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*Original Article*

# Goal-directed fluid management reduces gastrointestinal complications after abdominal surgery: a meta-analysis

Hai Guo, Jianjiang Wu, Haiping Ma, Xiaowen Dai, Hong Zheng

*Department of Anesthesiology, The First Affiliated Hospital of Xinjiang Medical University, No. 137, Liyushan Street, Urumqi 830011, China*

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**Abstract:** Aim: The present study aimed to determine whether goal-directed fluid management reduces incidence of post-surgery gastrointestinal complications and mortality in patients undergoing abdominal surgeries. Methods: Cochrane Central Register of Controlled Trials, MEDLINE, CINAHL, ISI, and Web of Science were searched for relevant randomized controlled trials. For qualitative data, relative risk (RR) was used to report effect sizes. For quantitative data, effect sizes were assessed using the mean difference. Results are presented as effect sizes and 95% confidence intervals (CI). Results: Incidence of gastrointestinal complications after goal-directed fluid management was lower than after standard fluid management (RR 0.48; 95% CI 0.33 to 0.69). Mortality rates at 30-day follow-ups were not significantly different between these two management methods. Concerning mortality rates within 60 days, goal-directed fluid management had a far lower mortality rate than standard fluid management (RR 0.32, 95% CI 0.11 to 0.93). Additionally, participants receiving goal-directed fluid management had significantly more volume of colloid solution than those with standard fluid management (MD 199.58, 95% CI 65.51 to 333.66, 10 studies). However, there were no significant differences in volume of crystalloid solution. Moreover, incidence of adverse events after goal-directed fluid management was significantly lower than after standard (routine) fluid management (RR 0.66; 95% CI 0.50 to 0.88). Conclusion: Goal-directed fluid management is an effective therapy for the reduction of GI complications and mortality within 60 days. Additionally, goal-directed fluid management can decrease incidence of postoperative adverse events.

**Keywords:** Goal-directed fluid management, gastrointestinal complications, major abdominal surgery, meta-analysis

## Introduction

Gastrointestinal (GI) complications are very common after abdominal surgery, leading to prolonged hospital stays in 50% of patients [1, 2]. Postoperative GI complications mainly present as abdominal distension, intolerance of enteral diet (either by mouth or feeding tube), nausea, vomiting, postoperative ileus, anastomotic leakage, and wound infections [3]. Fluid therapy is an important measure, stabilizing vital signs and avoiding tissue hypoperfusion during the perioperative period, especially in patients undergoing GI surgery [4]. Intraoperative tissue hypoperfusion increases incidence of postoperative complications and mortality and should be avoided if possible [5]. However, individualized, timely, and accurate fluid therapy for patients undergoing GI surgery has yet to achieve wide recognition [6].

Goal-directed fluid management involves determining the optimum hemodynamic parameters for an individual patient, starting a series of interventions (typically an intravenous fluid bolus) and determining the treatment duration [7]. This strategy is repeated until hemodynamic parameters reach set goals [8]. The key feature is that this is individualized fluid management based on patient responsiveness to fluid administration during the perioperative period, rather than a predetermined formula [9]. This approach effectively protects against both volume depletion and overload during the perioperative period. This is in contrast to traditional or non-goal-directed fluid therapy which involves perioperative fluid administration for mainte-

nance, replacement for fluid deficits, and "third space" fluid loss [10]. In some cases, traditional fluid therapy can be guided by routine monitoring indicators, such as mean arterial pressure, central venous pressure, and urinary output [10]. However, these traditional approaches do not consider the specific surgical procedures, anesthetic techniques, and anesthetic agents [11].

Many studies have suggested that goal-directed fluid management can stabilize patient hemodynamics, improve tissue oxygenation, and facilitate GI recovery, thus improving postoperative outcomes [12, 13]. Unfortunately, these studies included a relatively small number of patients. Therefore, high-quality evidence for the effectiveness of goal-directed fluid management is lacking.

