

## SYSTEMATIC REVIEW



# Is goal-directed fluid therapy beneficial for gastrointestinal surgery within an enhanced recovery program? A systematic review and meta-analysis

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**Abstract**

**Objectives:** To systematically evaluate the clinical effect of intraoperative goal-directed fluid therapy (GDFT) in gastrointestinal surgery within an enhanced recovery after surgery (ERAS) program. **Methods:** EMBASE, MEDLINE, Cochrane Library, PubMed, OVID, CNKI and other databases were searched for randomized controlled trials (RCTs) from the inception dates to December 2018. These studies included patients undergoing elective gastrointestinal surgery comparing regular fluid therapy versus GDFT within ERAS. The meta-analysis was carried on with RevMan 5.3. **Results:** A total of 10 RCT studies were included with 1216 patients. Compared with the regular fluid therapy group, the GDFT group reduced the rate of readmission [odds ratio, OR = 1.67, 95% CI (1.05, 2.65),  $P = 0.03$ ] in gastrointestinal surgery patients within ERAS. However, there was no significant decrease in length of hospital stay (LOHS) [mean difference, MD = -0.11, 95% CI (-1.22, 1.00),  $P = 0.85$ ], postoperative morbidity [OR = 0.78, 95% CI (0.55, 1.11),  $P = 0.17$ ], postoperative mortality [OR = 0.86, 95% CI (0.30, 2.49),  $P = 0.78$ ], postoperative ileus [OR = 1.24, 95% CI (0.70, 2.19),  $P = 0.45$ ], anastomotic leaks [OR = 0.66, 95% CI (0.29, 1.49),  $P = 0.31$ ] and the first gastrointestinal motility time [MD = -0.37, 95% CI (-1.07, 0.33),  $P = 0.30$ ]. **Conclusions:** The current evidence demonstrates that, in gastrointestinal surgery within ERAS, GDFT decreased the rate of readmission. However, there was no advantage over regular fluid therapy in the reduction of LOHS, postoperative morbidity, postoperative mortality, postoperative ileus and anastomotic leaks.

