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Perioperative Fluid Management Strategies in Major Surgery: A Stratified Meta-Analysis

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BACKGROUND: Both "liberal" and "goal-directed" (GD) therapy use a large amount of perioperative fluid, but they appear to have very different effects on perioperative outcomes. We sought to determine whether one fluid management strategy was superior to the others.
METHODS: We selected randomized controlled trials (RCTs) on the use of GD or restrictive versus liberal fluid therapy (LVR) in major adult surgery from MEDLINE, EMBASE, PubMed (1951 to April 2011), and Cochrane controlled trials register without language restrictions. Indirect comparison between the GD and LVR strata was performed.
RESULTS: A total of 3861 patients from 23 GD RCTs (median sample size = 90, interquartile range [IQR] 57 to 109) and 1160 patients from 12 LVR RCTs (median sample size = 80, IQR36 to 151) were considered. Both liberal and GD therapy used more fluid compared to their respective comparative arm, but their effects on outcomes were very different. Patients in the liberal group of the LVR stratum had a higher risk of pneumonia (risk ratio [RR] 2.2, 95% confidence interval [CI] 1.0 to 4.5), pulmonary edema (RR 3.8, 95% CI 1.1 to 13), and a longer hospital stay than those in the restrictive group (mean difference [MD] 2 days, 95% CI 0.5 to 3.4). Using GD therapy also resulted in a lower risk of pneumonia (RR 0.7, 95% CI 0.6 to 0.9) and renal complications (0.7, 95% CI 0.5 to 0.9), and a shorter length of hospital stay (MD 2 days, 95% CI 1 to 3) compared to not using GD therapy. Liberal fluid therapy was associated with an increased length of hospital stay (4 days, 95% CI 3.4 to 4.4), time to first bowel movement (2 days, 95% CI 1.3 to 2.3), and risk of pneumonia (RR ratio 3, 95% CI 1.8 to 4.8) compared to GD therapy.
CONCLUSION: Perioperative outcomes favored a GD therapy rather than liberal fluid therapy without hemodynamic goals. Whether GD therapy is superior to a restrictive fluid strategy remains uncertain. (Anesth Analg 2012;114:640–51)

Perioperative fluid therapy has been studied extensively, but the optimal strategy remains controversial and uncertain. Much of the current debate surrounds the type of fluids administered (colloid versus crystalloid), the total volume administered (restrictive versus liberal [LVR]), and whether the administration of fluids should be guided by hemodynamic goals (goal directed [GD] versus not goal directed).[1,2] Although guidelines have been produced to guide clinical practice, the evidence base for these recommendations remains questionable.[3] Evidence suggests that perioperative fluid balance has a substantial direct impact on outcomes.[4] Administering a large amount of IV fluid in the perioperative period is a common clinical practice. Although fluid loading may expand intravascular space, improve organ perfusion or tissue oxygenation,[5,6] and reduce minor postoperative complications in laparoscopic surgery,[7] excessive fluid may also increase some perioperative complications.[8]

More recently, fluid restriction has been used as part of fast-track surgery aiming at reducing length of stay compared to liberal use of fluid.[9] A systematic review has concluded that liberal use of fluid leading to a fluid overloaded state should be avoided in major surgery.[10] Establishing what exactly constitutes an excessive amount of fluid is difficult because the absolute amount of fluid administered varied substantially among the included trials, making its conclusion difficult to implement in clinical practice.[11]

Several meta-analyses have suggested that individualized GD therapy can reduce organ-specific complications in the acutely ill[12] and in those undergoing major surgery.[11,13,14] The increased amount of fluid administered to these patients to achieve the predefined hemodynamic goals was indeed very similar to the amount of fluid used for patients who were treated with a liberal fluid strategy in the LVR trials.[15] As such, the absolute amount of perioperative fluid administered may not be a major determinant of perioperative outcomes and titration of fluid according to a certain hemodynamic goal appears to be pivotal in improving perioperative outcomes.

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We hypothesized that liberal use of perioperative fluid therapy without hemodynamic goals is not equivalent to GD fluid therapy, and conducted a stratified meta-analysis to assess whether these 2 approaches of managing perioperative fluid therapy would have different effects on the outcomes of patients undergoing major surgery.

METHODS

Systematic Literature Search

We conducted a systematic literature search of MEDLINE (1950 to July 2009, via Ovid), EMBASE (1980 to July 2009, via Ovid), the Cochrane controlled trial register (second issue 2009), and PubMed (1951 to July 2009) with guidance from a research librarian. Each database was searched separately to improve the functionality and to allow mapping to relevant subject headings. The strategy used validated methods of the Cochrane Collaboration and the QUORUM statement.[16,17] Search terms included combinations of the Medical Subject Headings (MeSH): fluid therapy; surgical procedures, operative; perioperative care; postoperative complications; hemodynamics; colloids; isotonic solutions; crystalloid (or the closest relevant subject heading in each database), as well as combinations with the keywords: fluid*, *esophageal Doppler, goal-directed, Swan-Ganz, inotrop*, liberal, restrictive, pulse pressure variation, optimisation/optimization. Subject headings were then exploded to include all relevant subheadings but limited to humans, and there were no language restrictions. Two researchers (J.R. and S.C.) independently screened the articles by their titles and abstracts to identify eligible studies. All references of the identified articles were hand searched to avoid missing relevant trials. Any new study added also had its reference list manually searched. Finally, the gray literature was examined, comprising abstracts from the annual proceeding of the American Society of Anesthesiology, the European Society of Anaesthesiology, the Society of Cardiovascular Anesthesiologists, and the European Society of Intensive Care Medicine.[18] The preliminary search was repeated in April 2011 to avoid missing the latest randomized controlled trials (RCTs).

Study Selection, Data Extraction, and Quality Assessment

All published and unpublished studies that met all of the following criteria were eligible for inclusion: (a) RCT; (b) evaluation of different fluid amounts administered during and after surgery (standard/liberal fluid amount compared with restrictive) or evaluation of fluid administration strategies guided by conventional hemodynamic variables compared with GD fluid therapy. A therapy was considered GD therapy if it targeted a validated and objectively measurable hemodynamic variable, such as cardiac output, FTc on esophageal Doppler, or pulse pressure variation, other than conventional perioperative measures such as arterial blood pressure, urine output, or central venous pressure. (c) The study population underwent elective surgery or emergency surgery during which substantial systemic inflammatory response was not expected; and (d) the studies defined mortality, length of stay, or organ-specific complications as endpoints.