The present meta-analysis aimed to determine whether goal-directed fluid management reduces GI complications in adults undergoing major abdominal surgery.

## Materials and methods

### *Search strategy*

The following databases were searched: Current issue of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 12, 2015), MEDLINE (1966 to December 2016), EMBASE (1980 to December 2016), CINAHL (1982 to December 2016), and ISI Web of Science (1945 to December 2016). The search was conducted systematically by two independent researchers. The following key words were used: 1) Goal-direct*. af. or (goal direct*). af. or GDT. mp. or ((fluid or hemodynamic) adj3 management).mp; 2) Exp Digestive System Surgical Procedures/or GI Diseases/or ((gastro* or abdomen*) adj3 (surg* or operat* or complicat*)). mp.; 3) Combination of 1) and 2).

### *Inclusion and exclusion criteria*

Inclusion criteria were: 1 Randomized controlled trials (RCT reporting a comparison of goal-directed fluid management with standard fluid management during the intraoperative period; and 2 Participants aged 18 years and older undergoing major open abdominal surgery (including bowel resection, gastric resection, liver resection, esophageal resection, Whipple procedures, and similar significant GI procedures).

This meta-analysis excluded participants that had emergency surgery, low-risk surgery, and surgery restricted to management of minor problems and injuries.

### *Data extraction*

Two reviewers, independently, extracted, collected, and recorded data from included trials. Cross-checking was conducted to ensure the accuracy of extracted data.

### *Outcome measures*

GI complications included: 1 Postoperative ileus lasting > 24 hours; 2 Anastomotic leak requiring reoperation; 3 Postoperative nausea and vomiting requiring two or more than two antiemetic interventions; and 4 Inability to tolerate an oral diet over a 24-hour period. Criteria for diagnosis of GI complications were the same in the included studies. Mortality was induced by all causes. For subgroup analysis, the follow-up data was divided into short-term (30 days post-operation) data and medium-term (60 days post-operation) data. Total volume of intravenous fluid (mL) was evaluated. Incidence of adverse events (myocardial infarction, cerebrovascular accident, and central pontine myelinolysis) was analyzed.

### *Random sequence generation*

Random sequence generation was considered adequate if the sequence was generated using a computer or a random number table algorithm. Assignment according to birthday and participant hospital number was considered inadequate. If methods of randomization used were not mentioned in the study, the method of randomization was considered unclear.

### *Allocation concealment*

Allocation of concealment was considered adequate if participants and observers were unaware of the allocation of the next participant to be enrolled in the study. Acceptable allocation included central randomization (including telephone, network, and pharmacy-controlled randomization), sealed opaque envelopes, and an on-site locked computer.

