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Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: A systematic review and meta-analysis

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ABSTRACT

Purpose: Guidelines recommend crystalloids for fluid resuscitation in sepsis/shock and switching to albumin in cases where crystalloids are insufficient. We evaluated hemodynamic response to crystalloids/colloids in critically ill adults.

Materials and methods: The primary research question was: "Are crystalloids sufficient for volume replacement in severe indications (intensive care unit [ICU]/critical illness)?" Randomized, controlled trials (RCTs) were identified using PubMed and EMBASE, and screened against predefined inclusion/exclusion criteria. Meta-analyses were performed on extracted data.

Results: Fifty-five RCTs ($N = 27{,}036$ patients) were eligible. Central venous pressure was significantly lower with crystalloids than with albumin, hydroxyethyl starch (HES), or gelatin (all $p < .001$). Mean arterial pressure was significantly lower with crystalloids vs. albumin (mean difference [MD]: −3.5 mm Hg; $p = .03$) or gelatin (MD: −9.2 mm Hg; $p = .02$). Significantly higher volumes of crystalloids were administered vs. HES (MD: +1775 mL); volume administered was numerically higher vs. albumin (MD: +1985 mL). Compared with the albumin group, cardiac index was significantly lower in the crystalloid group (MD: −0.6 L/min/m^2, $p < .001$). All mortality and 90-day mortality were significantly lower for crystalloids compared with HES (relative risk 0.91; $p = .009$ and 0.9; $p = .005$, respectively).

Conclusions: Crystalloids were less efficient than colloids at stabilizing resuscitation endpoints; guidance on when to switch is urgently required.

1. Introduction

Intravenous (IV) fluid therapy is a common aspect of the daily management of critically ill patients and is essential to maintain cellular homeostasis and prevent organ dysfunction [1]. Fluid therapy encompasses a range of products that are categorized either as crystalloids or colloids, which can be natural or synthetic. For decades, research and debate has continued to evaluate which approach represents best practice for volume resuscitation in critically ill patients.

Current international guidelines from the Surviving Sepsis Campaign recommend crystalloids for initial resuscitation and subsequent volume replacement with albumin when patients require substantial amounts of crystalloids due to insufficiency, i.e., failure to reach predefined hemodynamic endpoints such as adequate central venous pressure (CVP) [2]. Importantly, there is considerable variability in the endpoints used to monitor the sufficiency of fluid resuscitation. A 2017 survey conducted by Miller et al. found that the three preferred indicators were blood pressure, CVP, and urine output; however, fluid resuscitation practices varied based on patient characteristics and clinical specialties of the treating physicians [3].

Fluid replacement with synthetic colloids, such as hydroxyethyl starch (HES), dextran, and gelatin, is cautioned against, particularly in severe sepsis and septic shock [2,4-6]. While caution against the use of dextrans and gelatins is predominantly a result of limited efficacy and safety evidence [5,7], use of HES has been associated with increased mortality and renal injury in several trials and meta-analyses performed in critically ill patients in the ICU [8-10].

Evidence indicates that crystalloids are associated with reduced mortality when compared with HES and gelatin [11]. Nonetheless, all fluids should be treated as drugs by physicians [12], and the risks associated with fluid overload should be noted [13,14]. Fluid therapy is moving away from the conventional 'one-size-fits-all' approach, and advice included in the 1-h Surviving Sepsis guideline bundle to administer 30 mL/kg of crystalloids within 1 h to all patients with sepsis/septic shock should not necessarily be followed in all cases [15,16]. The timing of fluid administration should be a consideration when treatment

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decisions are made, according to the phases of fluid therapy defined by the ROSE concept: resuscitation; optimization; stabilization; evacuation [1,13,14]. Recent studies have shown that administration of fluid in line with these phases can have notable positive effects on outcomes in critically ill patients and those undergoing surgery [17,18].

The recommendation from the Surviving Sepsis Guidelines to administer albumin in addition to crystalloids is based on limited evidence [2]. Albumin has demonstrated comparable safety with crystalloids, though not clear superiority in terms of resuscitation efficacy [19-21]. Some meta-analyses have shown that, compared with other resuscitation fluids, albumin significantly reduced mortality risk in patients with severe sepsis or septic shock [21-24]. While other meta-analyses have reported similar trends [11], some have failed to detect improved survival with albumin [25,26]; thus, definitive evidence is lacking. We performed a systematic review and meta-analysis of randomized, controlled trials (RCTs) to compare the efficacy of crystalloids with that of colloids for fluid resuscitation in a heterogeneous population of critically ill patients. Owing to the possibility of outcome differences between saline and balanced crystalloids, we performed sub-analyses treating these as individual groups and compared each of them with colloids, in keeping with the primary aim of the piece.

We examined whether crystalloids were adequate for volume replacement in the intensive care unit (ICU) and reviewed data on a range of resuscitation endpoints. Our analyses focused on clinical parameters such as hemodynamic outcomes, which are often underreported, in addition to patient- centered outcomes such as mortality.

2. Material and methods

Clinical studies evaluating the efficacy of crystalloids compared with colloids for fluid resuscitation in the ICU or critically ill patients were identified. The primary research question, in full, was “Are crystalloids sufficient for volume replacement in severe indications (intensive care unit [ICU]/critical illness)?”

2.1.1. Search criteria

Searches were performed on PubMed and EMBASE to retrieve articles published from inception to 5 July 2018. The search strategy, constructed based on the Populations, Interventions, Comparators, Outcomes (PICO) structure, is presented in Supplementary Table S1. Search results were managed via Excel (Microsoft Corporation, WA, USA), with duplicate references removed.

2.1.2. Study selection

A two-stage process was used for screening and selection. Initial screening was based upon checking the titles and abstracts of retrieved citations against predefined inclusion and exclusion criteria (Supplementary Table S2). Full texts of potentially relevant citations were reviewed and studies that met eligibility criteria and included at least one outcome measure of interest were retained. Any papers classified as ‘unclear’ after review of the full text were resolved by discussion.

Eligible studies included published RCTs comparing crystalloids with non-crystalloid comparators for acute volume resuscitation in critically ill adult patients. Critically ill patients included those who had a critical condition as a result of trauma, burns, surgery or sepsis, and/or who presented to an emergency department or ICU. The main types of outcomes of interest were: volume efficacy, patient-centered outcomes, e.g., mortality, and hemodynamic outcomes/stabilization. However, to ensure that all relevant records were captured, inclusion criteria did not limit outcomes. To be included in the analysis, studies had to meet all of the inclusion criteria and none of the exclusion criteria.

