comparing the need for vasopressor during hospital stay.
4C. Meta-analysis comparing the Intensive Care Unit length-of-stay (ICULOS). Result was expressed as Standardized Difference of Means (SDM).
4D. Meta-analysis comparing the hospital length-of-stay (HLOS). Result was expressed as Standardized Mean Difference (SMD).

Although our meta-analysis did not show a statistically significant benefit related to receiving restricted IVF volumes, there was a trend toward higher odds of mortality among patients receiving higher volumes of fluid. Previous studies have also suggested that compliance with the CMS mandate of 30 ml/kg is not associated with poor outcomes in patients with septic shock [36,37]. As a result, fluid resuscitation in critically ill patients should be approached with thoughtfulness, particularly in the subset of this population that is more susceptible to volume overload. A standard fluid infusion of 30 ml/kg for all septic patients, as mandated by CMS, may lead to increased mortality and worse clinical outcomes in these critically ill patients [28]. There remains a paucity of literature to definitively support or challenge this "one-size-fits-all" approach.

The existing body of evidence argues in favor of the use of clinical fluid status assessment rather than the implementation of a standardized approach for all septic patients. In addition to consideration of a documented history of FO, including CHF, ESRD, bedside sonographic assessment of volume status is another valuable tool that can guide the volume and rate of IVF resuscitation. Of the five studies included in this systematic review, only two [24,29] explicitly stated that bedside echocardiography was utilized to evaluate septic patients' fluid status. Interestingly, a study by Mosier et al. [38] found that evaluation of fluid status in critically ill patients with ultrasound prior to initiation of interventions correlated with increased mortality, likely due to delays caused by the additional workup. Additionally, evaluation of fluid status with point-of-care ultrasound is inherently user-dependent, and inter-user variability is unavoidable. Thus, the utility of bedside imaging techniques in septic patients remains unclear and warrants further exploration.

5. Conclusion

This systematic review and meta-analysis demonstrates that, while a 30 ml/kg fluid resuscitation does not appear to cause significant adverse events in septic shock patients with ESRD and/or CHF, further studies are needed to support this practice. As we see an increasing

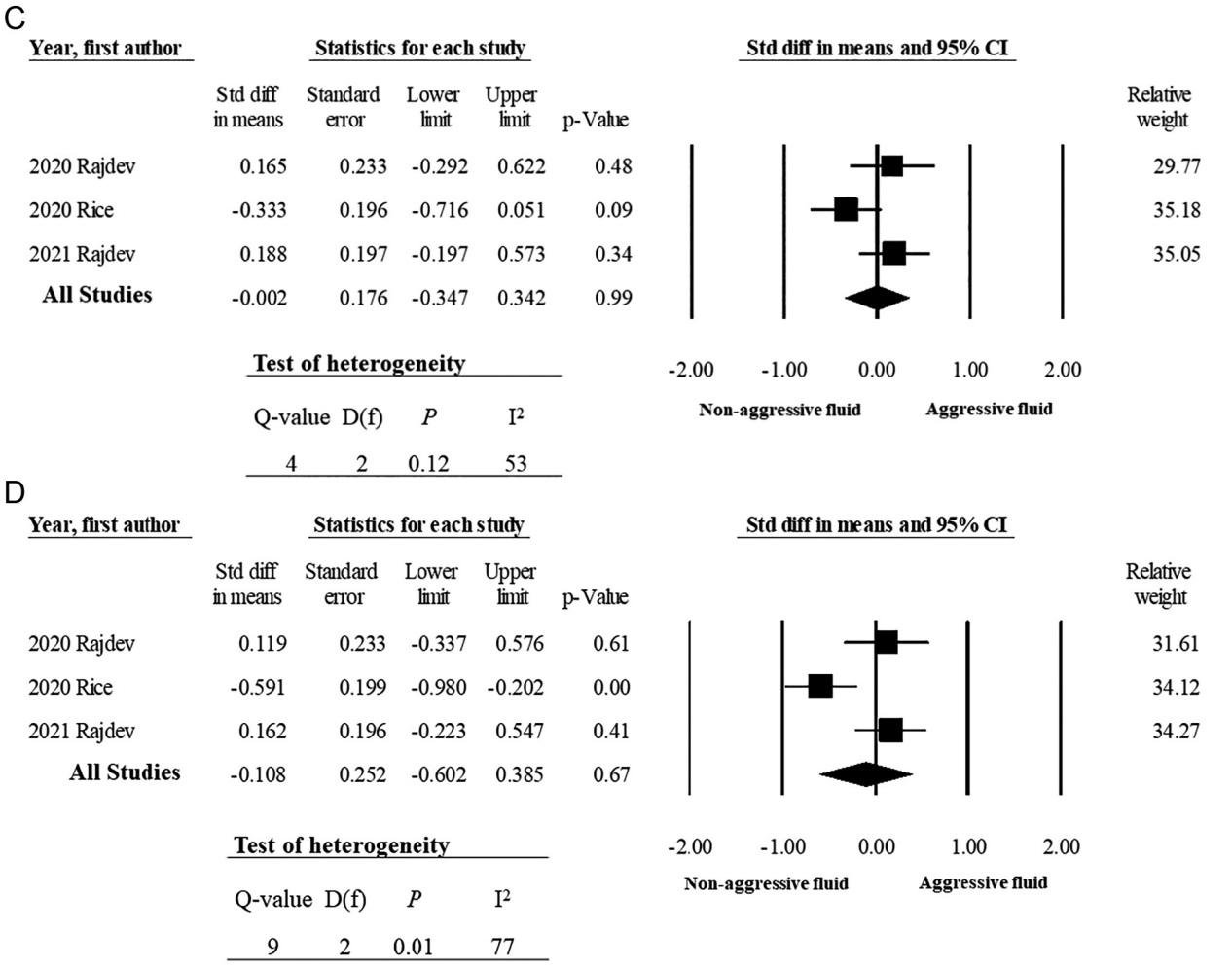

Fig. 4 (*continued*).

incidence of comorbid conditions in the general population, it is critical to understand how to appropriately resuscitate these patients presenting in septic shock.

Financial support

This is a non-funded study, with no compensation or honoraria for conducting the study.

Declaration of Competing Interest

The authors do not have a financial interest or relationship to disclose regarding this research project.

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