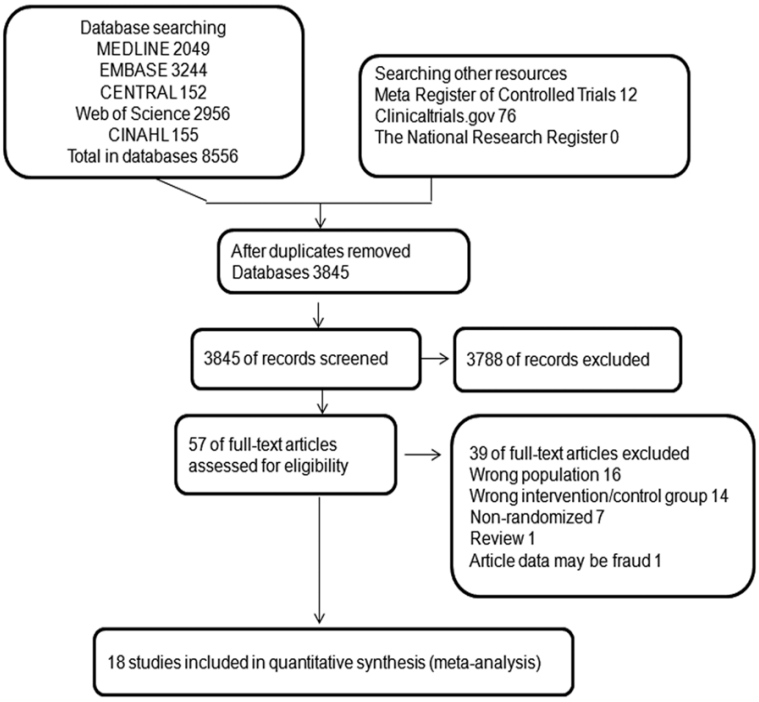


**Figure 1.** Flow chart summarizing study selection for the meta-analysis.

If the patients or the participants were aware of the grouping (alternate medical record numbers, reference to case record numbers or date of birth, open allocation sequence or unsealed envelopes), this was considered a high risk of bias. If means of concealment were not mentioned in the study or were described in insufficient detail to allow for assessment of the effectiveness of allocation concealment, the method of concealment was considered unclear.

*Blinding*

Blinding was considered adequate if both participants and observers were blinded. Blinding was considered unclear if the authors did not indicate anything and inadequate if the authors indicated that no blinding of participants or observers occurred. A risk of bias table was completed for each eligible study, with outcomes using the categories of low, high, and unclear risk of bias.

Reporting bias was assessed in a qualitative manner, using a funnel plot, if more than 10 studies were included in the meta-analysis.

*Statistical analyses*

Data from included trials were analyzed using Cochrane Review Manager (RevMan version 5.3.5, 2014; The Cochrane Collaboration, Copenhagen, Denmark). Pooled dichotomous data are presented as risk ratios (RRs) with 95% CIs using Mantel-Haenszel statistics. Mortality was assessed at the longest duration of follow-up. Summary estimates of continuous data are expressed as a mean difference (MD) with 95% CI using inverse variance. A random effects model was used for all analyses. Statistical heterogeneity was explored using the $I^2$ test with 95% uncertainty intervals. Summary effect measures were based on intention-to-treat data when available. Since the power of testing is low with small sample sizes, $P<0.01$, rather than $P<0.05$, indicates statistically significant differences.

## Results

*Literature search results*

Initially, 8,556 reports and 76 potential studies were retrieved. After eliminating duplicate reports, 3,845 reports were obtained. After review of the title and abstract, 3,788 reports were excluded. After examining the full text of the 57 articles, 18 RCTs (with 1,671 participants) were included in this review. The literature-retrieving process and results are shown in PRISMA 2009 Flow Diagram (**Figure 1**). All studies were screened for risk of bias and methodological quality using Cochrane's Collaboration tool.

Ten of the 18 studies were level one RCTs. Two studies were ranked as having a low risk of bias [14, 15] and sixteen studies were ranked as having a high risk of bias [12, 16-30], as shown in **Figure 2**.

*GI complications*

A total of 9 studies reported incidence of GI complications. Incidence of GI complications after the implementation of goal-directed fluid management in the perioperative period was lower than incidence after standard (routine) fluid management (RR 0.48; 95% CI 0.33 to