2.1.3. Data extraction and bias assessment

Data were extracted from full-text articles. Extracted information included: study design, patient demographics, intervention type, and study outcomes. Data were extracted for the following outcomes: study fluid volume, hemodynamic parameters, and mortality (Supplementary Table S3). Duplicate reports from the same study (sub-studies) were excluded.

Bias was assessed according to The Cochrane Collaboration's Risk of Bias tool [27]. The risk of bias was reported as low, unclear, or high risk for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Evidence of publication bias, which occurs when results of a study affect the likelihood of its publication, was also investigated. This was examined by producing Funnel plots of the size of effects for outcomes of interest, against the standard errors. The Egger's test was also performed to assess publication bias, with a significant result suggesting possible evidence of publication bias.

2.2. Statistical analysis

Analyses were performed for all crystalloids combined and for each colloid separately. Supplementary analyses were performed whereby balanced crystalloids and saline were treated as individual subgroups and compared with each colloid group. Continuous outcomes, e.g., study fluid volume and hemodynamic measures, were expressed as the mean difference (MD; calculated as values in the crystalloid group minus values in the comparator group) with 95% confidence intervals (CI). If only a median data range was reported, the mean and standard deviation were estimated according to the method provided in the Cochrane Handbook for Systematic Reviewers [27]. Mean values were assumed to be equivalent to the median value, while the standard deviation was assumed to be a quarter of the data range.

For study fluid volume and hemodynamic measures, a normal distribution was assumed in the analysis. For mortality outcomes, where no deaths were recorded for one study group, a continuity correction of 0.5 was added to each group.

The DerSimonian-Laird random-effects method was used regardless of the amount of heterogeneity between studies. Heterogeneity (i.e., variation in outcomes between studies) was assessed based upon the significance of the between-study variation using the Chi-square test and I^2 statistic. Substantial heterogeneity was assumed if the I^2 value was above 50% [27]. Statistical analyses were performed using the statistical software package Stata (version 13.1).

3. Results

3.1. Included studies

Fig. 1 shows identification and selection of relevant studies for the present meta-analysis. In total, 55 studies were included, with the earliest relevant study dating back to 1977. The most common settings were shock (17/55; 31%), trauma (11/55; 20%), and sepsis (10/55; 18%); eight studies (14.6%) were in a general critical care setting. Data for patients with critical illness due to pulmonary reasons, stroke, severe acute pancreatitis, or burn injury were each reported in two studies, and one study involved post-cardiac arrest survivors.

All 55 trials included a crystalloid arm (mostly saline, 33/55; 60%), and five trials included a second crystalloid arm (hypertonic saline). Other crystalloids included Ringer's lactate (20/55; 36%) and Ringer's acetate (9/55; 16%). Hartmann's solution (2 studies), mannitol (1 study), and Plasmalyte A (1 study) were rarely used, and three studies (5%) did not specify the type of crystalloid used. All trials included at least one colloid comparator arm. The retained studies reported a variety of outcomes (Supplementary Table S3).

3.2. Bias assessment

Of the included articles, random sequence generation was reported by 32 (58%), concealment of allocation by 33 (60%), blinding of