Studies using inotropic drugs as part of the fluid strategies aiming at optimizing a certain predefined hemodynamic goal were also included. Studies examining purely biochemical and laboratory endpoints, pediatric trials (age <18 years old), studies comparing different types of fluids, and studies comparing endoscopic against laparoscopic techniques were excluded. We also excluded trials that exclusively studied cardiac, neurosurgical, obstetric, trauma, burns, or critically ill patients. Two researchers (J.R. and S.C.) independently examined and recorded the trial characteristics and outcomes, using a predesigned data abstraction form. This abstraction form was used to record information regarding the quality of the trial such as allocation concealment, randomization, blinding, and inclusion and exclusion criteria. The grading of allocation concealment was based on the Cochrane approach, that is, adequate, uncertain, or clearly inadequate. Authors of the primary studies were contacted, when possible, if information was missing or unclear. Quality assessment was performed using previously validated scoring systems.[19,20]

Definition of Study Groups and Outcome Parameters

Studies were grouped into 2 strata, standard therapy with hemodynamic goals versus GD [GD stratum] and liberal versus restrictive [LVR stratum], in this meta-analysis. The primary outcome was postoperative mortality. Secondary outcomes were organ-specific complications, recovery of bowel function (time to first flatus, time to first bowel movement, and return to oral diet), and length of hospital stay. The organ-specific complications assessed included cardiac (cardiac failure, myocardial infarction, and arrhythmia), pulmonary (respiratory failure, pulmonary edema, pneumonia, and pleural effusion), and incidence of wound infections and gastrointestinal complications (bowel obstruction, anastomotic leak, ileus). In contrast to previous studies,[11] we did not create an amalgamated or composite end-point of all cause-morbidity comprising the total numbers of patients in each study who experienced at least 1 complication to avoid the problem of double-counting patients who had more than 1 complication. In studies that compared 2 different strategies of fluid therapy (e.g., GD and liberal groups) with a restrictive group, we included both comparisons as individual studies.

Subgroup analysis was performed for GD stratum to determine whether the modality of GD therapy (pulmonary artery catheter, esophageal Doppler, preload responsiveness, and others) influenced the observed differences in outcome. When information relating to continuous variables was supplied as median and range, we used a validated method to estimate the mean and SD.[21] To compare the volumes of fluids administered between trials, we multiplied any colloidal solution administered by 1.4 to achieve an approximation of hemodynamic equivalence.[22] We included both intraoperative and postoperative fluids, where possible, in this study.

Statistical Analysis

Difference in continuous outcomes is expressed as the mean difference [MD], using a random-effects inverse variance approach. Difference in categorical outcomes is expressed as risk ratio [RR], using the Mantel–Haenszel random-effects method.[23,24] The presence of heterogeneity between trials was assessed by the χ^2 statistics and the

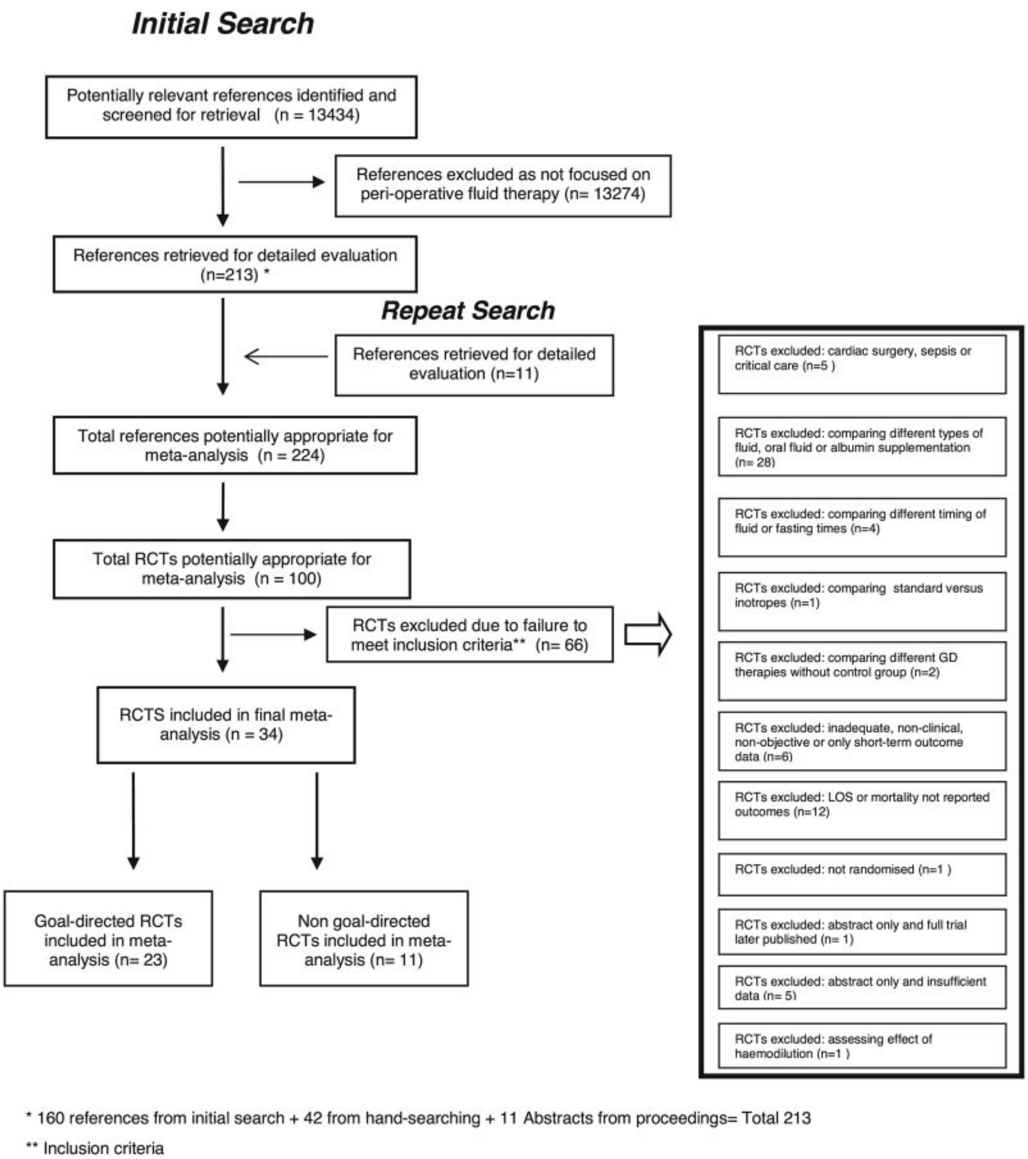

Figure 1. Flow diagram demonstrating the selection and exclusion of studies for the meta-analysis.

extent of inconsistency between the trials due to differences in case mix, study designs, and treatment protocols was assessed by I^2 statistics.[25] An I^2 >40% was regarded as having significant heterogeneity in this study. Meta-regression was not used because of a relatively low event rate in the primary outcome in most of the pooled studies. All P values were 2-sided, a P value <0.05 was taken as significant, and all analyses were conducted by Review Manager for Windows (version 5.0.24, Cochrane Collaboration, Oxford, UK).