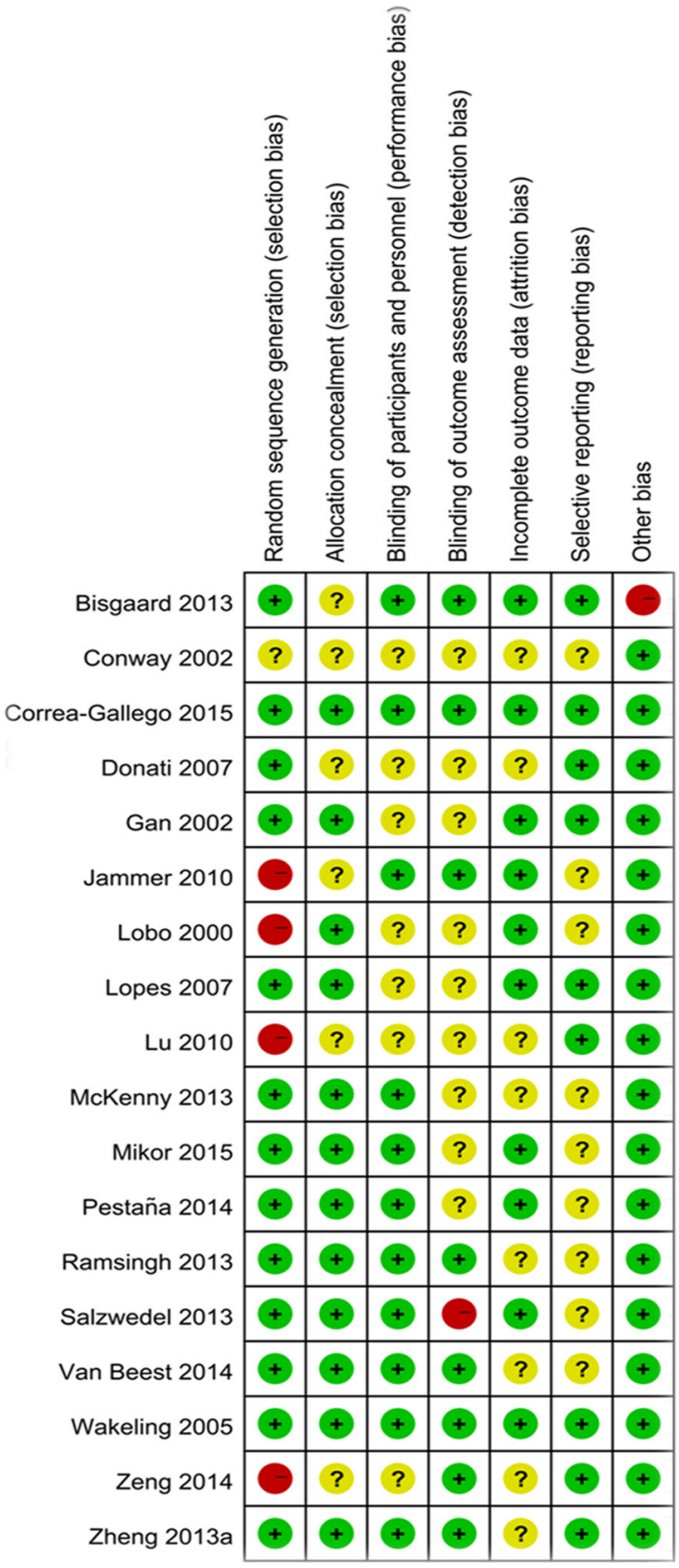


**Figure 2.** Risk of bias summary. Review judgements about each risk of bias item for each included study.

0.69, 9 studies, 846 participants) (**Figure 3**).

*Mortality*

Fifteen studies (1,373 participants) reported postoperative mortality. For subgroup analysis, differences in mortality rates at 30-day and 60-day post-operation were analyzed. Mortality rates at 30-day follow-up were not significantly different between perioperative goal-directed fluid management and standard fluid management (RR 0.60, 95% CI 0.34 to 1.06, 15 studies, 1373 participants). Regarding mortality rates within 60 days, however, goal-directed fluid management had a far lower mortality rate than standard fluid management (RR 0.32, 95% CI 0.11 to 0.93, 2 studies, 165 participants) (**Figure 4**).