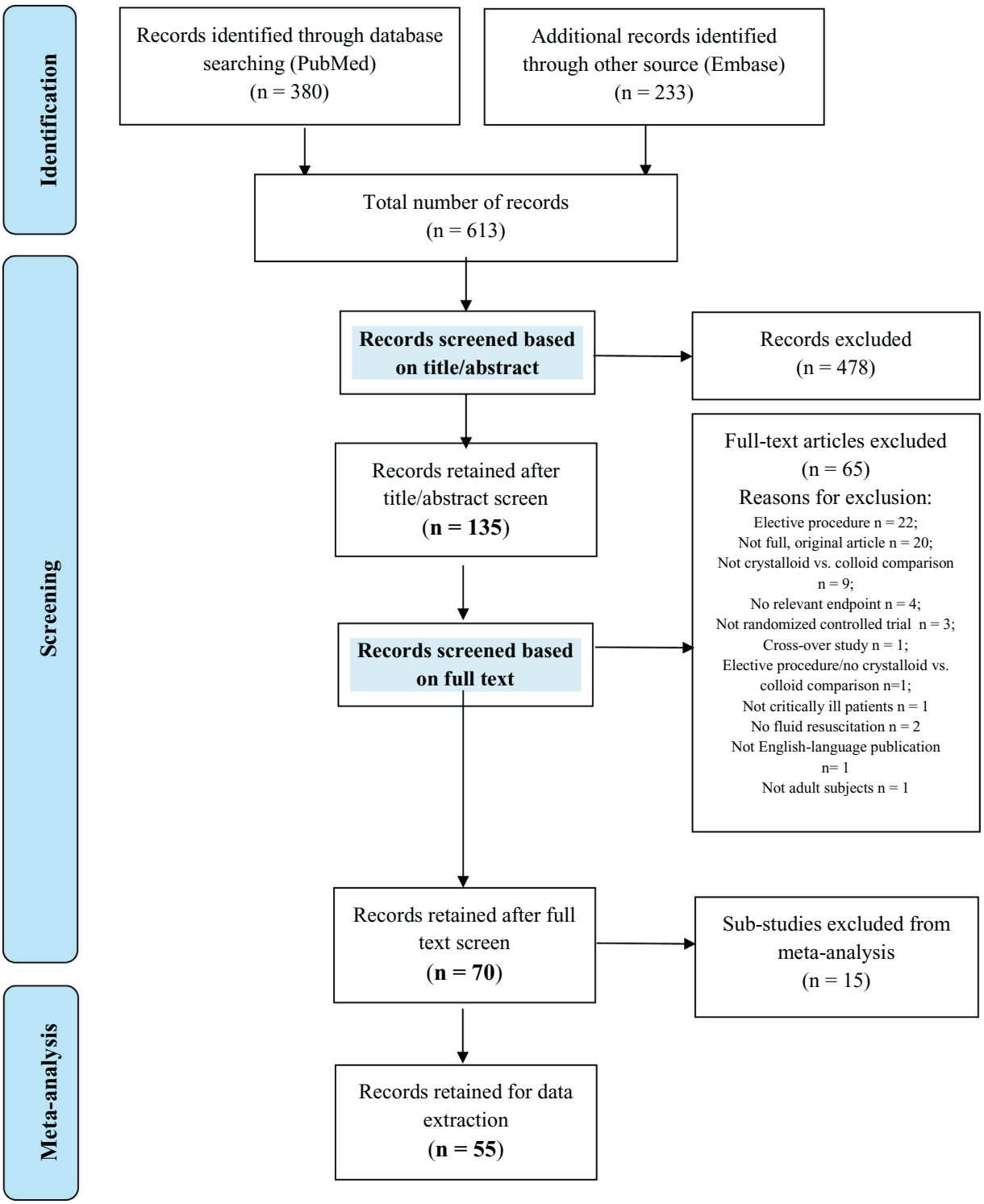

Fig. 1. PRISMA flow diagram summarizing the results from PubMed and EMBASE searches.

participants and personnel by 23 (42%), and blinding of outcome assessment by 12 (22%). Risk of bias due to either attrition or selective reporting was low in the majority of studies (50/55 [91%] and 48/55 [87%], respectively). Thirty-two (58%) RCTs had other sources of bias, including company involvement in the trial and an imbalance between patient groups at baseline. Publication bias analysis revealed little evidence of bias for cardiac index, stroke volume index, or mean arterial pressure (MAP; Supplementary Table S4), but did reveal some potential bias for studies reporting CVP and fluid volume. The funnel plots for CVP and fluid volume (Supplementary Fig. S1) suggest that smaller studies with larger standard errors tend to display greater treatment differences than those observed in larger studies.

3.3. Sufficiency of crystalloids

Fourteen studies ($n = 9629$) recorded data on target thresholds, such as CVP or MAP, used to estimate the sufficiency of crystalloids or colloids. Crystalloids were sufficient in achieving target thresholds in

11/14 (79%) studies overall [19,20,28-36]. In comparison, colloids were sufficient at raising CVP to the target threshold of 8–12 mm Hg in all 14 studies (100%). In three studies (21%), MAP was within the target range but crystalloids were deemed insufficient as they were unable to increase CVP to within the target range, with an average change from baseline of 0.5–1 mm Hg (Table 1) [37-39]. In contrast, in these three studies colloid therapy achieved the target CVP within 90 min and was associated with average increases from baseline of 3–5 mm Hg.

3.4. Efficacy of crystalloids vs. colloids

In all instances, maximum CVP values were significantly lower in the crystalloid group ($p < .001$) than in the colloid group, ranging from an MD of −2.0 mm Hg vs. the albumin group to −4.3 mm Hg vs. both the HES and gelatin groups (Fig. 2A). Similarly, maximum MAP was significantly lower with crystalloids than with either albumin (MD: −3.5 mm Hg [−6.7, −0.4]; $p = .03$) or gelatin (−9.2 [−17.0, −1.4]; $p = .02$). The difference in maximum MAP achieved with crystalloids vs. HES was not statistically significant (MD: −5.9 mm Hg [−14.0, 2.2]) (Fig. 2B). There was a large degree of heterogeneity between studies for all the colloid groups with regards to both CVP and MAP (Table 2).

Supplementary analyses showed that when saline was separated from balanced crystalloids, CVP was significantly lower for saline compared with HES, albumin and gelatin (MD: −4.8 mm Hg [−7.4, − 2.2; $p < .001$]; MD: −3.3 mm Hg [−6.3, −0.2; $p = .04$]; MD: −5.8 mm Hg [− 9.1, −2.4; $p = .001$], respectively). MAP was significantly lower for saline vs. gelatin (MD: −11.7 mm Hg [−21.2, −2.3; $p = .02$]). There were no significant differences between saline and HES or albumin with regards to MAP (Supplementary Table S5).

CVP was significantly lower for balanced crystalloids compared with HES and gelatin (MD: −2.7 mm Hg [−5.0, −0.4; p = .02]; MD: -3.0 mm Hg [−4.0, −1.9; $p < .001$], respectively), and MAP was significantly lower compared with albumin and HES (MD: -14.8 mm Hg [−20.6, −9.0; p < .001]; MD: −12.9 mm Hg [−18.5, −7.3; p < .001], respectively) (Supplementary Table S6).

3.4.1. Fluid volume

We next examined the total amount of fluid administered for both HES and albumin vs. crystalloids. The volume administered was significantly higher with crystalloids than with HES (MD: +1775 mL [503.56, 3046.70]; $p = .006$), and was numerically larger than that seen with albumin (MD: +1985 mL [−401.01, 4371.88]) (Fig. 3), although this difference did not reach statistical significance. No eligible studies reported volume data for either gelatin or dextran.

The total volume of fluid administered was not significantly greater in the saline group vs. HES or albumin, whereas the volume administered was significantly greater for balanced crystalloids vs. HES (MD: +3260 mL [1743, 4777; $p < .001$]), although only one study was eligible for this sub-analysis (Supplementary Table S7).

3.4.2. Hemodynamic parameters

We also examined hemodynamic outcomes. Compared with albumin, cardiac index was significantly lower in the crystalloid group, by a mean of −0.6 L/min/m^2 at the end of fluid challenge (p < .001; Fig. 4A). Improvements in cardiac index with albumin were evident within the first 24 h and 24–48 h post-infusion (Table 2). Differences with both HES and gelatin vs. crystalloids were smaller and were not statistically significant. Although the largest decrease was observed when crystalloids were compared with dextran at the end of fluid challenge (MD: −2.70 L/min/m^2 [−5.75, 0.35]), this included data from only one study and the difference was not statistically significant (Fig. 4A). For the two studies that reported data at 24 h and 24–48 h post-infusion, the cardiac index was significantly lower in the crystalloid group compared with the albumin group (MD: −1.24 L/min/m^2 [−2.44, −0.03] and MD: −0.73 L/min/m^2 [−1.40, −0.05] for the 24 h and 24–48 h time points, respectively; both $p = .04$). Of note, significant

Table 1
Sufficiency of crystalloids versus colloids in achieving CVP and MAP target thresholds.