**Keywords**

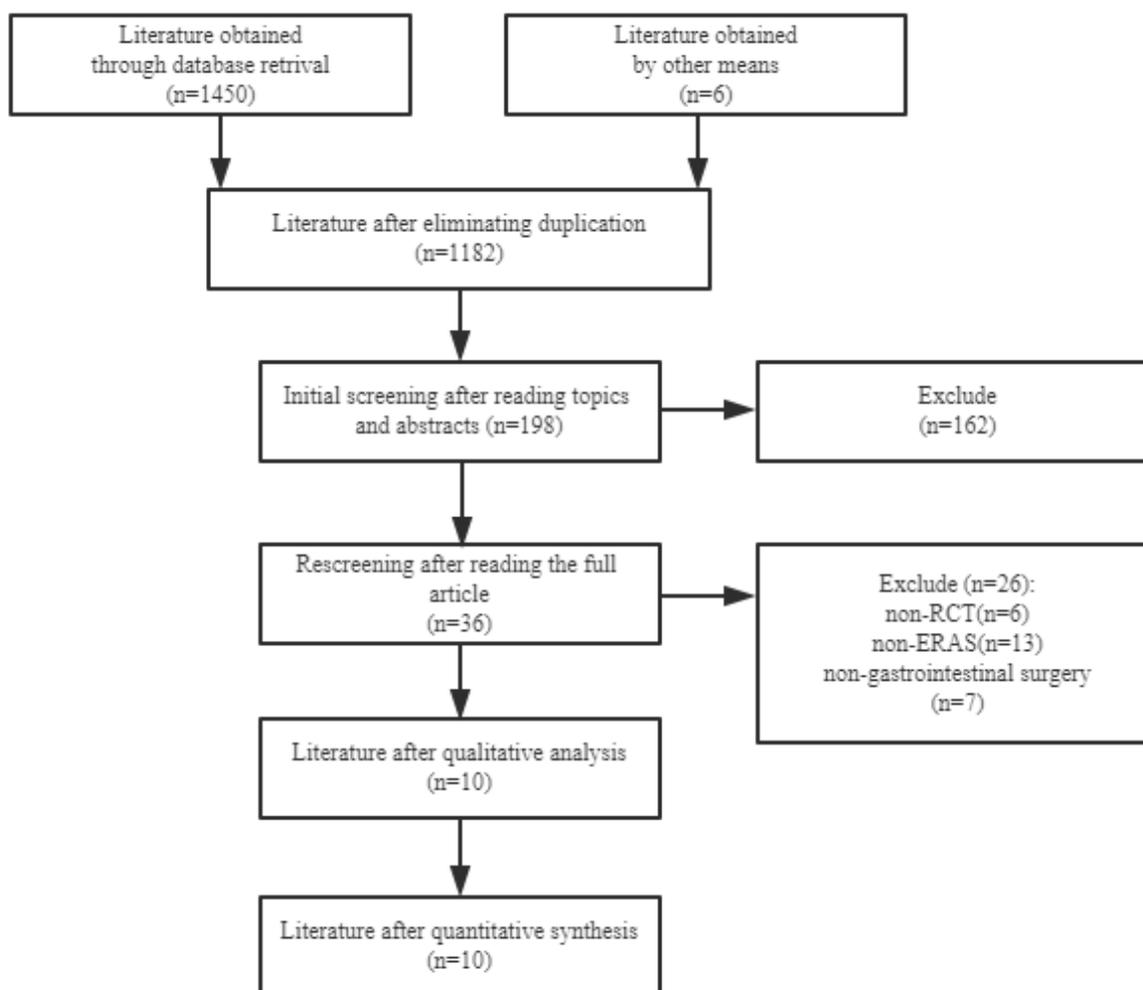
Enhanced recovery after surgery; Goal-directed fluid therapy; Gastrointestinal surgery; Meta-analysis; Randomized controlled trial

## 1. Introduction

Perioperative fluid management for surgical patients is controversial [1]. Traditional fluid therapy is prone to excessive volume loading and tissue edema. There is no only criterion for restrictive fluid therapy, which has been demonstrated to improve oxygenation and lung function [2]. However, it is apt to circulatory insufficiency. Goal-directed fluid therapy (GDFT) refers to an individualized rehydration regimen, which is based on the sufferer's general condition, and intraoperative volume status by monitoring hemodynamic parameters such as stroke volume (SV), pulse pressure variation (PPV) and descending aortic corrected flow time (FTc) [3, 4]. In the perioperative period, GDFT can provide appropriate tissue oxygen supply and organ perfusion, protect gastrointestinal function, correct hemodynamic abnormalities in critical patients, prevent severe inflammatory reactions, and reduce the incidence of cardiovascular complications [5]. Previous studies showed that GDFT significantly reduced wound infections,

postoperative hypotension, cardiovascular complications, and improved prognosis of patients [6, 7].

Grounded on evidence-based medicine, enhanced recovery after surgery (ERAS) aims to cut down the physical and psychological traumatic stress of surgical sufferer [8]. ERAS combines a range of clinical practices in anesthesia, surgery, and nursing. These have been proven to reduce postoperative complications [8, 9]. ERAS optimizes clinical pathways and strategies [10] which allows sufferers to take clear liquids two hours prior to anesthesia, uses laparoscopy instead of a larger incision, and begins patient mobilization shortly after surgery. ERAS preserves the functional reserve of organs prior to surgery, regulates homeostasis, reduces traumatic stress and complications, promotes rehabilitation of organ function, accelerates postoperative recovery and shortens length of hospital stay (LOHS) [9]. In previous studies [11–14], ERAS shortened LOHS from 30% to 50%, reduced complications, readmissions and medical costs.