*Total volume of fluid intravenous fluid (mL)*

Seven studies (718 participants) compared the perioperative use of crystalloid solution between participants receiving goal-directed and those receiving standard fluid management. Results showed that participants receiving goal-directed fluid management did not have significantly different volumes of crystalloid solution, compared to those receiving standard fluid management (MD-497.55; 95% CI-1165.89 to-170.78, 7 studies, 718 participants) (**Figure 5**). In contrast, participants receiving goal-directed fluid management received significantly

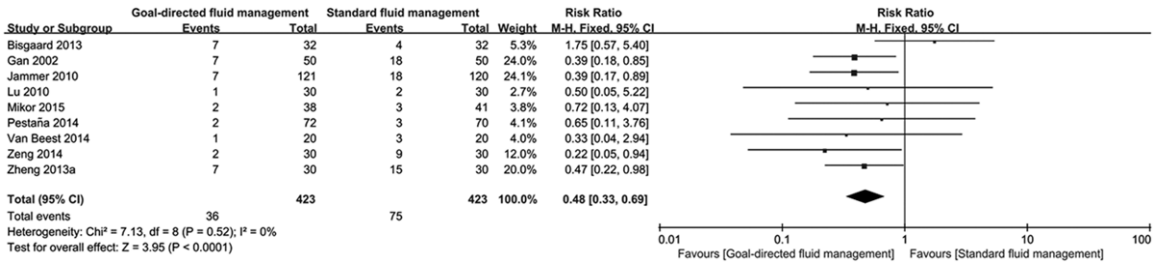


**Figure 3.** Forest plot of the comparison between goal-directed fluid management and standard fluid management. Gastrointestinal complications were analyzed. Rates of postoperative gastrointestinal complications for each of the studies with ORs and 95% CIs are shown. Pooled RR and 95% CI are shown as the total. The size of the box at the point estimate of the RR gives a visual representation of the 'weighting' of the study. The diamond represents the point estimate of the pooled RR and the length of the diamond is proportional to the CI.

more volume of colloid solution than those receiving standard fluid management (MD 199. 58, 95% CI 65.51 to 333.66, 10 studies, 951 participants) (**Figure 6**).

*Incidence of adverse events*

Adverse events were defined as myocardial infarction, cerebrovascular accidents, or central pontine myelinolysis. Thirteen studies (1,303 participants) compared adverse events between participants receiving goal-directed and those receiving standard fluid management. Incidence of adverse events after the implementation of goal-directed fluid management in the perioperative period was significantly lower than incidence after standard (routine) fluid management (RR 0.66; 95% CI 0.50 to 0.88,15 studies, 1303 participants) (**Figure 7**).

## Discussion

This meta-analysis included 18 studies involving 1,671 patients. Overall incidence of postoperative GI complications after abdominal operations is as high as 50% [1]. Of the various causes of postoperative GI complications, insufficient perioperative effective circulating volume plays an important role [10]. In participants undergoing abdominal surgery, it is difficult to accurately assess the fluid status because of pathophysiological changes of the underlying disease, bowel preparation before surgery, intraoperative fluid loss, and stress response [31]. The renin-angiotensin system maintains the body's blood pressure and decreases blood flow to the GI complications tract in response to hypoperfusion, thereby ensuring the perfusion of vital organs [32]. Therefore, the body can compensate for a 25% to 30% decrease in ef-f ective circulating volume [33]. However, the GI tract is extremely sensitive to changes in effective fluid volume. A reduction of 10% to15% of effective circulating volume will result in GI hypoperfusion [13]. During surgery, monitoring the heart rate and blood pressure will not detect insufficient perfusion of the GI tract. Therefore, unrecognized prolonged hypoperfusion of the GI tract may lead to injury of the GI tract [34].

Standard fluid management usually does not take into account the type of surgery, method of anesthesia, or patient preoperative fluid status [35]. Therefore, standard fluid management may be inadequate in patients undergoing GI surgery that are at risk for hypoperfusion of the GI tract [36]. Goal-directed fluid management, in contrast, uses various monitoring techniques to detect insufficient intraoperative effective circulating volume, seeking to maintain adequate circulating volume to ensure adequate tissue perfusion and oxygenation [11]. Therefore, goal-directed fluid management promotes optimal postoperative recovery of the GI tract.