The overall estimates of the 2 strata of trials (LVR stratum and GD stratum) were compared to assess whether the outcomes were different when both strategies used a large amount of perioperative fluid compared to their respective comparative arm in the trials.[26] Their relative difference was reported as relative risk ratio (RRR).

Sensitivity analyses were conducted by restricting the analysis to trials that had both double-blind and adequate allocation concealment, or trials that examined patients undergoing open abdominal surgery only. Publication bias was assessed by funnel plot using the risk of pneumonia as an end-point. "Trim and fill" method (Comprehensive Meta Analysis, version 2.2.034, 2006, Biostat, Englewood, NJ) was used to adjust for any publication bias.[27]

RESULTS

Characteristics of the Included Studies

Twenty-four (23 published RCTs and 1 conference abstract) GD therapy studies including 3861 patients (median sample size = 90, interquartile range [IQR] 57 to 109) from 10 countries were identified and subject to meta-analysis[28–50] (GD stratum) (Fig. 1). One study that was retracted was excluded.[51] Twelve studies on LVR fluid therapy involving 1160 patients (median sample size = 80, [IQR] 36 to 151) from 9 countries were also identified and subject to meta-analysis[8,52–62] (LVR stratum).

Table 1. Details of Studies Subjected to Meta-Analysis

Author, country, journal, year	Fluid management strategy	Type of surgery	Elective/emergency	Risk category
Benes et al.[29]	GD	Major abdominal	Elective	High risk (ASA 2–4)
Berlauk et al., USA, Ann Surg 1991[30]	GD	Vein bypass for limb salvage	Elective	High risk (vasculopaths)
Buettner et al., Germany, BJA 2008[32]	GD	Major bowel resection	Elective	High risk (ASA 1–3)
Conway et al., UK, Anaesthesia 2002[33]	GD	Major bowel resection	Elective	High risk (ASA 1–3)
Donati et al., Italy, Chest 2007[34]	GD	Extensive abdominal	Elective	High risk (ASA 2–4)
Gan et al., USA, Anesthesiology 2002[35]	GD	Major abdominal (general/gyne/urology)	Elective	High risk (ASA 1–3)
Harten et al., Scotland, Int J Surgery 2008[36]	GD	Major abdominal	Emergency	High risk (ASA 1–4)
Senagore et al., USA, Dis Colon Rectum 2009[42]	GD	Laparoscopic segmental colectomy	Elective	High risk (ASA 1–3)
Shoemaker et al., USA, Chest 1988[43]	GD	High-risk surgical operations	Both	High risk
WenKui et al., China, Surgery 2010[48]	GD	GI operations for malignancy	Elective	High risk (ASA 1–3)
Bonazzi et al., Italy, Eur J Vasc Surg 2002[31]	GD	Infrarenal AAA repair	Elective	High risk
Ramsingh et al., California, ASA Annual Meeting 2010 (abstract)[40]	GD	Major abdominal	Elective	Low–moderate risk
Brandstrup et al., Denmark, Annals of Surgery 2003[8]	LVR	Colorectal	Elective	High risk (ASA 1–3)
Gonzalez-Fajardo et al., Spain, Eur J Endovasc Surg 2009[52]	LVR	Infrarenal graft repair	Elective	High risk (ASA 1–3)
Holte et al., Denmark, Br J Anaesth 2007[53]	LVR	Colon	Elective	High risk (ASA 1–3)
Holte et al., Denmark, Anesth Analg 2007[54]	LVR	Knee arthroplasty	Elective	Low risk (ASA 1–3)
Hubner[62]	LVR	Colon resection	Elective	High risk (ASA 1–4)
Kabon et al., USA/Austria/Switzerland, Anesth Analg 2005[55]	LVR	Colon resection	Elective	High risk (ASA 1–3)
Lobo et al., UK, Lancet 2002[56]	LVR	Hemicolectomy or sigmoidectomy for carcinoma	Elective	High risk
McArdle et al., Northern Ireland, Ann Surg 2009[58]	LVR	Open infrarenal AAA repair	Elective	High risk
Vermeulen, The Netherlands, Trials, 2009[61]	LVR	Elective general abdominal surgery	Elective	High risk (ASA 1–3)
Nisanevich, Israel, Anaesthesiology, 2005[60]	LVR	Major elective abdominal surgery	Elective	High risk (ASA 1–3)
Muller, Switzerland, Gastroenterology, 2009[59]	LVR	Open elective colonic resection with a primary anastamosis	Elective	High risk (ASA 1–3)
MacKay, UK, Br J Surg, 2006[57]	LVR	Elective colorectal resection with primary anastamosis	Elective	High risk (ASA 1–4)
Sandham, Canada, N Engl J Med, 2003[41]	GD	Urgent or elective major abdominal, thoracic, vascular, or hip fracture surgery	Urgent and elective	High risk (ASA 3–4)
Pearse, UK, Crit Care, 2005[39]	GD	Major general surgery at high risk of postoperative complications	Urgent and elective	High risk (ASA 3 or 4)
Noblett, UK, Br J Surg, 2006[38]	GD	Elective colorectal resection	Elective	High risk
Sinclair, UK, BMJ, 1997[44]	GD	Emergency femoral neck fracture surgery	Emergency	High risk (ASA 2–3)
Szakmany, Hungary, Intens Care Med, 2005[45]	GD	Elective esphagectomy, total gastrectomy, pancreatectomy, or liver resection due to tumor removal	Elective	High risk
Venn, UK, Br J Anaesth, 2002[46]	GD	Proximal femoral fracture repair under GA	Urgent	High risk (ASA 2–4)
Wakeling, UK, Br J Anaesth, 2005[47]	GD	Elective or semielective large bowel surgery	Elective	High risk
Lopes, Brazil, Crit Care, 2007[37]	GD	Elective high-risk surgery (GI/hepatobiliary/urological)	Elective	High risk (ASA 1–3)
Bender, USA, Ann Surg, 1997[28]	GD	Elective vascular surgery	Elective	High risk
Wilson, UK, BMJ, 1999[49]	GD	Major elective surgery	Elective	High risk
Ziegler, USA, Surgery, 1997[50]	GD	Elective aortic reconstruction or limb salvage procedures	Elective	High risk

LVR = liberal versus restrictive strategies; GD = goal directed versus not goal directed; GA = general anesthesia; GI = gastrointestinal; AAA = abdominal aortic aneurysm; ASA = American Society of Anesthesiology physical status classification system.