**FIGURE 1. Flow chart of literature filtering.**

Researchers have tried to combine GDFT and ERAS in clinical practices [15–20], but its impact on postoperative recovery was inconsistent. GDFT can protect gastrointestinal function [5], but has not been found to be superior to GDFT, especially in the colorectal surgery [21].

We therefore performed this study to ascertain the clinical effect of GDFT versus regular fluid therapy in gastrointestinal surgery based on ERAS.

## 2. Methods

Registration information of this meta-analysis could be inquired on PROSPERO ([www.crd.york.ac.uk/prospero](http://www.crd.york.ac.uk/prospero)). Registration number: CRD 42018083908.

### 2.1 Inclusion and exclusion criteria

#### 2.1.1 Type of study

A randomized controlled trial (RCT) of GDFT based on ERAS for gastrointestinal surgery published in international journals.

#### 2.1.2 Research objective

Elective gastrointestinal surgery patients; adults; not limited to surgical type (laparoscopy or laparotomy); patients were

managed using ERAS; and were not critically ill.

#### 2.1.3 Intervention

Test group: GDFT based on a series of hemodynamic parameters; control group: regular fluid therapy based on traditional vital signs, urine volume, and intraoperative loss.

#### 2.1.4 Outcome indicator

Incidence of readmission, LOHS, postoperative morbidity (defined as one or more complications after surgery), postoperative mortality, postoperative ileus, anastomotic leakage, gastrointestinal motility.

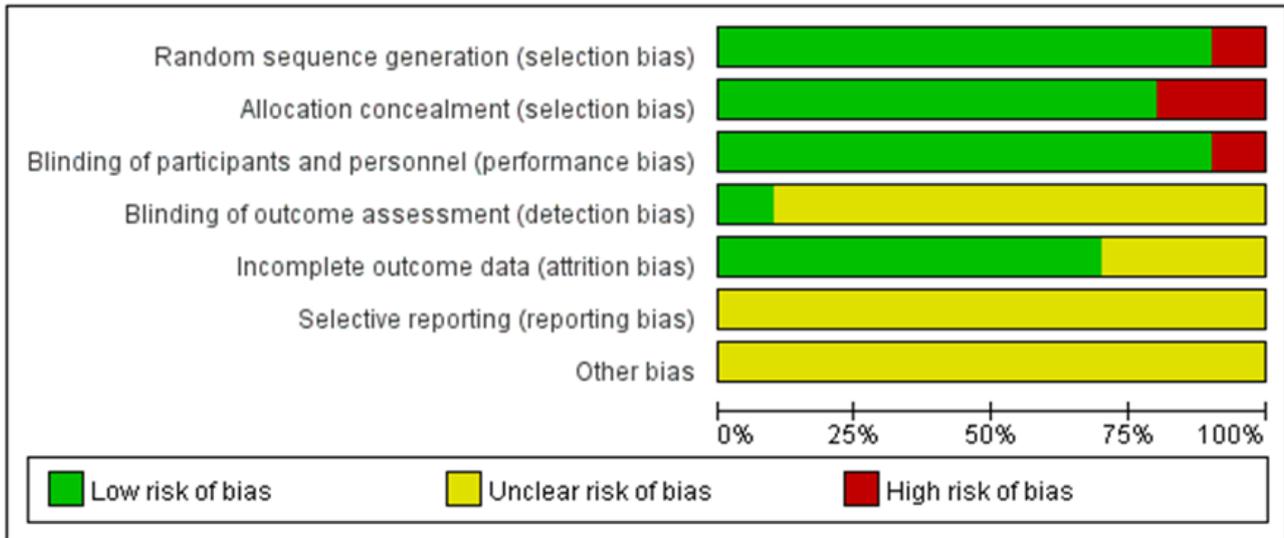
#### 2.1.5 Exclusion criteria

Non-Chinese or English literature; no abstracts or full texts available; original study data cannot be extracted; inconsistent outcomes' research; redundant or duplicate publication.