The ultimate purpose of goal-directed fluid management is to maximize oxygen delivery $DO_2$ [37]. $DO_2$ is the oxygen delivered to the peripheral tissues through the circulatory system per unit time, namely, the velocity of the arterial blood transporting the oxygen. $DO_2$ value is the product of the cardiac output and oxygen content in the arterial blood [37]. Studies have shown that diminished blood flow leads to hypoxia of the body and mitochondrial damage, resulting in tissue dysfunction [25]. Adequate oxygen supply (reaching 600 $mL/min^{-1}$ $m^{-2}$) can support organ recovery after surgery [22]. Therefore, goal-directed fluid management in the perioperative period will support optimal tissue oxygen delivery, likely improving patient postop-

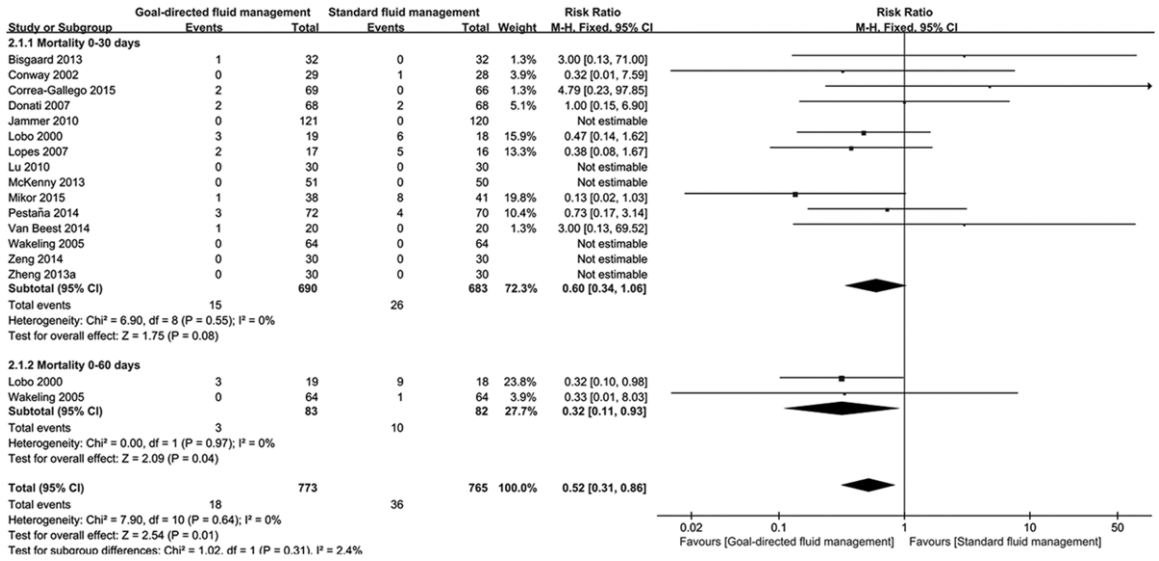


**Figure 4.** Forest plot of the comparison between goal-directed fluid management and standard fluid management. Mortality was analyzed. Rates of postoperative Mortality for each of the included studies, with ORs and 95% CIs are shown. Pooled RR and 95% CI are shown as the total. The size of the box at the point estimate of the RR gives a visual representation of the 'weighting' of the study. The diamond represents the point estimate of the pooled RR and the length of the diamond is proportional to the CI.

