

Resuscitation Fluid Types in Sepsis, Surgical, and Trauma Patients: A Systematic Review and Sequential Network Meta-analyses

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Research

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Abstract

Background: Crystalloids and different component colloids, used for volume resuscitation, are sometimes associated with serious adverse events (AEs). Clinical trial findings for such fluid types in different patients' conditions are conflicting. Whether the mortality benefit of balanced crystalloid than saline can be infer from sepsis to other patient group is uncertain, and other AEs is not comprehensive. This study aims to compare the survival benefits and AEs of seven fluid types with network meta-analysis in sepsis, surgical, trauma, and traumatic brain injury patients.

Methods: Searched databases (PubMed, EMBASE, and Cochrane CENTRAL) and reference lists of relevant articles occurred from inception until January 2020. Studies on critically ill adults requiring fluid resuscitation were included. Intervention studies reported on balanced crystalloid, saline, iso-oncotic albumin, hyperoncotic albumin, low molecular weight hydroxyethyl starch (L-HES), high molecular weight HES, and gelatin. Network meta-analyses were conducted using random-effects model to calculate odds ratio (OR) and mean difference. Risk of Bias tool 2.0 was used to assess bias. CINeMA (Confidence in Network Meta-Analysis) web application was used to rate confidence in synthetic evidence.

Results: Fifty-eight trials (n=26,351 patients) were identified. Seven fluid types were evaluated. Among patients with sepsis and surgery, balanced crystalloids and albumin achieved better survival, fewer renal AEs, and smaller blood transfusion volumes than saline and L-HES. In those with sepsis, balanced crystalloids reduced mortality more than saline (OR, 0.84; 95% CI 0.74 to 0.95) and L-HES (OR, 0.81; 95% CI 0.69 to 0.95) and reduced renal AEs more than L-HES (OR, 0.80; 95% CI 0.65 to 0.99). However, they required the largest resuscitation volume among all fluid types, especially in trauma patients. In patients with traumatic brain injury, saline and L-HES achieved lower mortality than albumin and balanced crystalloids; especially saline was superior to iso-oncotic albumin (OR, 0.55; 95% CI 0.35 to 0.87).

Conclusions: For sepsis and surgical patients, we recommend balanced crystalloids and albumin, rather than L-HES and saline. For traumatic brain injury patients, we recommend saline or L-HES, rather than iso-oncotic albumin or balanced crystalloids. These findings could guide physicians' fluid selection.

Trial registry: PROSPERO website, registration number: CRD42018115641).

Introduction

Fluid resuscitation is one of the most common and important management methods in critically hypotensive patients. Crystalloids, mineral salts, or other water-soluble molecule solutions have been used for more than 100 years for fluid resuscitation (1, 2). In the past decades, several colloids, larger insoluble molecular solutions, have been developed to improve intravascular volume more effectively. However, since the integrity of the endothelial glycocalyx layer might be interrupted under inflammatory conditions, such as sepsis, surgery, trauma, or traumatic brain injury, evaluation of the efficacy and safety of colloids in such patients are challenging (3, 4).

Insoluble molecules in colloids include starch, bovine protein (gelatin), and human protein (albumin). Hydroxyethyl starch (HES) of higher molecular weight has a longer half-life in plasma, but it reduces plasma coagulation factors more than HES of lower molecular weight (5) and albumin (6). Starch macromolecule accumulation also impairs glomerular filtration and is associated with a higher risk of acute renal failure than

gelatin (7); however, gelatin is associated with a higher incidence of anaphylactic shock (8, 9). Compared to iso-oncotic albumin, hyperoncotic albumin leads to a higher osmotic pressure, which may alter intra-glomerular oncotic force and osmotic nephrosis, and is associated with worse kidney damage (10). Chemical components, molecular weights, and colloid concentration might expose the human body to different levels of hazards (11). Among crystalloids, saline worsens acidosis and bleeding tendency compared to balanced crystalloids (12). Consequently, classifying resuscitation fluids into colloids or crystalloids was no longer comprehensive.

From 2012 to 2018, of 15 meta-analyses published on fluid resuscitation in critically ill patients (appendix pp 5–7), 12 (80%) grouped high and low chloride crystalloids or colloids of different components into a single type of treatment, and 5 (33.3%) grouped sepsis, surgical, and trauma patients into one meta-analysis. Furthermore, no meta-analyses compared the required fluid volumes for the resuscitation target. This study aimed to compare the survival benefit and any potential adverse effects of seven fluid types using network meta-analysis (NMA) in sepsis, surgical, trauma, and traumatic brain injury patients, and investigated the trend in treatment difference using sequential NMA.

Methods

Data Sources and Searches

We registered our systematic review process on the PROSPERO website (13) (registration number: CRD42018115641). This NMA followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension guideline which incorporated NMA for health care interventions (appendix pp 8-13) (14). The searched databases included PubMed, EMBASE, and Cochrane CENTRAL. The search strategies combined terms for patients' conditions, clinical outcomes, and fluid types (appendix pp 14-15).

Study Selection

We included randomized controlled trials (RCTs) on adult critically ill patients requiring fluid resuscitation from inception until January 2020, and excluded trials on children with dengue fever, burn injury patients, or retrospective observational studies.