Study	CVP (8–12 mm Hg)				MAP (>65 mm Hg)			
	Crystalloid		Colloid		Crystalloid		Colloid	
	Baseline; Peak	Time to resolution	Baseline; Peak	Time to resolution/peak effect	Baseline; Peak	Time to resolution/peak effect	Baseline; Peak	Time to resolution/peak effect
Smorenberg et al. 2015 [37]	3 (1−11)*; 4 (1–9)*	*Did not achieve*	7 (1–14)*; 11 (2–17)*	**90 min**	78 (65–100)*; 87 (75–93)*	90 min	76 (60–105)*; 89 (65–119)*	**90 min**
van der Heijden et al. 2009 [39]	3.5 (1–11)*; 4 (1–11)*	*Did not achieve*	6.5 (0–16)*; 10.5 (2–18)*	**90 min**	–	–	–	–
Harutjunyan et al. 2005 [31]	–	–	–	–	82 (64–98)*; 85 (74–100)*	30 min	84 (68–92)*; 83 (69–105)*	**10 min**
Trof et al. 2010 [38] -Sepsis	4 (4); 5 (3)	*Did not achieve*	6 (3); 9 (3)	**90 min**	82 (12); 84 (6)	90 min	82 (15); 93 (15)	90 min
Trof et al. 2010 [38] Non-Sepsis	5 (2); 6 (4)	*Did not achieve*	8 (4); 13 (4)	**90 min**	74 (10); 83 (10)	90 min	75 (10); 89 (16)	90 min
Finfer et al. 2004 [20]	10 (4.5); 10.7 (4.4)	Within 24 h	11.2 (4.8); 11.6 (4.8)	Within 24 h	80.9 (14.5); 88.4 (16.1)	Within 24 h	81.4 (14.4); 88.3 (15.9)	Within 24 h
Wu et al. 2001 [36]	4.3 (1.9); 10.3 (1.8)	30 min	4.2 (2.1); 13.1 (1.8)	**15 min**	60 (11); 91 (12)	60 min	62 (15); 92 (6)	60 min
Rackow et al. 1983 [35]	5.4 (1.7); 11.3 (1.7)	DNS	**Colloid 1**: 6.1 (1); 11.8 (0.7) **Colloid 2**: 6.4 (1.4); 10.3 (1.5)	DNS	54.7 (2.8); 72.4 (8.8)	DNS	**Colloid 1**: 60.3 (3); 73 (3) **Colloid 2**: 63.7 (5.4); 79.8 (5.2)	DNS
Gondos et al. 2010 [29]	9.7 (5.1); 11.7 (1.7)	DNS	**Colloid 1**: 11 (4.8); 15.2 (5.4) **Colloid 2**: 9.8 (5.2); 14.4 (6.6) **Colloid 3**: 9 (5.7); 14.1 (7.4)	DNS	83.8 (13.9); 81.8 (13.4)	DNS	**Colloid 1**: 84.2 (16.8); 96 (14.8) **Colloid 2**: 81.9 (14.4); 94.71 (15.2) **Colloid 3**: 82.6 (16.3); 96.6 (16)	DNS
Caironi et al. 2014 [19]	DNS; 10.3 (4.3)	6 h	DNS; 11.4 (4.7)	6 h	DNS; 77 (13)	6 h	DNS; 79 (14)	6 h

DNS – did not state. All values are mean ± SD unless indicated (* median [range]). Bold indicates studies where time to resolution was faster with colloids.
N.B. James et al. 2011; Guidet et al. 2012; Dubin et al. 2010; McIntyre et al. 2008; Heradstveit et al. 2010 also recorded data on CVP/MAP; however, we were unable to extract data from the figures or raw data values were not reported.

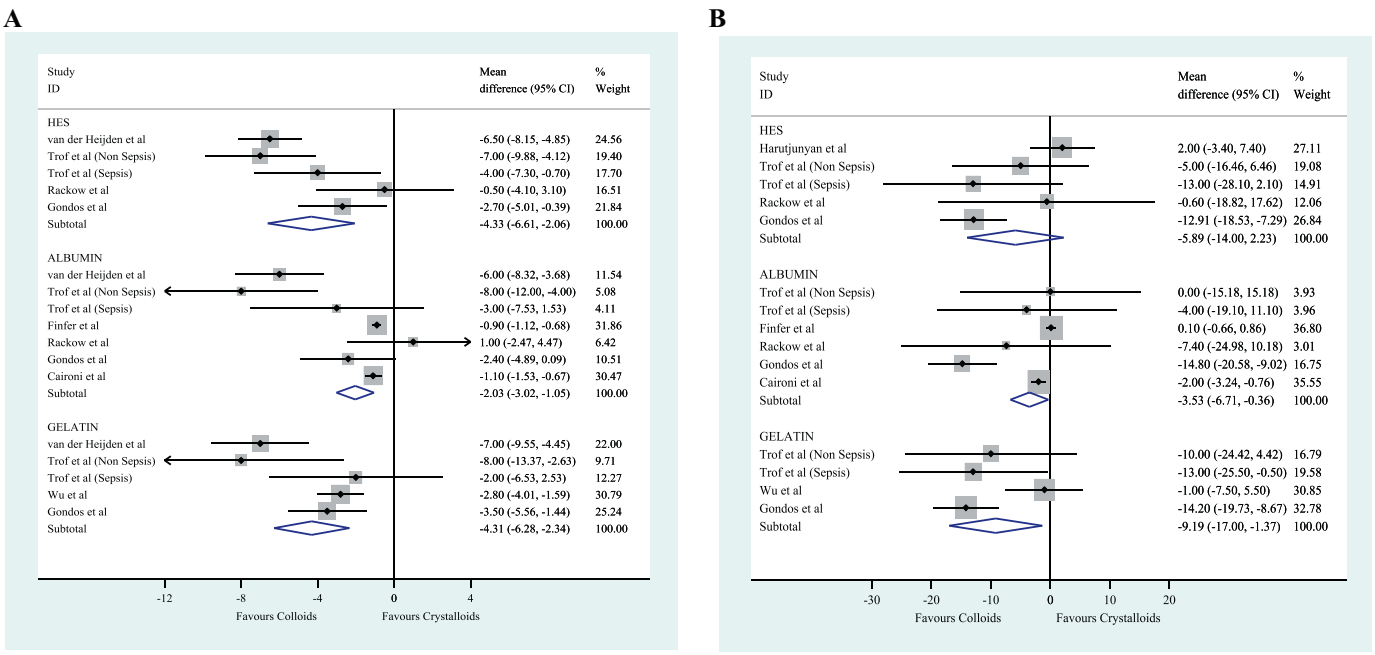

Fig. 2. Comparison of peak CVP (A) and MAP (B) values following crystalloids vs. colloids [19,20,29,35,36,38,39]. CI, confidence interval; CVP, central venous pressure; HES, hydroxyethyl starch; MAP, mean arterial pressure. CVP and MAP were measured in mm Hg.

heterogeneity was observed for the studies reporting data at 24 h (I^2 88%; $p = .004$).