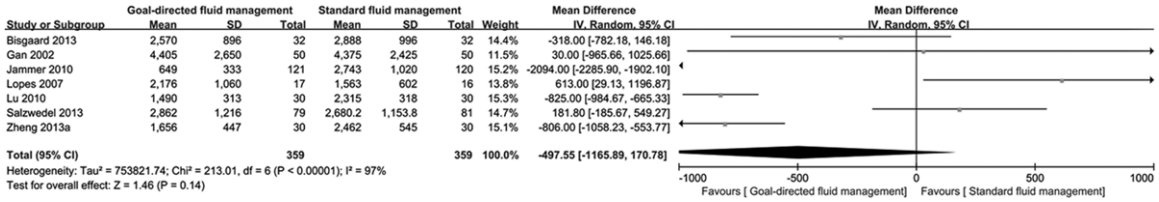


**Figure 5.** Forest plot of the comparison between goal-directed fluid management and standard fluid management. Total volume of crystalloid solution was evaluated. Total volume of crystalloid solution for each of the studies included, with RRs and 95% CIs are shown. Pooled RR and 95% CI are shown as the total. The size of the box at the point estimate of the RR gives a visual representation of the 'weighting' of the study. The diamond represents the point estimate of the pooled RR and the length of the diamond is proportional to the CI.

erative recovery and reducing related complications.

The present meta-analysis also compared types of fluid solution used between the two groups of participants. It was found that the goal-directed fluid management group used more colloid solution and less crystalloid solution, compared to the standard fluid management group. Total perioperative fluid requirement includes five components, such as volume of intraoperative fluid deficit, maintenance fluid for basic needs, vascular expansion, fluid redistribution (fluid in the third space), and intraoperative loss [30]. In GI surgery, the requisite fluid volume must be adjusted based on these five categories. The appropriate ratio of crystalloid solution to colloid solution has been debated for 20 years, but evidence-based studies are still lacking. Crystalloid solution has a shorter intravascular residence time and more rapidly moves into the third space [25]. A large volume and more frequent administration of crystalloid solution (two to three times to six to eight times the volume of blood loss) would, therefore, be necessary to maintain a steady effective circulating volume [23]. Such large volume of fluid infusion may cause GI anastomotic edema or pulmonary edema, increasing incidence of postoperative GI dysfunction [2]. Colloid solution has a longer residence time in the intravascular space. Thus, it is able to maintain intravascular volume for a longer duration of action, compared to crystalloid solution [24].

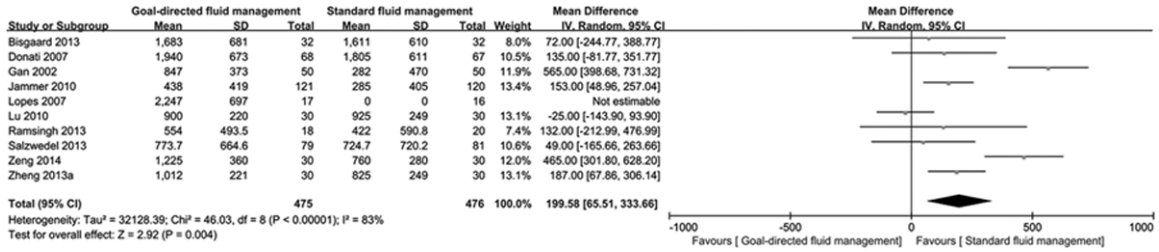


**Figure 6.** Forest plot of the comparison between goal-directed fluid management and standard fluid management. Total volume of colloid solution was evaluated. Total volume of colloid solution for each of the studies included, with RRs and 95% CIs are shown. Pooled RR and 95% CI are shown as the total. The size of the box at the point estimate of the RR gives a visual representation of the 'weighting' of the study. The diamond represents the point estimate of the pooled RR and the length of the diamond is proportional to the CI.