Data Extraction and Quality Assessment

We divided patients requiring fluid resuscitation into the following groups for extraction of data and separate analyses: sepsis, surgical, trauma, and traumatic brain injury. The 7 interventions included 2 crystalloids: [balanced crystalloids, including lactated Ringer's or PlasmaLytes and saline (0.9% sodium chloride)]; and 5 colloids: [iso-oncotic albumin (4%, 5%); hyperoncotic albumin (20%, or 25%); HES with molecular weight ≤ 130 k (L-HES); HES with molecular weight ≥ 200 k (H-HES); and gelatin]. The outcomes included all-cause mortality rate; fluid resuscitation volume; major renal adverse events defined as acute kidney injury and/or requiring renal replacement therapy; transfusion volume; and allergic reaction rate. Two authors (CH Tseng and TT Chen) screened the literatures on RCTs independently, extracted data, and assessed the risk of bias of studies using the revised Cochrane risk of bias tool (RoB 2 tool) at study level (15).

Data Synthesis and Analysis

Transitivity assumption was assessed by checking the distribution of potential confounding factors across studies grouped by interventions. Those characteristics included age, male percentage, disease severity scores, source of sepsis from the lung, and publication year in the seven interventions. We first used the 'network' suite of STATA version 14.0 (16) (StataCorp, Texas, USA) statistical software, which implements a frequentist approach to the contrast-based model meta-analyses (16), to undertake random effect NMA (17). We then used network map to illustrate the distribution of the direct and indirect evidence between all treatment comparisons. The size of the nodes in the map was proportional to the number of patients who received this intervention in the network, and the thickness of the edges was proportional to the number of trials that compared the two treatments. Certainty of the evidence was assessed using CINeMA (Confidence in Network Meta-Analysis) web application, which allows for confidence in the results to be graded as high, moderate, low, and very low. This approach was based on a methodology developed by the Grading of Recommendations Assessment, Development and Evaluation Working Group for pairwise meta-analyses (18).

To adjust for the multiplicity of statistical testing, we further conducted sequential NMA, proposed by Nikolakopoulou et al., who extended the rationales of sequential meta-analyses for defining sample-path, efficacy boundaries, futility boundaries, and information size in meta-analyses (19). In sequential NMA, we undertook a series of NMA, providing a path of estimates for each pairwise comparison, by including studies incrementally into the analysis according to their publication years (19). When the path crossed the efficacy boundaries, defined by the α -spending function derived from the O'Brien-Fleming method (20), the difference between the two treatments exceeded the threshold for statistical significance. In contrast, when the path fell within the futility area defined by the β -spending functions (21), the two interventions showed no difference in their effects. We used the R software package "sequentialnma" to undertake sequential NMA (22). Results from these additional analyses were then compared to the results from the NMA.

Results

The literature search identified 18,802 citations, and 377 full-text articles were assessed for eligibility. Of 58 RCTs which included 26,351 patients in the analysis, 5 large RCTs included more than one condition – sepsis, surgery, trauma, and traumatic brain injury. Thus, we extracted the subgroup data of patients with different conditions. As a result, 23 RCTs on sepsis patients, 24 on surgical patients, 10 on trauma patients, and 4 on traumatic brain injury patients were included for further analysis (Figure 1, appendix pp 17-48). No significant differences occurred in baseline variables between interventions within our NMA (appendix pp 49-60).

Sepsis Patients

Most RCTs used the 2001 International Sepsis Definitions Conference sepsis definition (23) and included sepsis patients with shock status or those who had evidence of tissue or organ hypoperfusion. The average mean study fluid volume was 2397.4 mL \pm 1019.1 mL in each arm, and the total resuscitation fluid volume was 7615.6 mL \pm 1729.7 mL (appendix pp 22-31, 61-64).

Sepsis Patients-Mortality

Between 1983 and 2018, 23 RCTs with 14,659 participants presented with usable results on mortality. Balanced crystalloids reduced mortality more than saline and L-HES with odds ratios (OR) of 0.84 (95% CI 0.74-0.95) and 0.81 (95% CI 0.69-0.95), respectively (Figure 2A). Sequential NMA further supported the difference by demonstrating that the trend in cumulative evidence went beyond the efficacy boundary between balanced crystalloids vs. saline and L-HES. The cumulative evidence went below the futility boundary in balanced crystalloids vs. albumin but fell between efficacy and futility boundary in balanced crystalloids vs. gelatin (Figure 3). According to SUCRA ranking probability, balanced crystalloid appeared to be the best option; however, saline, L-HES, and H-HES were not favored (Figure 4).

Sepsis Patients- Fluid Resuscitation Volume

Thirteen trials with 10,970 participants reported usable results for fluid resuscitation volume in sepsis patients. Balanced crystalloids and saline required more fluid volume than iso-oncotic albumin with mean differences (MD) of 2122 mL (95% CI -300 to 4544 mL) and 1964 mL (95% CI 89 to 3840 mL), respectively (Figure 2B). SUCRA ranking probability revealed that the colloids were associated with less resuscitation fluid volume than crystalloids (Figure 4).

Sepsis Patients- Renal Adverse Events

Eleven trials with 10,569 participants reported usable results for renal adverse events. Balanced crystalloids significantly reduced renal adverse events than L-HES (OR, 0.80; 95% CI 0.65-0.99), and H-HES (OR, 0.54; 95% CI 0.37-0.84) (Figure 2C). SUCRA ranking revealed that gelatin, balanced crystalloid, saline, and iso-oncotic albumin reduced renal adverse events more than L-HES and H-HES (Figure 4).

Sepsis Patients- Red Blood Cell Transfusion Volume

Ten trials with 11,979 participants reported usable results for the packed red blood cell transfusion volume. Balanced crystalloids required less volume of red blood cell transfusion than hyperoncotic albumin (MD, 274 mL; 95% CI 5 mL to 548 mL), L-HES (MD, 232 mL; 95% CI 35 mL to 430 mL) and H-HES (MD, 497 mL; 95% CI 141 mL to 854 mL). (Figure 2D). SUCRA ranking probability revealed that the crystalloids and iso-oncotic albumin were associated with less transfusion volume than other colloids (Figure 4).