At the end of the infusion, there was no significant difference in stroke volume index between crystalloids and any of the colloids (HES, albumin, and gelatin; Fig. 4B).

There were no significant differences found between saline and any colloid with regards to cardiac index or stroke volume index (Supplementary Table S5). However, cardiac index was significantly lower with balanced crystalloids vs. HES, albumin and gelatin at the end of fluid challenge (MD: −0.68 L/min/m^2 [−1.10, −0.26; $p = .002$]; MD: −0.70 L/min/m^2 [−1.01, −0.38; $p < .001$]; MD: −0.57 L/min/m^2 [−0.96, −0.18; $p = .005$], respectively) (Supplementary Table S6).

At 24 h and 24–48 h, only studies comparing balanced crystalloids with albumin reported data, and cardiac index was significantly lower with balanced crystalloids (MD: −1.24 L/min/m^2 [−2.44, −0.03; $p = .04$]; MD: −0.73 L/min/m^2 [−1.40, −0.05; p = .04] at 24 and 24–48 h, respectively). Stroke volume was significantly lower in the albumin group compared with balanced crystalloids at 0–12 h post-infusion (−13.0 mL/beat.m^2 (−18.5, −7.5; p < .001) (Supplementary Table S5).

3.4.3. Clinical outcomes

Data on mortality were available for 26,329 patients across 46 studies. The results for all mortality suggested a significant increase in the risk of death with HES compared with crystalloids (Fig. 5). There was no significant difference in mortality in patients treated with albumin, gelatin, or dextran, compared with crystalloids (Fig. 5, Table 3). Similarly, 90-day mortality was significantly lower in the crystalloid group

Table 2
Summary of meta-analyses of hemodynamic parameters for crystalloids vs. colloids.

Outcome	Colloid	Number of studies	Heterogeneity		Treatment effect (crystalloids relative to colloids)	
			p-value	I^2	Mean (95% CI) (+)	P-value
CVP (max) (mm Hg)	HES	5	**0.004**	74%	−4.3 (−6.6, −2.1)	<**0.001**
	Albumin	7	<**0.001**	82%	−2.0 (−3.0, −1.1)	<**0.001**
	Gelatin	5	**0.02**	65%	−4.3 (−6.3, −2.3)	<**0.001**
MAP (max) (mm Hg)	HES	5	**0.004**	86%	−5.9 (−14.0, 2.2)	0.16
	Albumin	6	<**0.001**	91%	−3.5 (−6.7, −0.4)	**0.03**
	Gelatin	4	**0.02**	89%	−9.2 (−17.0, −1.4)	**0.02**
Cardiac index (L/min/m^2)	HES	5	**0.006**	72%	−0.25 (−0.94, 0.43)	0.47
End fluid challenge	Albumin	7	0.15	36%	−0.61 (−0.87, −0.34)	<**0.001**
	Gelatin	4	0.14	45%	−0.30 (−0.82, 0.22)	0.26
	Dextran	1	–	–	−2.70 (−5.75, 0.35)	0.08
First 24 h	Albumin	2	**0.004**	88%	−1.24 (−2.44, −0.03)	**0.04**
24–48 h	Albumin	2	0.67	0%	−0.73 (−1.40, −0.05)	**0.04**
Stroke volume index (mL/m^2)						
End of infusion	HES	3	0.48	0%	+2.5 (−3.8, 8.8)	0.44
	Albumin	4	0.36	7%	−0.4 (−6.5, 5.8)	0.91
	Gelatin	2	0.65	0%	−3.4 (−15.9, 9.1)	0.60
0–12 h	HES	1	–	–	−6.7 (−17.5, 4.1)	0.22
	Albumin	1	–	–	−13.0 (−18.5, −7.5)	<**0.001**

(+) Calculated as values in crystalloids group relative to colloids group.
Significant *p*-values (<0.05) are highlighted in bold text.
CI, confidence interval; CVP, central venous pressure; HES, hydroxyethyl starch; MAP, mean arterial pressure.