## 2.2 Search strategy

Computer search database such as EMBASE, MEDLINE, Cochrane Library, PubMed, OVID, CNKI and other Chinese and English databases, were used to collect RCT of GDFT in gastrointestinal surgery within an ERAS program from the

A



B

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Brandstrup 2012	+	+	+	?	+	?	?
Challand 2012	+	+	+	?	+	?	?
Juan 2017	+	+	+	?	+	?	?
Lai 2015	+	-	+	?	+	?	?
Noblett 2006	-	-	+	+	+	?	?
Phan 2014	+	+	+	?	?	?	?
Srinivasa 2013	+	+	+	?	+	?	?
Wakeling 2005	+	+	+	?	+	?	?
Zakhaleva 2012	+	+	+	?	?	?	?
Zheng 2013	+	+	-	?	?	?	?

FIGURE 2. Risk of bias.

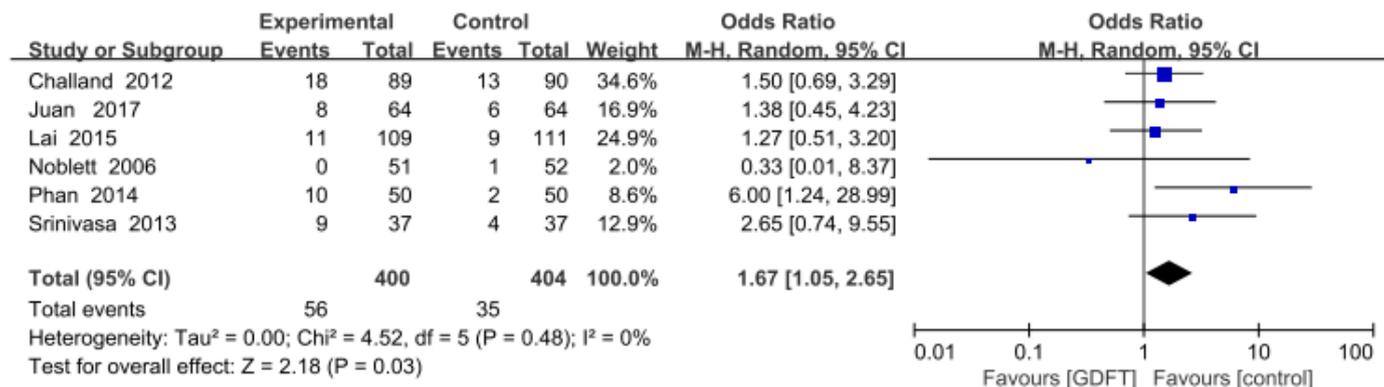


FIGURE 3. Forest plots of readmission.