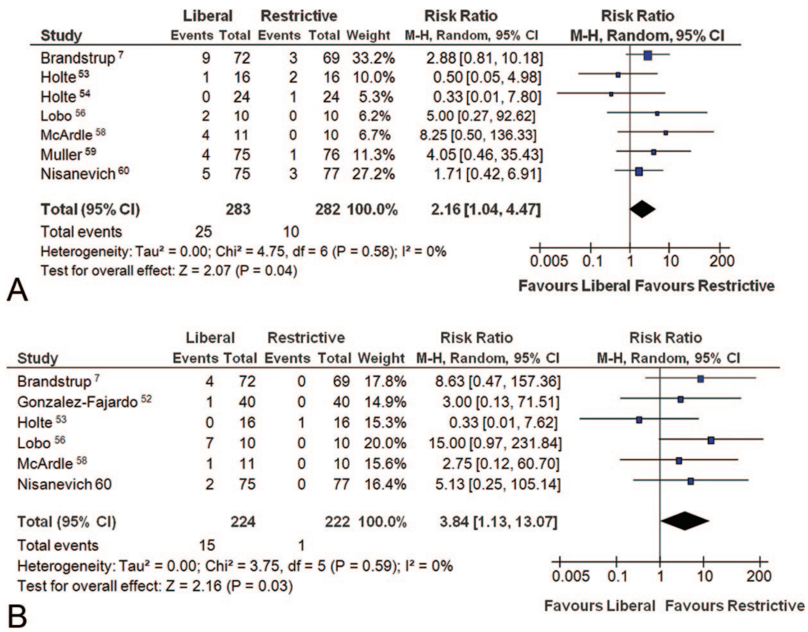

Figure 2. The influence of restrictive versus liberal fluid regimens on the risk of (A) pneumonia and (B) pulmonary edema.

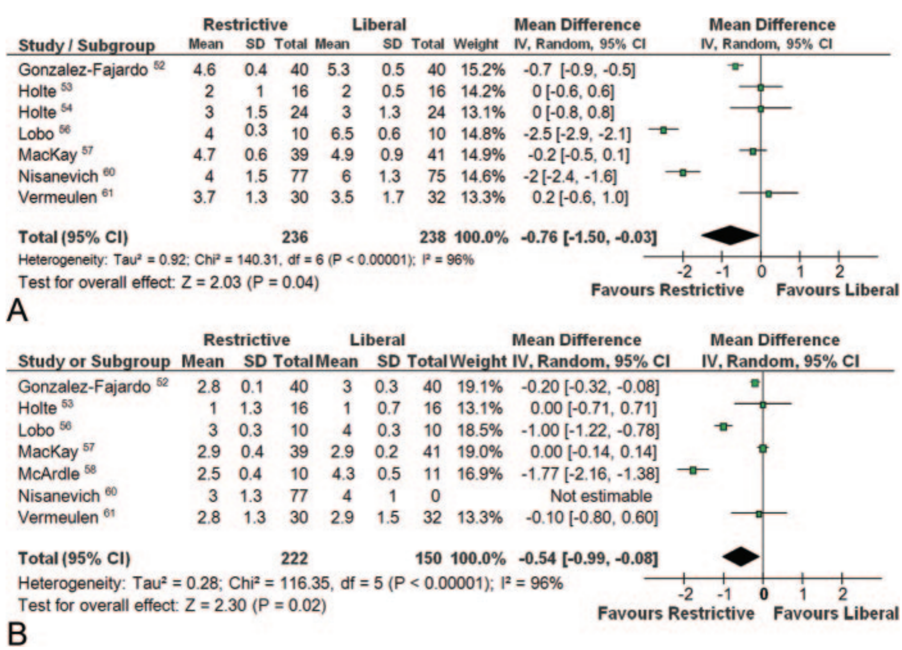

Figure 3. The influence of restrictive versus liberal fluid regimens on (A) time to first bowel movement (days) and (B) time to passage of first flatus (days).

Seven GD trials[38,42,44,46,47,49,51] and 6 non-GD trials[8,53–55,60,61] were double-blind and had adequate allocation concealment. The median Jadad scores of all trials and GD trials were 3 (IQR 2 to 4) and 3 (IQR 2 to 5), respectively. The characteristics of the studies and their interventions are summarized in Table 1.

Outcomes

LVR Stratum

Patients in the liberal groups received a larger amount of intraoperative and total perioperative fluid than patients in the restrictive groups, predominantly due to a larger amount of intraoperative crystalloid (MD 1570 mL, 95% confidence interval [CI] 986 to 2154). Both pneumonia (RR 2.2, 95% CI 1.0 to 4.5, $P = 0.04$) and pulmonary edema (RR 3.8, 95% CI 1.1 to 13, $P = 0.03$) were more common in the liberal groups (Figs. 2A and 2B). The time taken to first bowel movement (MD 0.8 day, 95% CI 0.1 to 1.5), passage of flatus (MD 0.5 day, 95% CI 0.1 to 1) (Figs. 3A and 3B), and length of hospital stay (MD 2 days, 95% CI 0.5 to 3.4) were also longer in the liberal group (Fig. 4A), although there was significant heterogeneity in the latter outcome ($I^2 = 94\%$). The incidences of wound infection, myocardial infarction, renal complications, wound dehiscence, and mortality (RR 1.7, 95% CI 0.5 to 5.6) were not different between patients who were treated with liberal and restrictive therapy (Fig. 5A).