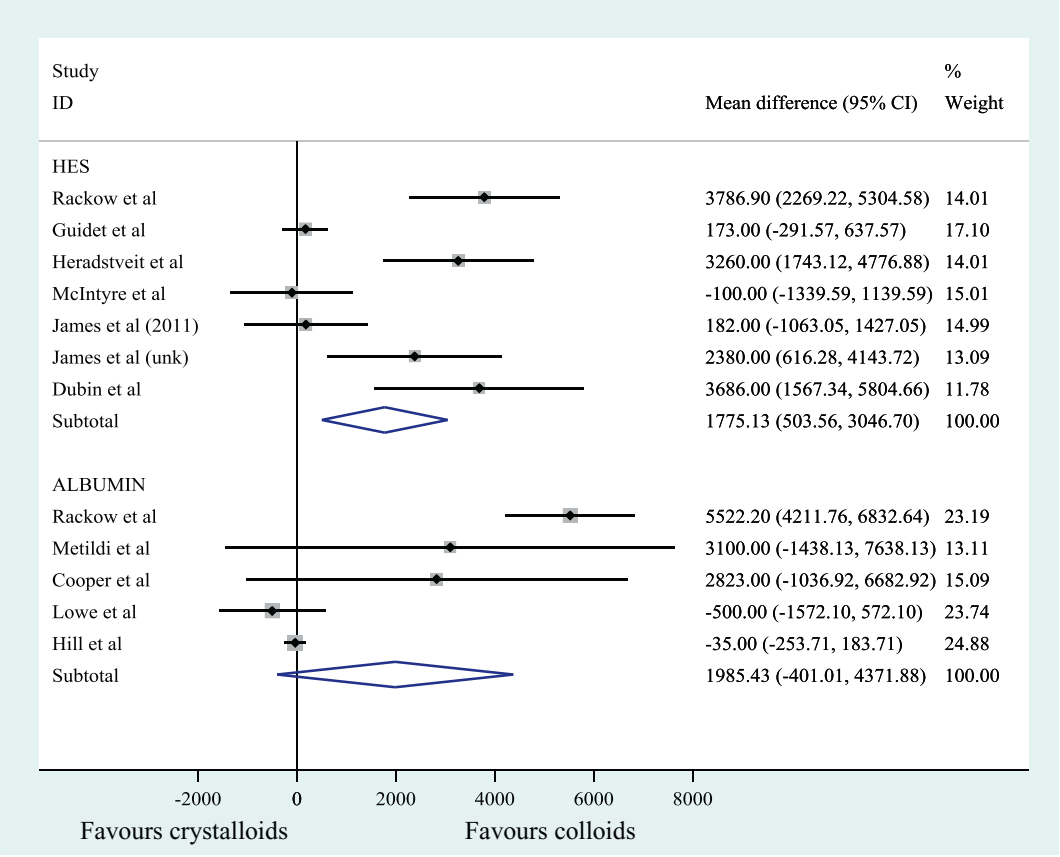

Fig. 3. Comparison of fluid volume (mL) administered with crystalloids vs. colloids [28,30,32-35,64-67]. CI, confidence interval; HES, hydroxyethyl starch.

compared with the HES group (relative risk 0.9 (RR) [95% CI 0.83, 0.97]; $p = .005$); however, there was no significant difference between HES and crystalloids at 28 days (Table 3).

There were no significant differences between saline and any colloid with regards to mortality (Supplementary Table S8). All mortality and 90-day mortality were significantly higher for HES compared with balanced crystalloids (RR: 0.86 [0.76, 0.96; $p = .01$]; RR: 0.85 [0.75, 0.96; $p = .009$], respectively). No significant difference was found between balanced crystalloids and any other colloid (Supplementary Table S9).

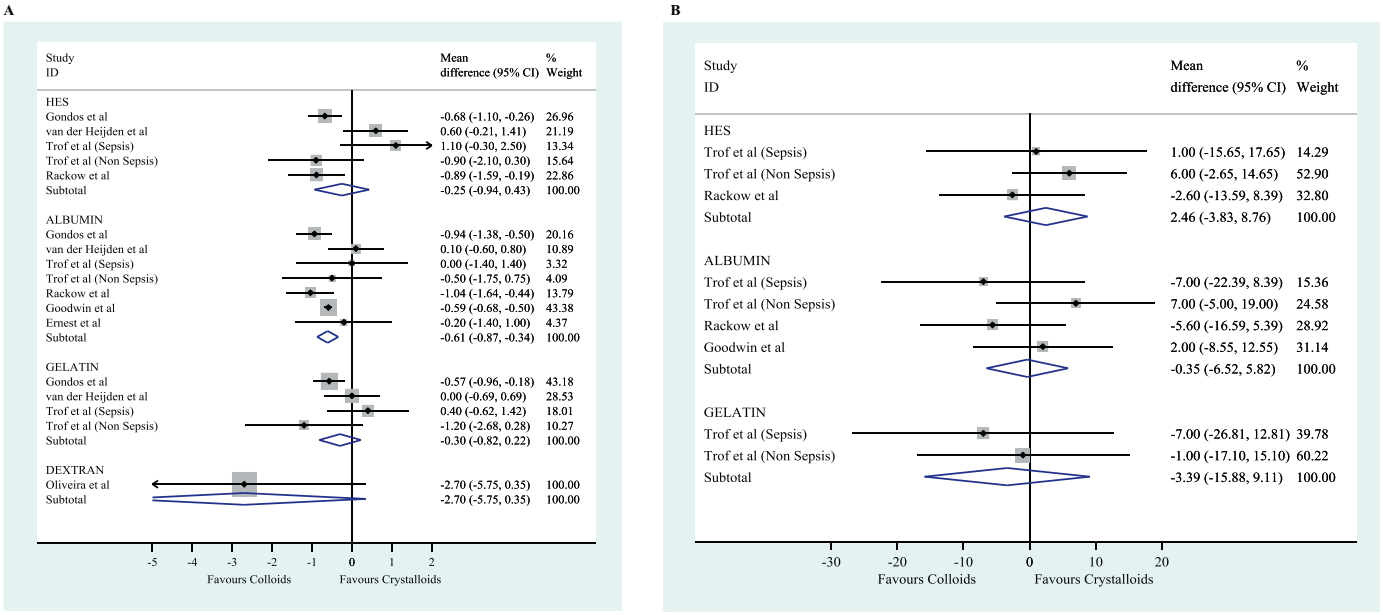

Fig. 4. Comparison of A) cardiac index and B) stroke volume index at end of infusion of crystalloids vs. colloids [29,35,38,39,68-70]. CI, confidence interval; HES, hydroxyethyl starch. Cardiac index was measured in L/min/m^2; stroke volume index was measured in mL/m^2.