The funnel plot and Egger's test did not detect any significant publication bias (appendix pp 114-116). Loop inconsistency and design inconsistency were also not detected (appendix pp 124-129). The meta-regression did not change the ranking order (appendix pp 138-139). The evidence certainty in mortality revealed a moderate to high evidence confidence in comparison, including balanced crystalloids, saline and L-HES; low to moderate in iso-oncotic albumin and hyperoncotic albumin; very low in gelatin, and H-HES (appendix pp 139-142).

Surgical Patients

During 1979 to 2020, in 23 RCTs (8 [34.80%], 6 [26.00%], 6 [26.00%], and other RCTs were conducted in cardiac surgery, aortic surgery, major abdominal surgery, and hip arthroplasty and cystectomy, respectively), different resuscitation fluids were compared in surgical patients. Most trials reported that fluid resuscitation was provided

during surgical procedures to maintain hemodynamic parameters, and the mean resuscitated fluid of interest was 3327.5 mL (appendix pp 32-36, 65-67).

Surgical Patients- Mortality

Twenty-three trials with 4,646 participants had valid results on mortality. There were no significant differences in mortality between 7 interventions (Figure 5); and SUCRA ranking probability revealed that hyperoncotic albumin and balanced crystalloid were associated with less mortality than gelatin, HES, and saline (Figure 4).

Surgical Patients- Fluid Resuscitation Volume

Twenty trials with 4,512 participants had valid results on resuscitation fluid volume. Balanced crystalloids group required significantly more fluid resuscitation volume than iso-tonic albumin (MD, 2612 mL; 95% CI 1416-3800), hypertonic albumin (MD, 2852 mL; 95% CI 742-4962), L-HES (MD 1494 mL; 95% CI 345-2644), H-HES (MD, 1462 mL; 95% CI 418-2505), and gelatin (MD, 1154 mL; 95% CI 64-2240), (Figure 5). SUCRA ranking revealed that colloids (albumin, HES, and then gelatin) were associated with less fluid resuscitation volume than crystalloids (Figure 4).

Surgical Patients- Renal Adverse Events

Fourteen trials with 4,248 participants presented usable results for renal adverse events. The ORs among seven treatments were not significant (Figure 5). SUCRA ranking probability revealed iso-oncotic albumin, and balanced crystalloids were associated with less renal adverse events than HES and gelatin.

Surgical Patients- Red Blood Cell Transfusion Volume

Sixteen trials with 2,818 participants presented usable results for red blood cell transfusion volume. Ranking probabilities showed that albumin, L-HES, and then gelatin were associated with less transfusion volume than H-HES and crystalloids (Figure 5).

Publication bias and inconsistency were not significant (appendix pp 118-121). The confidence ratings were low to very low among all comparisons in surgical trials (appendix pp 143-146).

Trauma and Traumatic Brain Injury Patients

During 1977 to 2018, 10 RCTs compared between different resuscitation fluids in trauma patients who required fluid resuscitations, and 4 RCTs in traumatic brain injury patients. Patients' mean age was 48.6 years, predominantly male (69.8%), and mean resuscitation study fluid was 5,481 mL among trauma trials. (appendix pp 37-39, 82-86)

Ten trials with 5,076 participants had valid results on mortality in trauma patients, and differences in mortality were not significant between interventions in trauma patients. Balanced crystalloid required less volume of red blood cell transfusion than saline (MD, 350 mL; 95% CI 160 mL to 540 mL), and L-HES (MD, 964 mL; 95% CI 400

mL to 1527 mL). Four trials with 1,970 participants had valid results on mortality in traumatic brain injury patients, and saline reduced mortality than albumin with OR of 0.55 (95% CI 0.35-0.87) (appendix pp 103-114). The confidence ratings were low to very low among all comparisons in traumatic and traumatic brain injury trials (appendix pp 123-124, 128, 148-150).

Discussion

To our knowledge, this analysis is the largest NMA in the field of fluid resuscitation, as we considered a larger number of outcomes and undertook separate analyses for patients with different conditions. In sepsis patients, balanced crystalloids and iso-oncotic albumin were associated with lower mortality, fewer renal adverse events, and less red blood cell transfusion volume. In surgical patients, non-significant differences in mortality and renal event rates occurred among the seven interventions, but balanced crystalloids required the most fluid resuscitation volume than all other fluid. In traumatic brain injury trials, iso-oncotic albumin was associated with higher mortality than saline.

Previous Studies and Important Differences from this Study

In many previous meta-analyses on fluid resuscitation, sepsis, surgical, trauma, and traumatic brain injury patients grouped and combined balanced and non-balanced crystalloids or different component, high and low molecular weight, iso- and hyperoncotic colloids grouped into a single treatment. In 2013, Perel et al. published a meta-analysis in the Cochrane database (24) in critically ill patients of all causes. All types of colloids were grouped into one single treatment, while the comparison arm was balanced crystalloid and saline as a group. In 2013, another meta-analysis on HES (25), including patients with different causes were grouped as one. Our analyses used a more comprehensive classification of those resuscitation fluids according to the current knowledge (11) and separated patients' conditions, which yielded more clinically meaningful information.