GD Stratum

Patients in the GD group also received a larger amount of intraoperative and total perioperative fluid than patients in

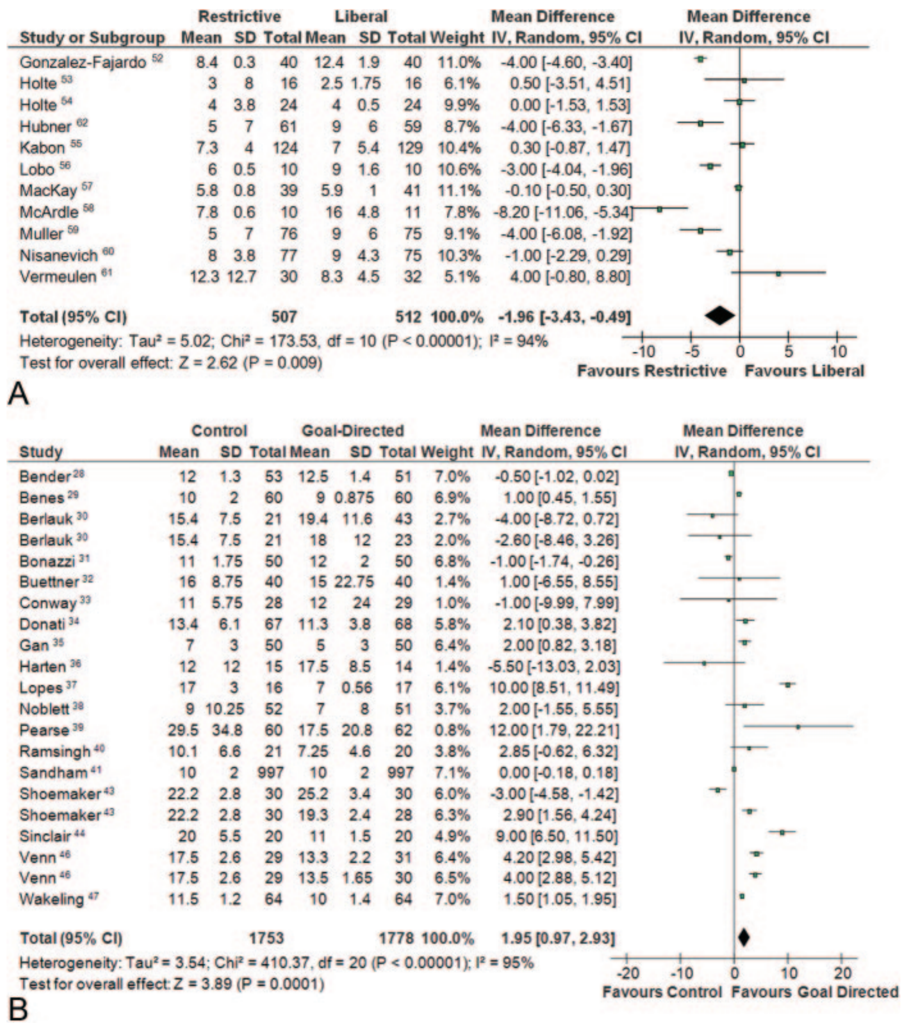

Figure 4. The effect of (A) restrictive versus liberal fluid regimens and (B) goal-directed strategies on length of stay (days).

the non-goal-directed group, and this was accounted for by a larger amount of intraoperative colloid (MD 467 mL, 95% CI 331 to 603). There was significant heterogeneity in the length of hospital stay between the included trials, and when pooled, patients in the GD group had a shorter hospital stay than those managed without using specific hemodynamic goals (MD 2 days, 95% CI 1 to 3) (Fig. 4b). Pneumonia (RR 0.7, 95% CI 0.6 to 0.9) and renal complications (RR 0.7, 95% CI 0.5 to 0.9) were also less common in the GD groups (Figs. 6A and 6B), and the time taken to first bowel movement (MD 1 day, 95% CI 0.8 to 1.2) and resumption of normal diet (MD 1.4 days, 95% CI 0.8 to 1.9) was also shorter after GD therapy (Figs. 7A and 7B). The incidence of noninfective pulmonary complications, wound infection, sepsis, myocardial infarction, pulmonary edema, arrhythmias, transfusion requirements, anastomotic leak, or mortality (RR 1.1, 95% CI 0.9 to 1.4) were similar between the 2 groups (Fig. 5B). There were no differences in most outcomes, including risk of acute renal failure, between studies that used different hemodynamic goals of GD therapy (Fig. 8).

Comparing the GD and LVR Strata

When the 2 strata of trials were compared indirectly, liberal use of perioperative fluid without using any hemodynamic goal was associated with an increased length of hospital stay (MD 4 days, 95% CI 3.4 to 4.4), time to first bowel movement (MD 2 days, 95% CI 1.3 to 2.3), and risk of pneumonia (RRR 3, 95% CI 1.8 to 4.8) compared to using GD therapy. Mortality (RRR 2, 95% CI 0.6 to 6.5), wound infection (RRR 2, 95% CI 0.8 to 3.9), and renal failure (RRR 0.8, 95% CI 0.2 to 3.2) were, however, not significantly different between liberal and GD therapy. Restricting the analysis to trials studying open abdominal procedures only did not alter the results significantly (mortality: RRR 3, 95% CI 0.6 to 18; acute renal failure: RRR 1, 95% CI 0.1 to 18).

Sensitivity Analysis and Publication Bias

Restricting the analysis of the LVR stratum to higher-quality studies did not change the mortality results (RR 0.6, 95% CI 0.1 to 15) or wound infection (RR1.1, 95% CI 0.4, 2.8). Difference in hospital stay did, however, become insignificant after excluding lower-quality studies (MD −0.1 day, 95% CI −1 to 0.9; $P = 0.9$).