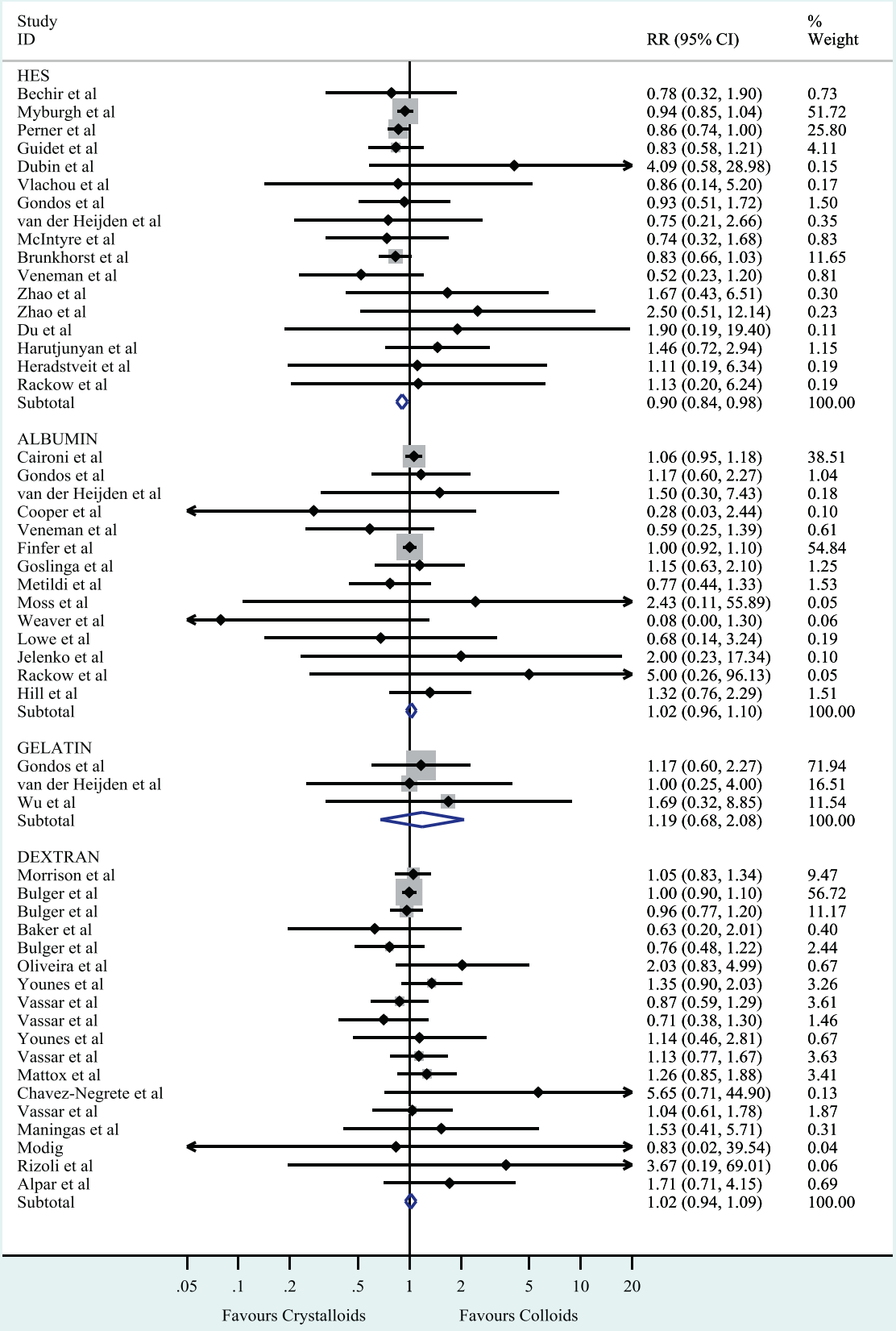

Fig. 5. Comparison of overall mortality for crystalloids vs. colloids [8,9,19,20,28-32,34-36,39,64-66,70-98]. CI, confidence interval; HES, hydroxyethyl starch; RR, relative risk.

Table 3
Summary of meta-analyses of mortality for crystalloids vs. colloids.

Outcome	Colloid	Number studies	Heterogeneity		Treatment effect (crystalloids relative to colloids)	
			P-value	I^2	RR (95% CI) (+)	P-value
Mortality						
All	HES	18	0.82	0%	0.91 (0.84, 0.98)	**0.009**
	Albumin	14	0.60	0%	1.02 (0.96, 1.10)	0.49
	Gelatin	3	0.89	0%	1.19 (0.68, 2.08)	0.55
	Dextran	19	0.56	0%	1.02 (0.95, 1.10)	0.67
28 days	HES	7	0.98	0%	0.93 (0.85, 1.03)	0.15
	Albumin	3	0.51	0%	1.00 (0.93, 1.08)	0.95
	Dextran	3	0.51	0%	0.98 (0.90, 1.07)	0.67
90 days	HES	6	0.84	0%	0.90 (0.83, 0.97)	**0.005**
	Albumin	2	0.45	0%	1.07 (0.95, 1.18)	0.22

(+) Calculated as values in crystalloids group relative to colloids group.
Significant p-values (<0.05) are highlighted in bold text.
CI, confidence interval; HES, hydroxyethyl starch; RR, relative risk.

4. Discussion

This systematic review and meta-analysis evaluated data from RCTs of crystalloids and colloids for fluid resuscitation in ICU patients, encompassing 55 studies and approximately 27,000 critically ill adult patients. At all timepoints assessed (including at 24 and 24–48 h post-infusion), treatment with albumin was associated with a significantly higher cardiac index than treatment with crystalloids. Furthermore, CVP was significantly higher in patients treated with albumin, HES, or gelatin compared with those treated with crystalloids, while MAP was also significantly higher with albumin or gelatin vs. crystalloids. HES was the only colloid found to significantly increase the risk of mortality compared with crystalloids, and did so even at 90 days.

The recently updated international guidelines from the Surviving Sepsis Campaign recommend crystalloids as the fluid of choice in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence) [2]. Albumin is recommended "when patients require substantial amounts of crystalloids" (weak recommendation, low quality of evidence). Several guidelines recommend against HES (strong recommendation, high quality of evidence) due to well-documented safety concerns observed in major trials [8,10,25], consistent with the significantly increased risk of mortality evident in our meta-analysis. Crystalloids are suggested over gelatin (weak recommendation, low quality of evidence) due to the lack of high-quality evidence for gelatin. Furthermore, in a recent meta-analysis, gelatin was associated with increased risk of anaphylaxis, bleeding, renal failure, and mortality when compared with crystalloids or albumin for treatment of hypovolemia [5].

Importantly, the guidelines do not include a clear recommendation to guide physicians on what constitutes a substantial amount of crystalloids and consequently when albumin should be administered. Our analysis suggests that in some clinical settings, crystalloids alone may not be sufficient for fluid resuscitation in circumstances where colloids are sufficient; however, exactly when physicians should switch to colloids remains an important unanswered question. It has been suggested that beyond crystalloid infusion volumes of 3–4 L, colloids should be considered [40]. Greater volumes of crystalloids have been associated with fatal pulmonary edema and systemic organ dysfunction [40,41]. The question of when to switch to colloids, however, is complex and must take into account several factors, including blood loss, patient weight, and hemoglobin concentration [41]. To this end, it has not yet been established how best to accurately monitor cumulative fluid balance. Daily fluid balance can be calculated based on input and output volumes recorded on patient charts, and by body weight measured at defined timepoints; however, both have been criticized as non- robust, insensitive, and unreliable predictors of fluid overload in critically ill patients [42]. Bioelectrical impedance analysis (BIA) is an alternative tool that is used to measure body composition. Total body water and fluid distribution can be obtained using BIA in efforts to monitor fluid balance and the risk of overload. Electrical impulses are transmitted through patients' tissues, which can help to guide fluid therapy based on individual patient requirements [43].