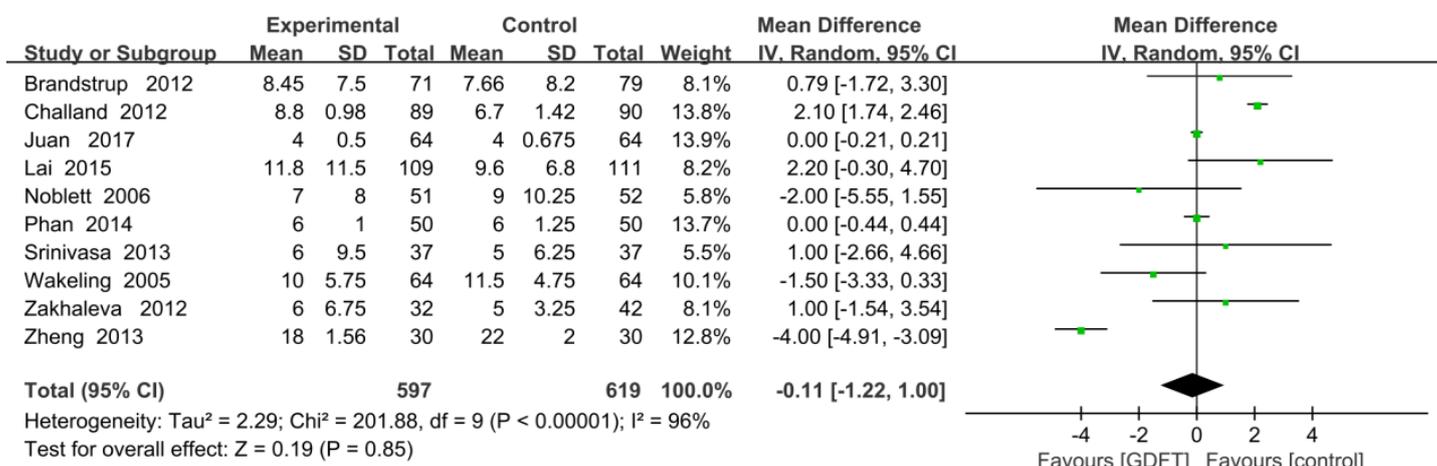


FIGURE 4. Forest plots of LOHS.

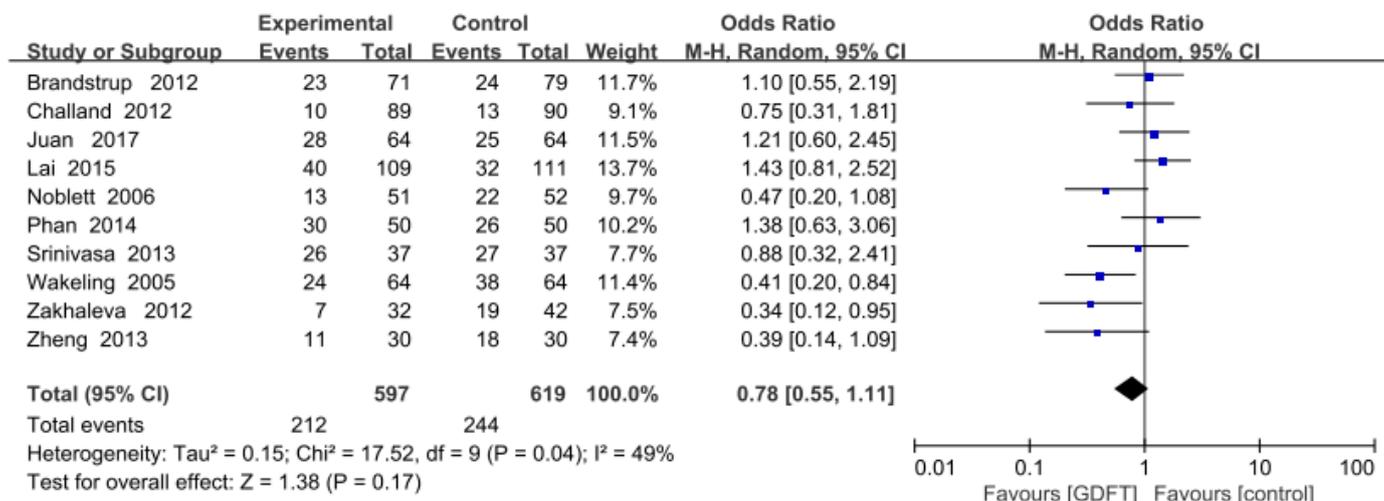


FIGURE 5. Forest plots of morbidity.