Restricting the analysis of the GD stratum to higher-quality studies did not change the results of GD fluid therapy on mortality (RR 0.7, 95% CI 0.3 to 1.7) or wound infection (RR1.1, 95% CI 0.3 to 4.7) compared to the non-GD therapy. Hospital stay remained significantly shorter for those patients who received GD fluid therapy (MD −0.1

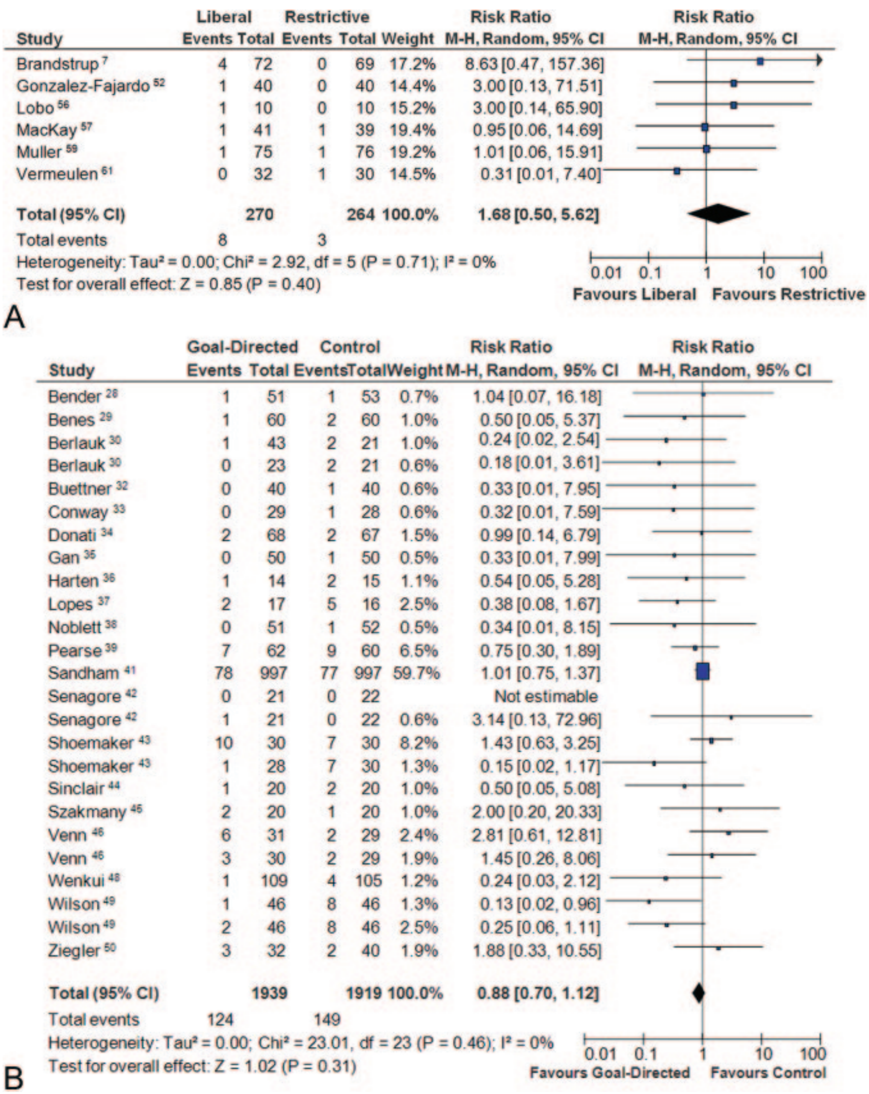

Figure 5. The effect of (A) restrictive versus liberal fluid regimens and (B) goal-directed strategies on mortality.

day, 95% CI −1 to 0.9; $P = 0.9$) compared to non-GD fluid therapy.

Using pneumonia as an end-point, the funnel plot suggests that there may be a small publication bias favoring small positive studies using GD therapy (Fig. 9), but the beneficial effect of GD therapy on risk of pneumonia remained unchanged after the trim and fill adjustment (RR 0.7, 95% CI 0.5 to 0.9, $P = 0.026$). Publication bias was not apparent among the LVR studies, and the risk of pneumonia remained unchanged after the trim and fill adjustment, favoring restricted fluid therapy (RR 0.43, 95% CI 0.2 to 0.9).

DISCUSSION

The principal findings of this meta-analysis were that (i) GD fluid therapy reduced renal complications, pneumonia, time to first bowel movement, resumption of normal diet and length of stay compared to non-GD therapy; (ii) a restrictive fluid strategy reduced the incidence of pulmonary edema and pneumonia, time to first bowel movement, and the length of stay compared to liberal fluid therapy without using hemodynamic goals; (iii) both patients randomized to have GD fluid strategy and liberal fluid therapy without hemodynamic goals received more perioperative fluid than those managed with non-GD therapy and a restrictive fluid strategy, respectively; (iv) although both GD and liberal fluid therapy both used a large amount of perioperative fluid, their effects on perioperative outcomes were different; patients in the GD groups had a shorter length of stay, time to recovery of gastrointestinal function, and a lower incidence of pneumonia compared to those in the liberal groups; (v) no specific fluid management strategy was associated with an improvement in mortality; and (vi) significant heterogeneity in continuous outcome was observed, but publication bias was not apparent.

The cardinal discrepancy in perioperative outcomes between studies using GD and liberal fluid strategies requires careful consideration. In the first instance, our results suggest that some form of GD therapy may be better than liberal use of IV fluid without hemodynamic goals. Restricting our analysis to higher-quality studies did not change the positive association between GD therapy and improvement in perioperative outcomes.