Crystalloids: Balanced Crystalloids and Saline

Several meta-analyses and current sepsis guideline recommended that crystalloids are fluid of choice for resuscitation (24,26), but evidence revealed saline and balanced crystalloids are quite different in survival benefit and renal adverse events (12). This study found that among crystalloids, both survival benefit and renal events were better for balanced crystalloids than saline in sepsis and surgical patients, and the relationship was reversed in traumatic brain injury patients. Instead of considering crystalloids as a group, we should be more specific in recommending balanced crystalloids for sepsis and surgical patients, and saline for traumatic brain injury patients. However, both crystalloids required higher volume to achieve resuscitation goals. Therefore, we should carefully assess fluid responsiveness in hemodynamically unstable adults, based on passive leg raising followed by cardiac output measurement, to avoid fluid overload (27).

Albumin: Iso-oncotic and Hyperoncotic Albumin

The osmotic pressure in iso-oncotic solution was similar to plasma, and hyperoncotic solution was higher than plasma. Iso-oncotic albumin was designed for fluid resuscitation and has volume-sparing effect; hyperoncotic

albumin was used to maintain target serum albumin concentration, which helps to maintain effective volume by recruiting endogenous fluid¹¹. This study found that iso-oncotic albumin was associated with better survival benefit in sepsis patients who suffer hypovolemia due to extravascular fluid loss caused by increased vascular permeability. However, hyperoncotic albumin achieved better survival possibilities in surgical patients, whose blood loss were caused by uncorrected blood loss. This indicated that iso-oncotic albumin helps in providing more volume for sepsis resuscitation, while hyperoncotic albumin is more beneficial for uncorrected blood loss patients with normal vascular permeability. Besides, iso-oncotic albumin in hypotonic solution was associated with higher mortality rate in traumatic brain injury patients, and greater fluid volume and hypotonic solution may further raise intracranial pressure, leading to higher mortality (28).

Hydroxyethyl starch (HES): L-HES and H-HES

HES of higher molecular weight has been retracted from the market, but the HES of lower molecular weight is still in use in daily practice, especially in surgical or trauma patients. However, this study found that L-HES was associated with the highest mortality in sepsis, surgical, and trauma patients, and more renal adverse events and more transfusion volume was required during resuscitation period. However, for traumatic brain injury patients, L-HES and saline, both hypertonic solutions, were associated with better survival than hypotonic solution, including iso-oncotic albumin and balanced crystalloid.

Gelatin

Many review articles are opposed to gelatin use for fluid resuscitation due to the risk of anaphylaxis and renal injury, but those opinions were based on animal studies, case series, or RCTs designed for other purposes (11,29,30). Recent large RCTs reveal opposing results, in that gelatin is associated with a non-significant, lower mortality than balanced crystalloids and saline³. Our study using sequential NMA demonstrated that the sample path over balanced crystalloids vs. gelatin was flat and far from efficacy or futility boundary, which indicated that the evidence was largely insufficient (Figure 2).

Strengths and Limitations

The present NMA analyzed all outcomes from previous RCTs, especially on the fluid resuscitation volume, which has never been considered in previous meta-analyses. This study also categorized seven fluid types and patients' conditions and demonstrated that the benefit or harmful effects of the fluid types was largely dependent on the patient's condition. Our NMA still has some limitations: first, in sepsis trials (no. of cases=14,659), there was adequate evidence for balanced crystalloids, saline, and L-HES, but insufficient for gelatin. The confidence rating was low in surgical (n=3,871) and traumatic trials (n=5,076) because the sample size was inadequate and confidence intervals were wide. The confidence rating was very low for traumatic brain injury trials (n=1,970) because the direct and indirect evidence were inconsistent and sample sizes were inadequate. Secondly, the benefit or harm of gelatin could not be determined from current evidence. Renal adverse event was ranked best for gelatin in sepsis population (only one trial) but was worse in surgical population (only two trials). Survival benefit was also inconsistent between sepsis and surgical patients (Table). As very few trials included gelatin, the evidence on gelatin should be interpreted with caution.

Table 1
 Characteristics of the fluids assessed and qualitative summary from this network meta-analysis

Components	Plasma	Balanced crystalloid	Saline	Albumin (Iso-/Hyperoncotic)	L-HES	Gelatin
Osmolarity* (mOsm/kg)	291	Hypotonic (254-273)	Isotonic (286)	Hypotonic** (4%, 260; 5%, 250; 20%, 200; 25%, 250)	Isotonic to Hypertonic (283-304)	Isotonic to Hypertonic (274-301)
Na/Cl (mmol/l)	140/103	130-140/98-111	154/154	130-160/128-130	137-154/110-154	145-154/120-145
K/Ca (mmol/l)	40/4	4-5/2-2.7	0/0	<2/0	0-4/0-2.5	0-5.1/0-6.25
Conditions	Outcome	Balanced crystalloid	Saline	Albumin	L-HES	Gelatin
Sepsis	NMA results	Lowest mortality Lowest renal adverse events Lowest transfusion volume More fluid volume required	Higher mortality More fluid volume required	Lower mortality (Iso-oncotic). Least fluid volume required	Highest mortality More renal events More transfusion volume	
	Comments	Fluid of choice for sepsis.	Not recommend for sepsis.	Iso-oncotic albumin for sepsis patients with risk of fluid overload	Not recommend for sepsis.	Require further trials
Surgery	NMA results	Most fluid volume required Lower renal adverse events.	More fluid volume required More blood transfusion volume.	Lower mortality (Hyper-oncotic). Less fluid volume required Less renal adverse events. Less blood transfusion volume.	Highest mortality Less fluid volume required	Less fluid volume required
	Comments	More favored for surgery.	Less favored for surgery.	Recommended for surgery.	Not recommend for surgery.	Require further trials
Trauma	Mortality	Lower mortality	Lower mortality	Higher mortality. Less renal adverse events.	Higher mortality.	