Our results showed that significantly higher volumes of crystalloids were administered compared with HES. In addition, although not statistically significant, there was a trend toward higher volumes of crystalloids administered compared with albumin. This highlights the risk of positive fluid balance that occurs in response to large infusion volumes and is associated with poorer patient outcomes [44], although our findings are lower than other estimates of crystalloid/colloid ratios that have suggested a three- to four-fold volume difference [5,45,46]. Of note, when saline and balanced crystalloids were treated as distinct groups, there was a significant difference between HES and balanced crystalloids but not saline with regards to volume of fluid infused. This suggests that saline may be more adept at reaching fluid resuscitation goals than balanced crystalloids. However, it is important to note that these sub-analyses included few studies and heterogeneity among them was high, which may have affected the results. Recent evidence has shown outcome differences between normal saline and balanced crystalloid solutions [47], where balanced crystalloids led to a lower rate of mortality and/or renal function compared with saline. In line with this, our analyses showed that for saline compared with each colloid, there was no significant difference in regards to mortality or any hemodynamic outcomes. However, all mortality and 90-day mortality were significantly higher for the HES group compared with balanced crystalloids, suggesting indirectly that balanced crystalloids may be associated with a lower risk of mortality than saline.

Our approach has some limitations. For example, our search and selection criteria were broad, with no restrictions on ICU setting or publication date. As a result, there was significant heterogeneity between included studies in terms of their design, comparators, and efficacy measures; thus, some of the analyses lacked sufficient statistical power. Adequately powered studies will be required to provide further data on these outcomes. Nonetheless, a degree of heterogeneity was anticipated and our intentionally broad and inclusive approach meant that each meta-analysis was performed on the largest available data set and reflects the reality that crystalloids and colloids are in widespread use for fluid resuscitation across a broad range of ICU indications.

Secondly, monitoring of hypo- as opposed to hypervolemia is a key consideration in the ICU that relates specifically to intravascular fluid volume. Hypovolemia reduces the efficiency of oxygen transport and may result in multiple organ failure [48]. Accurate monitoring of hypovolemia can be achieved using biomarkers, e.g., plasma electrolytes, serum creatinine and arterial blood gas, imaging techniques such as chest x-ray or ultrasound, hemodilution parameters such as hemoglobin concentration, and intravenous catheters [48-50]. We did not analyze the instance of hypovolemia in response to crystalloids vs. colloids in this study.

The majority of the RCTs meeting our selection criteria were conducted in the fields of sepsis, shock, trauma, or critical care (46/55; 84%). Other settings, such as burns, cardiac, hepatology, pulmonary, and stroke, were therefore under-represented by comparison, with only one or two studies included for each. Use of crystalloids and colloids for fluid resuscitation in these settings warrants further study, as do pediatric and elective surgery populations, both of which were excluded from our analyses.

Our study looked at hemodynamic and physiological parameters, such as CVP, as measures of fluid resuscitation [51-54]; however, their validity has been questioned. Many of the studies looking at hemodynamic indices were performed in controlled environments on ventilated patients; therefore, confounding variables, e.g., spontaneous breathing, may affect their predictive value in routine clinical practice [55]. It is important to note that fluid responsiveness is dependent on organ-organ interactions such as between the heart and lungs, based

on the aggressiveness of the ventilator settings, e.g., absence of lung protective ventilation, high mean airway pressure, high positive end- expiratory pressure (PEEP) or high driving pressure. We did not collect data on these parameters; however, they should be considered in future studies that evaluate response to fluid therapy. In addition, deresuscitation (the active removal of fluids), may be more important than initial resuscitation to restore negative fluid balance and avoid the adverse effects of fluid overload [56,57]. Evidence shows that this approach reduces length of stay in the ICU and increases the number of ventilator-free days [56]. Furthermore, although the effect of capillary leak on body fluid composition was not taken into account in this meta-analysis, evidence indicates that it is an important predictor of changes in extravascular fluid volume and net fluid balance [58], and capillary leak should serve as a stimulus to physicians to initiate deresuscitation [59]. The achievement of negative fluid balance in patients with capillary leak results in reduced extravascular lung water and intraabdominal pressure, which improves overall outcomes [60].

Recommendations now endorse the use of dynamic measures, such as passive leg raises or variations in systolic pressure and pulse pressure instead of static markers such as CVP, to monitor response to fluid resuscitation and guide further therapy [2,52,54,61,62]. While CVP may be useful when used in conjunction with other measures, future studies will likely focus on dynamic measures, which we were unable to report on in this review as no data were captured in the eligible studies.

With regards to the measurement of hemodynamic parameters, these analyses were not based on the volume of colloid administered in each case, and no normalization technique was used. Importantly, rigorous statistical analysis was used to calculate all hemodynamic parameters. Finally, we did not treat different concentration albumin solutions as distinct subgroups in this study. While there is some evidence to suggest that low-concentration albumin solutions lead to more positive fluid balance [63], this is yet to be fully established and warrants future study.

While the potential for publication bias is a further limitation, we attempted to limit the impact of any such bias by undertaking and reporting publication bias assessments.

5. Conclusions

This systematic review and meta-analysis, which included only high-level evidence from RCTs conducted in intensive care settings, revealed that crystalloids were less effective than colloids at stabilizing hemodynamic resuscitation endpoints such as CVP, MAP, and cardiac index. There is a possibility that saline is more effective than balanced crystalloids at reaching resuscitation endpoints; however, the evidence for this was not conclusive and the known risks associated with saline must be noted.

HES was the only colloid associated with increased mortality vs. crystalloids. Therefore, alternative fluid therapy with colloids such as albumin may be appropriate to restore hemodynamic endpoints in a more timely and effective manner.

These findings highlight an urgent need for further research and guidance for physicians regarding when to administer colloids to ensure optimal fluid therapy for resuscitation of critically ill patients.

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Declaration of interest

Greg Martin has the following interests to declare:

Served as a grant reviewer for Grifols; served as an advisor for Cheetah Medical; received research funding from NIH and Bristol-Myers Squibb; served on the board of directors for the Society of Critical Care Medicine.

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