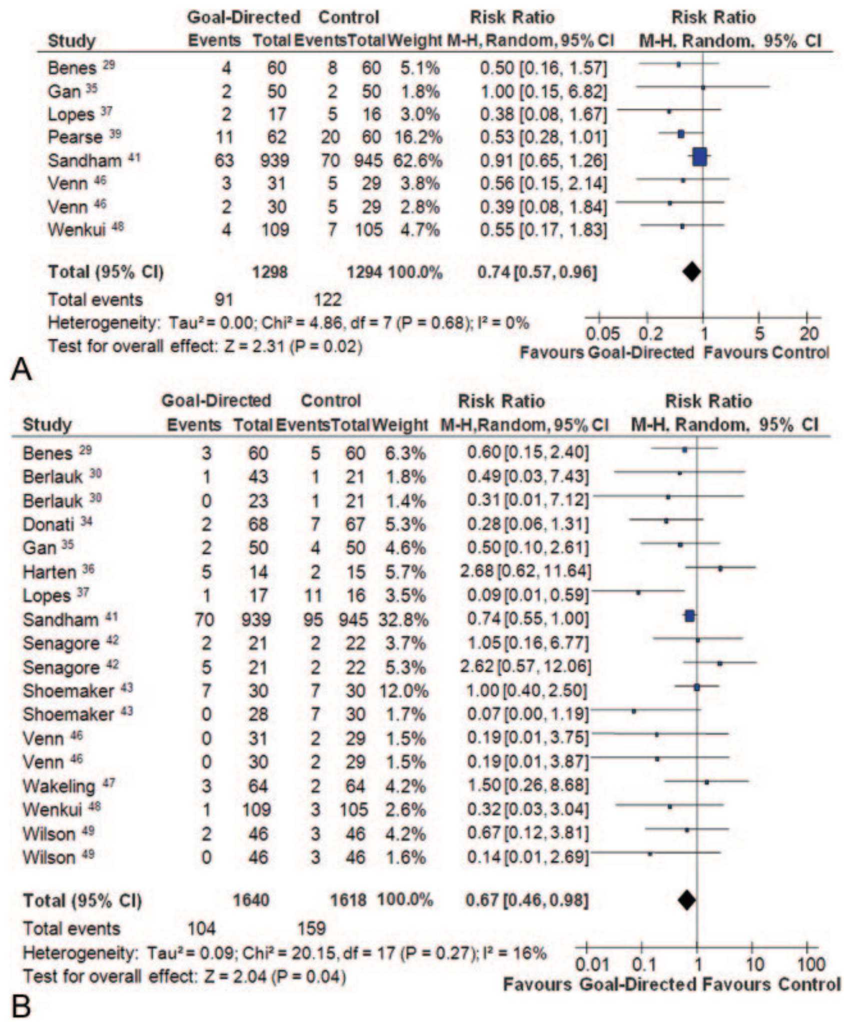

Figure 6. The influence of goal-directed versus non-goal-directed fluid regimens on (A) the risk of pneumonia and (B) renal complications.

This result is, perhaps, not surprising, because individualized fluid therapy according to the clinical condition of the patients should, at least theoretically, avoid the problem of excessive resuscitation or underresuscitation. It may also be that GD monitoring gives information on fluid responsiveness, hence indicating when a fluid bolus is needed for organ perfusion,[63] as opposed to the risk of fluid accumulation from unnecessary excessive fluid.[64] The ability to avoid both hyper- and hypovolemia is challenging,[10,65] and our limited data did not suggest that one form of hemodynamic goal is better than the other.

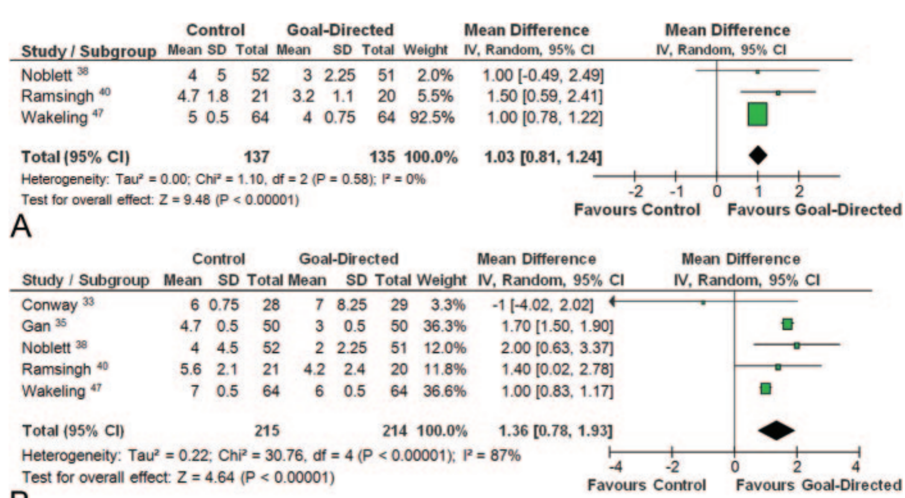

Figure 7. The influence of goal-directed versus non-goal-directed fluid regimens on (A) time to first bowel movement (days) and (B) time to resumption of normal diet (days).