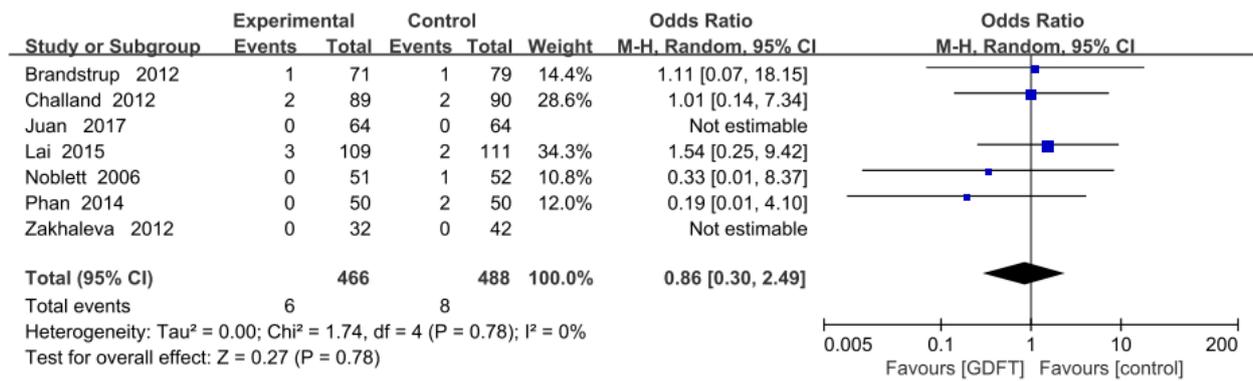


FIGURE 6. Forest plots of mortality.

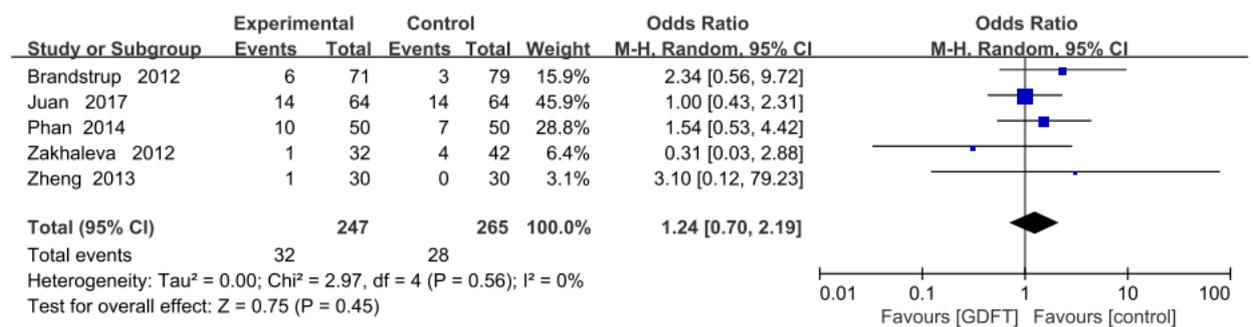


FIGURE 7. Forest plots of postoperative ileus.

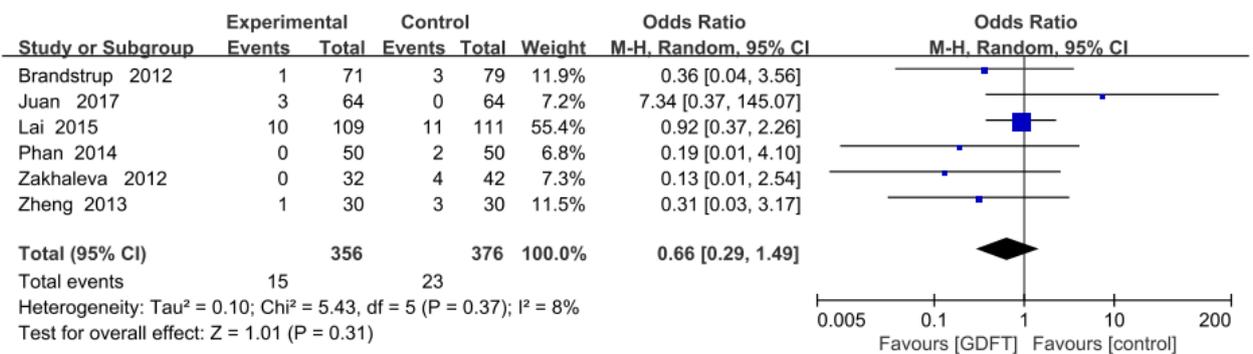


FIGURE 8. Forest plots of anastomotic leak.

inception dates to December 2018. Search words included goal directed, goal target, goal oriented, fluid therapy, fluid optimization, fluid administration, hemodynamic goal, intravenous fluid therapy, intravenous fluid restriction, intravenous fluid titration, fluid resuscitation, randomized controlled trial, controlled clinical trial, colorectal resection, colorectal surgery, gastrointestinal surgery, colectomy, bowel surgery, intestinal abdominal surgery, colonic resection, and gastric surgery. In addition, other relevant journals and conference papers were manually searched.