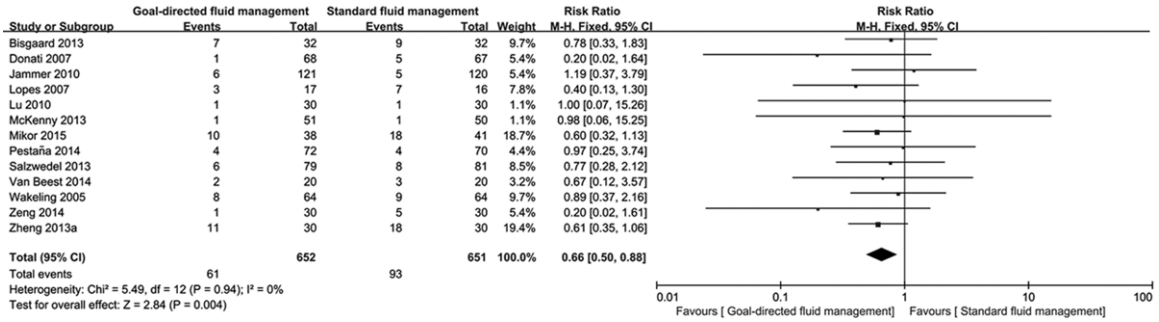


**Figure 7.** Forest plot of the comparison between goal-directed fluid management and standard fluid management. Incidence of adverse events was assessed. Rates of postoperative adverse events for each of the studies included, with RRs and 95% CIs are shown. Pooled RR and 95% CI are shown as the total. The size of the box at the point estimate of the RR gives a visual representation of the 'weighting' of the study. The diamond represents the point estimate of the pooled RR and the length of the diamond is proportional to the CI.

The present meta-analysis retrieved relevant studies from the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, and ISI Web of Science. Additionally, ongoing studies were retrieved. Therefore, all clinical tests related to goal-directed fluid management and standard fluid management were collected. A total of 18 studies were ultimately examined.

Gómez-Izquierdo et al. investigated whether goal-directed fluid management can promote the recovery of GI function after open surgeries [38]. Their study included 13 trials with 1,399 patients. Findings suggested that goal-directed fluid management could reduce the time to recover bowel motion, time to tolerate oral intake, and occurrence rates of post-surgical vomiting. Giglio et al. found that goal-directed fluid management could decrease incidence of GI complications [11]. The present study found consistent results, indicating that incidence of GI complications after surgery is reduced by goal-directed fluid management.

Incidence of postoperative GI complications in participants undergoing abdominal surgery, however, remains high. The main etiology is believed to be perioperative GI hypoperfusion [1]. Goal-directed fluid management uses real-time monitoring of perioperative hemodynamic parameters to guide appropriate fluid and/or vasoactive drugs therapy, optimizing an individual patient's stroke volume or cardiac output [30]. Results of this meta-analysis suggest that goal-directed fluid management is an effective tool in reducing incidence of GI complications and mortality within 60 days.

The present study, however, had some limitations. First, all studies included in the meta-analysis had already been published. There may have been publication bias. Although all authors of the included studies were contacted, only a few responded and provided their study protocol. Thus, it was not determined whether the results of published reports were consistent with original protocols. Some studies included in this systematic review did not

detail concrete blinding and random methods. The heterogeneity of some results was high, while numbers of patients included in some RCTs were small. In addition, differences existed in hemodynamics monitors applied in some intervening measures. Regarding GI complications, analysis was only conducted on minor GI complications, to avoid bias. Second, long-term mortality was not investigated. According to the duration of the follow-up, post-operation mortality within 30 days and 60 days was analyzed. However, there were no reports concerning long-term mortality within 3 months. Thus, long-term prognosis of patients after goal-directed fluid management could not be evaluated. Third, some of the included studies only reported median and interquartile ranges. Converting those data into mean and standard deviation may have led to differences in reported results.

In conclusion, the present review demonstrates that goal-directed fluid management in abdominal surgery reduces postoperative GI complications. However, more RCTs with larger sample sizes are necessary. These trials should include correct randomization and allocation-concealment methods, with a longer duration of follow-up. A multi-center trial would also be useful.

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## Disclosure of conflict of interest

None.

## Abbreviations

RR, Relative Risk; CI, Confidence Interval; GI, Gastrointestinal.

**Address correspondence to:** Dr. Hong Zheng, Department of Anesthesiology, The First Affiliated Hospital of Xinjiang Medical University, No. 137, Liyushan Street, Urumqi 830011, China. Tel: 86-15276730030; Fax: 86-0991-4366167; E-mail: gyra001@qq.com; 115173948@qq.com

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