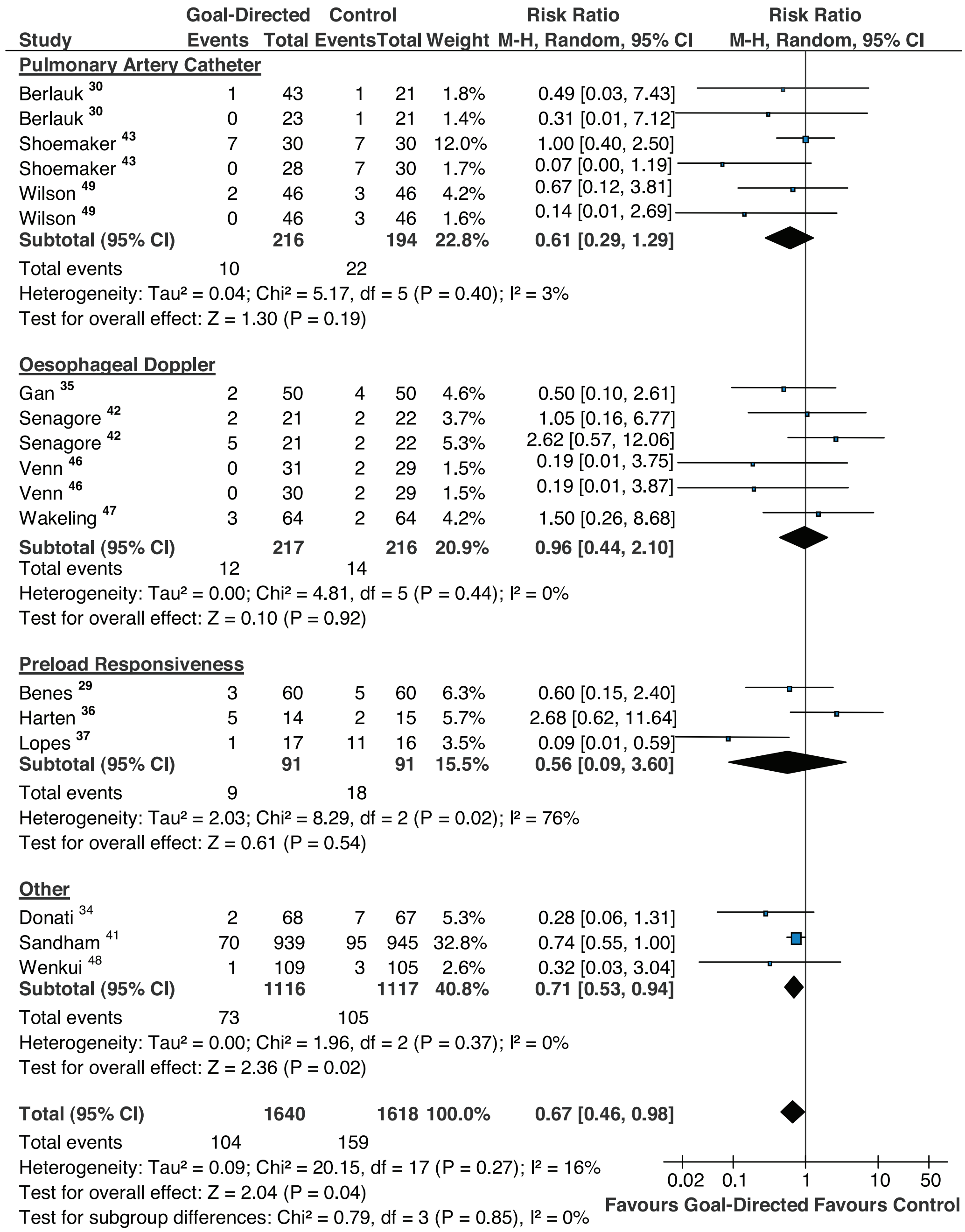

Figure 8. The influence of individual goal-directed modalities on renal outcome. Patients in the liberal group of the restrictive versus liberal (LVR) stratum were incorporated into the goal-directed side of the analysis because of their comparable volume of perioperative fluid administered.

Second, studies that used GD strategies administered a larger amount of colloid, and liberal strategies used more crystalloid fluids. Although a large RCT on critically ill patients has shown that outcomes after using crystalloid were comparable to albumin-based colloid fluid,[22] a similar conclusion cannot be reached for patients undergoing major surgery, because trials comparing colloids and crystalloids on perioperative patients are all underpowered to detect clinically important benefits and risks. Third, although our results showed that GD therapy may be superior to not using hemodynamic goals by simply using a liberal amount of fluids, we must interpret these results with caution because the primary outcome, hospital mortality, was not different despite reduced complications.

This study has several methodological strengths. First, previous meta-analyses have restricted their focus to a specific GD modality or surgical subgroup. Meta-analyses of the use of esophageal Doppler as a component of GD therapy has suggested an improvement in outcomes when applied to a subgroup of patients undergoing colonic surgery[13,66–68] or a broader group of patients undergoing major elective, cardiac, or trauma surgery.[69] Our results

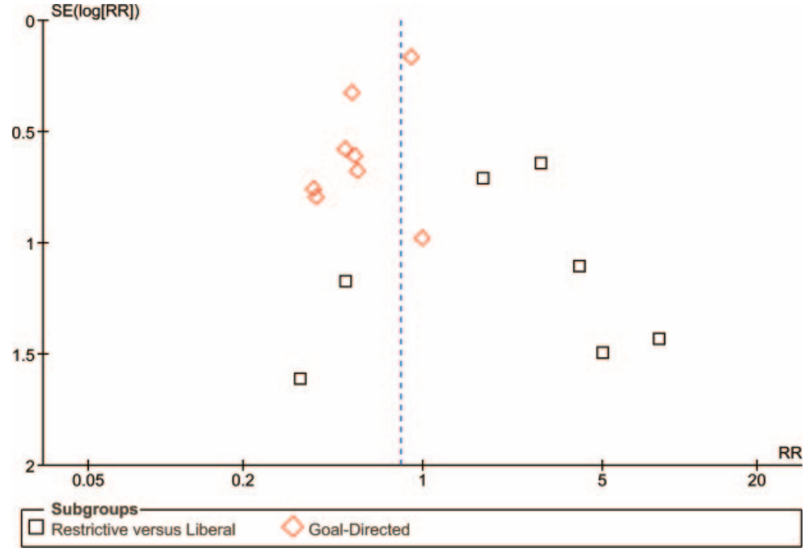

Figure 9. Funnel plot of risk of pneumonia according to fluid strategy comparison.

differ from these previous meta-analyses. We sought to exclude studies on procedures (e.g., trauma, cardiac, sepsis) that would induce a very strong inflammatory response than that observed in elective or emergent surgical procedure. A dramatic perturbation of hemodynamic physiology is an important confounder that may undermine meta-analysis of this intervention.[10] Second, we have included data from the gray literature, used a conservative random-effects model analysis, and did not amalgamate the total numbers of complications as a composite end-point to reduce the risk of double-counting and false positive results.[70] Third, we have included studies that used any form of advanced hemodynamic monitoring as part of the GD therapy. Apart from a slightly more precise signal in the reduction of length of hospital stay with the use of esophageal Doppler, we found that all forms of hemodynamic monitoring appeared to be equally effective in the reductions in perioperative complications.

This meta-analysis also has some limitations. First, there was significant heterogeneity in the continuous outcomes. This is not unexpected because, in general, continuous outcomes are associated with a larger variance. Furthermore, heterogeneity in the continuous outcomes can also be explained by the differences in case mix, standard management of the patients, and the trial design among the included studies. For example, of the GD trials examined, the interventions began preoperatively in 7 trials, intraoperatively in 14 and postoperatively in 2 trials. Second, although many promising trials were initially identified, most were excluded for failing to meet the strict inclusion criteria of this study. Furthermore, many trials were single-center trials, and the total sample size may still have been too small to detect a clinically important difference in mortality. With 3800 patients, the sample size only had a power of 72% to detect a reduction in hospital mortality from 2% to 1%. Third, the types of fluid used between the 2 strata of studies were different. GD therapy trials used predominantly colloids, whereas LVR trials used predominantly crystalloids. Concern has been expressed in relation to the potential toxicity of certain colloids,[7] with some authorities advising against their use outside of the context of clinical trials.[71] Finally, we have assumed that the large amount of fluid used in the GD therapy and liberal therapy was the only common denominator between the 2 strata of studies so that they could be compared indirectly. Such extrapolations will have some inherent limitations, and the RRRs obtained should be interpreted as hypothesis generating.

In summary, our study has shown that both GD fluid therapy and liberal use of fluid without using hemodynamic goals used a large amount of perioperative fluid, but the perioperative outcomes after such therapies differed significantly, favoring the use of specific hemodynamic goals to titrate fluid therapy. With the limited data available, significant uncertainty remains concerning the relative benefits of GD and restrictive fluid strategies, or the superiority of one modality of hemodynamic monitoring over another. An adequately powered factorial-designed RCT of GD versus non-GD and liberal versus restrictive fluid strategies, controlling for specific subgroups of surgery, will be needed to resolve the controversial issue of optimal perioperative fluid management strategy.

DISCLOSURES

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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Tomas Corcoran has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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