		Less renal adverse events	More renal adverse events	Less transfusion volume.		
		Less transfusion volume	More transfusion volume			
		More fluid volume required				
	Comments	More favored for trauma.	Damage control resuscitation.	May consider blood products for resuscitation.		
Traumatic brain injury (TBI)	Mortality	Higher mortality.	Lower mortality.	Highest mortality (Iso-oncotic).	Lowest mortality.	
	Comments	Hypotonic solution was not suggested for TBI.	Favored for TBI.	Iso-oncotic albumin with hypotonic solution was not recommended for TBI.	May consider for TBI.	Require further trials

Conclusions

Among sepsis and surgical patients, balanced crystalloids and albumin attained lower mortality rates, fewer renal adverse events, and less red blood transfusion volume than did saline and L-HES. Balanced crystalloids required the highest fluid resuscitation volume than all the other fluid types. In traumatic brain injury patients, saline and L-HES improved mortality more than hypotonic solutions, including iso-oncotic albumin and balanced crystalloids.

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of supporting data

All data generated or analysed during this study are included in this published article and its supplementary files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CT and TT performed systemic reviews. CT, MY and MC analyzed data and did the sequential network meta-analysis. TT, MY and MC provided clinical aspects implications. CH and YK were major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

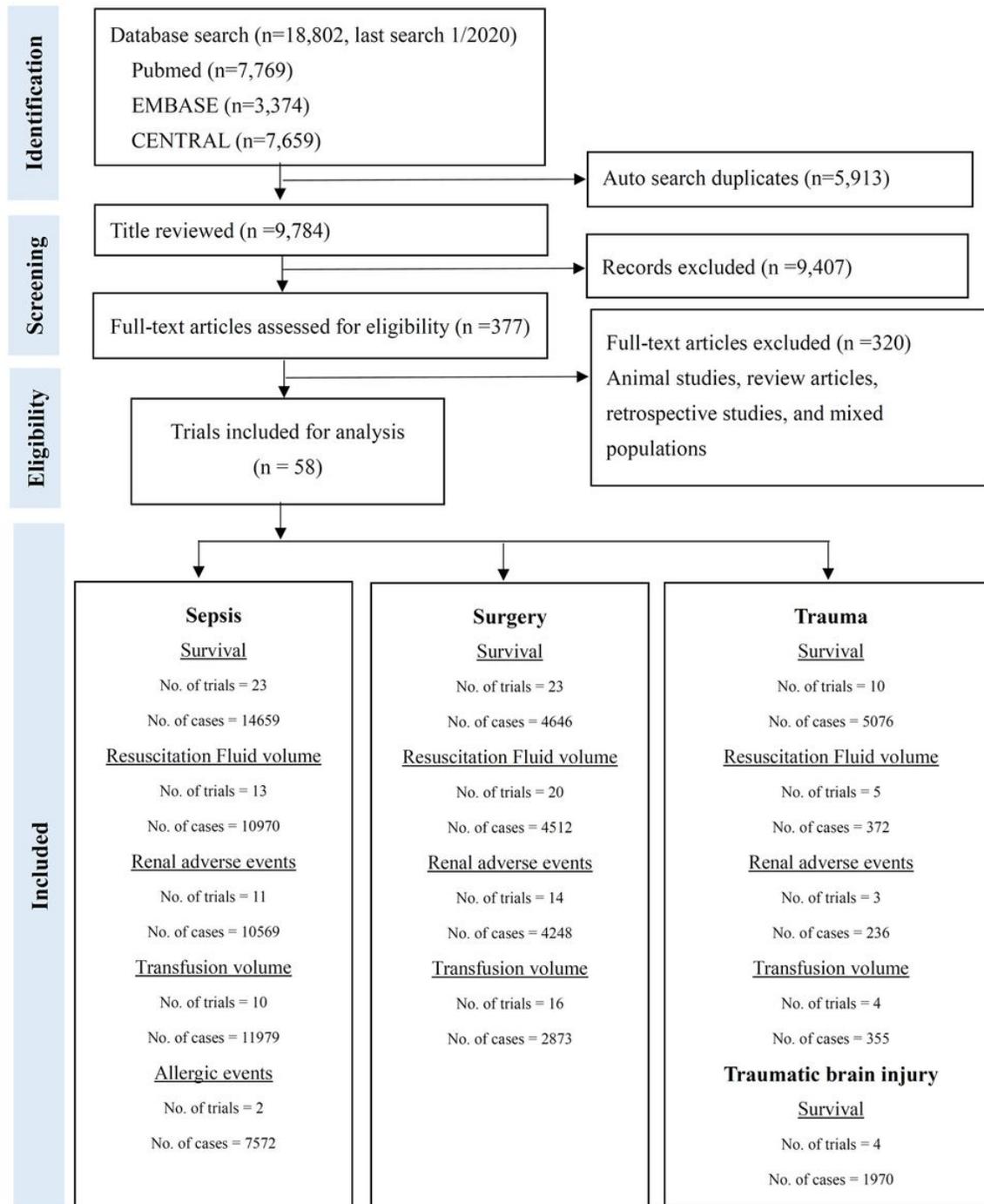


Figure 1

Summary of evidence search and selection

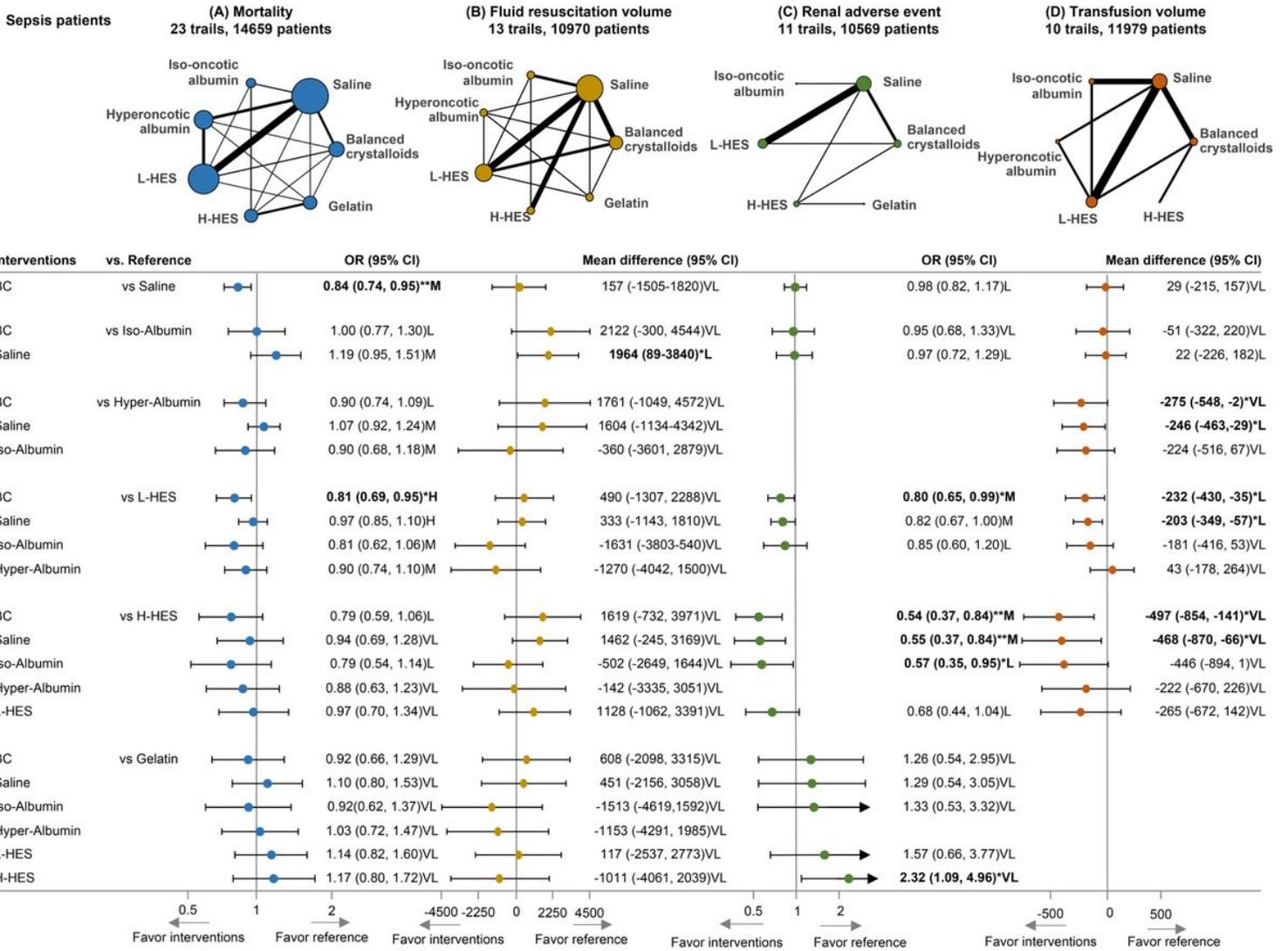


Figure 2

Network geometry and forest plot in sepsis patients (A) Mortality, (B) Fluid resuscitation amount, (C) Renal adverse events, (D) Transfusion amount. (OR, odds ratio; *, $p < 0.05$; **, $p < 0.01$; H, high confidence rating; M, moderate confident rating; L, low confidence rating; VL, very low confidence rating; BC, balanced crystalloids; Iso-albumin, iso-oncotic albumin; Hyper-albumin, hyperoncotic albumin; L-HES, low molecular weight hydroxyethyl starch; H-HES, high molecular weight hydroxyethyl starch)

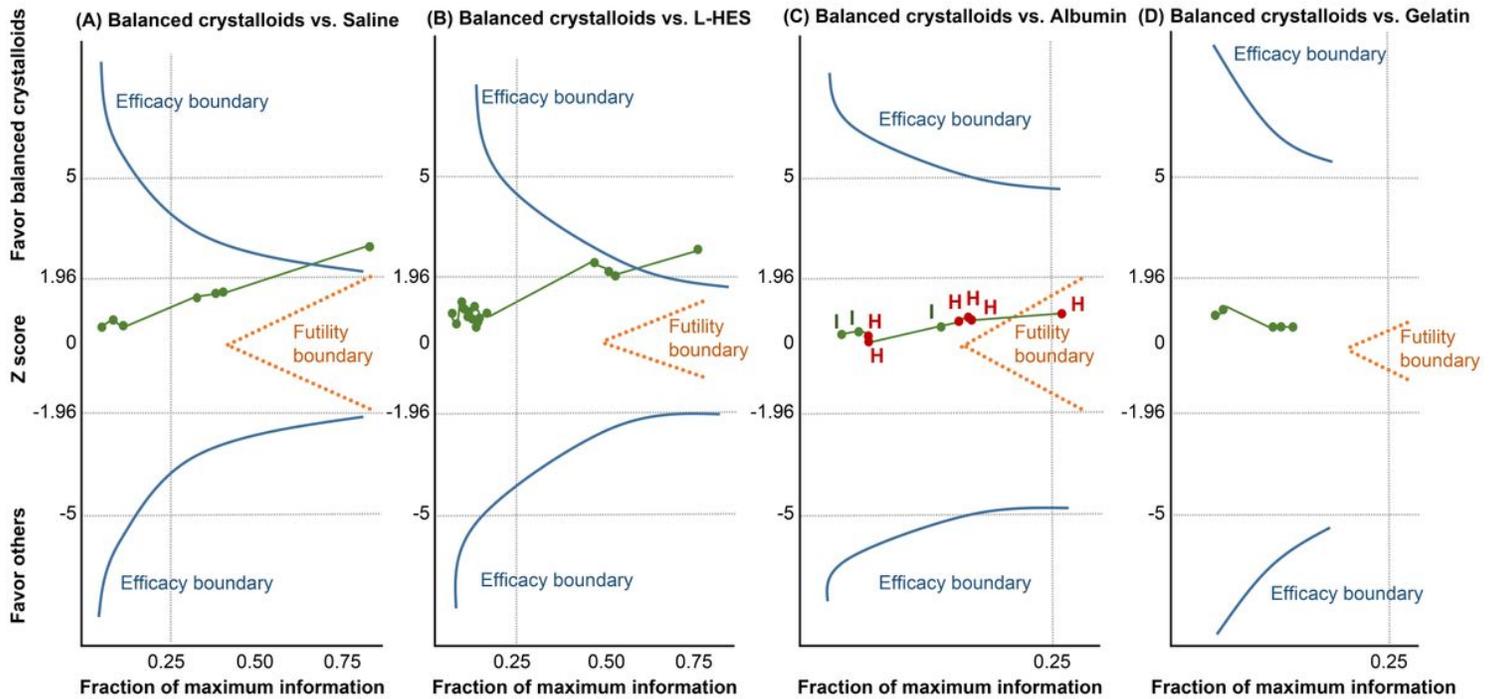


Figure 3

Sequential network meta-analyses (SNMA) over sepsis patient mortality analysis (A) Balanced crystalloids vs. saline, (B) balanced crystalloids vs. low molecular weight hydroxyethyl starch (L-HES), (C) balanced crystalloids vs. albumin, (D) balanced crystalloids vs. gelatin. Green dot represents trials ranging in years from left to right, grey line over 1.96 is the traditional efficacy limit, blue line represents the SNMA efficacy boundary, and orange line represents the futility boundary. (I, iso-oncotic albumin; H, hyperoncotic albumin)

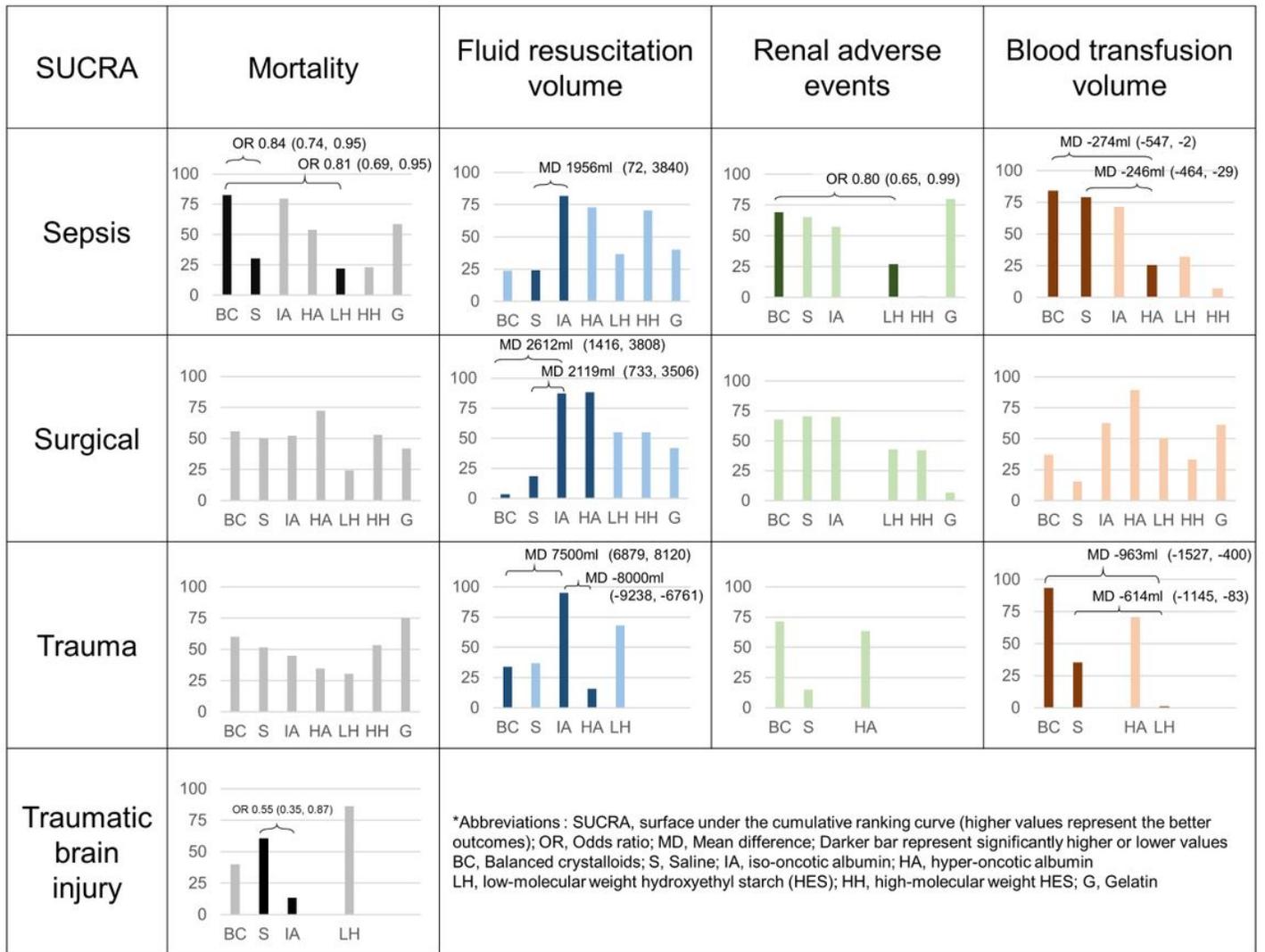


Figure 4

SUCRA result in sepsis, surgical and trauma patients

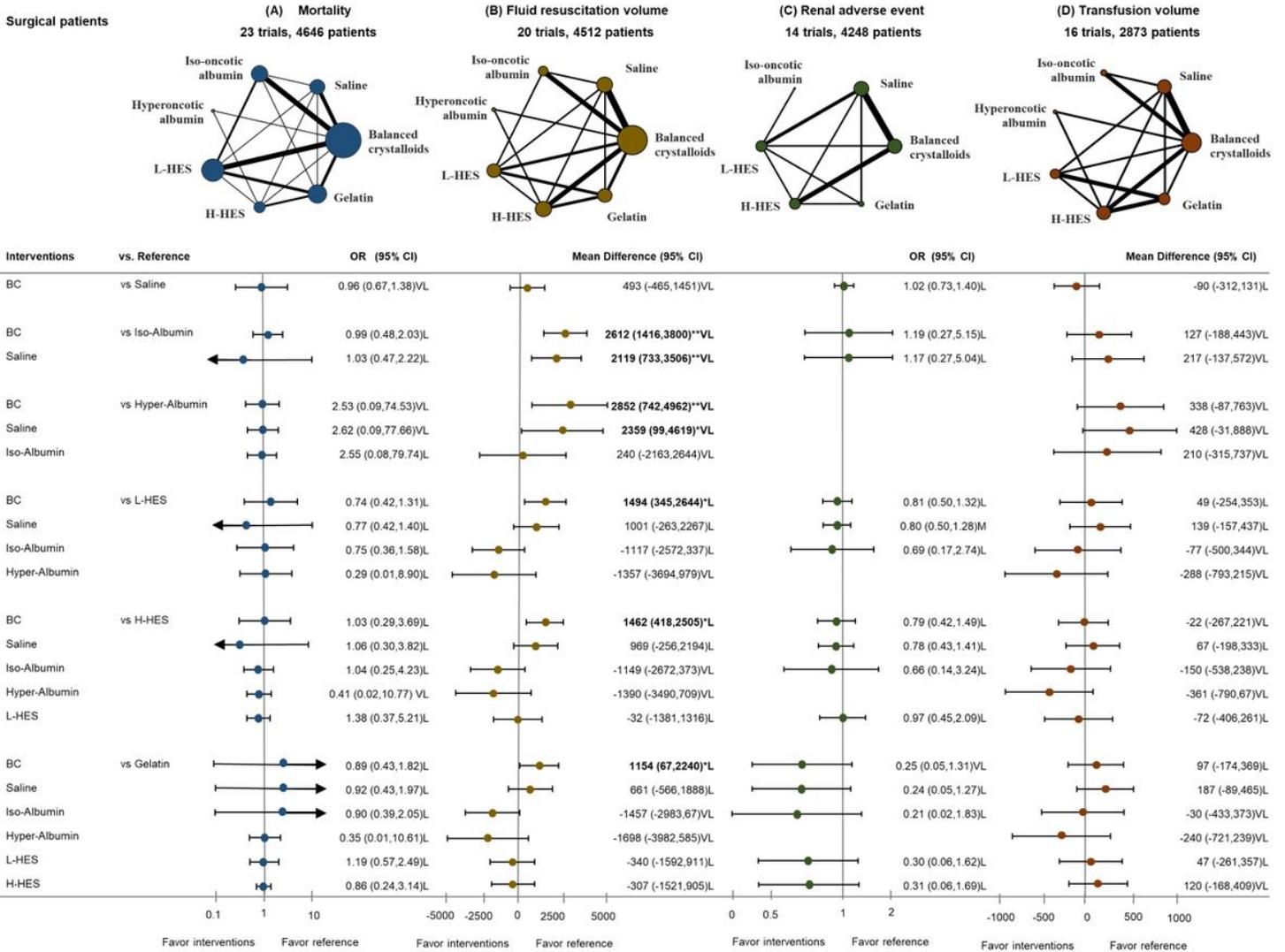


Figure 5

Network geometry and forest plot in surgical patients (A) Mortality, (B) Fluid resuscitation amount, (C) Renal adverse events, (D) Transfusion amount. (OR, odds ratio; *, $p < 0.05$; **, $p < 0.01$; H, high confidence rating; M, moderate confident rating; L, low confidence rating; VL, very low confidence rating; BC, balanced crystalloids; Iso-albumin, iso-oncotic albumin; Hyper-albumin, hyperoncotic albumin; L-HES, low molecular weight hydroxyethyl starch; H-HES, high molecular weight hydroxyethyl starch)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix.pdf](#)