### 2.3 Data extraction

By two reviewers, the data extraction was carried out independently, any disagreement was discussed and resolved with the third independent reviewer. The data extraction includes: essential information of each study, including name of journal, authors, publication time; patient information such as American Society of Anesthesiology (ASA) classification, surgical site, surgical approach (laparoscopy or laparotomy); specific details of the intervention; major factors of bias risk assessment; related outcomes.

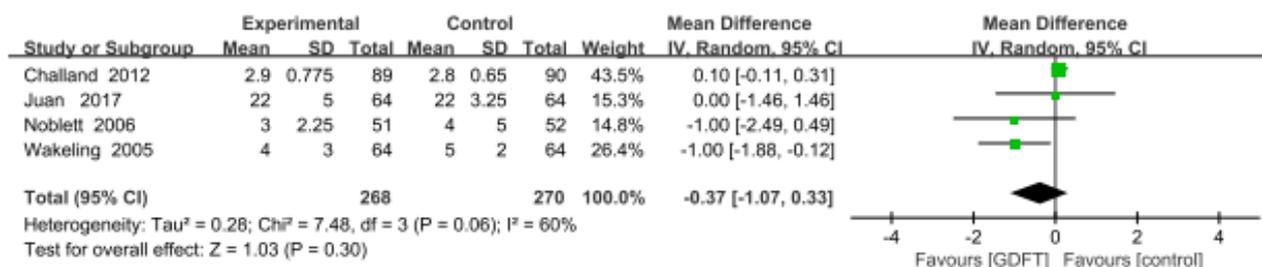


FIGURE 9. Forest plots of first postoperative gastrointestinal motility time.

## 2.4 Bias risk assessment

The bias risk assessment used the Cochrane Collaboration tool and Review Manager 5.3 (RevMan; The Nordic Cochrane Centre, Copenhagen, Denmark) which is recommended by the Cochrane Handbook. Two reviewers individually completed the assessment of bias risk and then cross checked the results, any disagreement was discussed and settled with the third reviewer.

## 2.5 Statistical analysis

Statistical analysis was carried on by using RevMan 5.3. The two categorical variable data were odds ratio (OR) and 95% confidence intervals (CI) as effect quantities, and the continuous variable data was mean difference (MD) and 95% CI as effect quantities. Both variable analysis was analyzed by using a random effects model. The heterogeneity between the included studies was analyzed by chi-square test (if  $I^2$  is less than 25%, the heterogeneity is low; if  $I^2$  is more than 25% and less than 50%, it is moderately heterogeneous; if  $I^2$  is greater than 50% is highly heterogeneous). If the results show low heterogeneity, they were further analyzed by the fixed effect model and on the contrary they were further analyzed by the random effects model.

## 3. Results

### 3.1 Literature filtering process and results

Initially 1,456 related articles were detected. After reading the title and abstract, 198 articles were considered for preliminary qualification. After carefully reading the full text, 10 RCTs [22–31] with 1216 patients were finally included, of which 597 patients underwent GDFT and 619 patients underwent regular fluid therapy. The process of study selection and results are displayed in Fig. 1.

### 3.2 Basic characteristics and risk assessment of included literature

The basic characteristics are displayed in Table 1. Risk of bias is displayed in Fig. 2.

### 3.3 Meta-analysis results

#### 3.3.1 Readmission

A total of 6 RCTs were included [23, 24, 27, 29–31]. There was no statistical heterogeneity between the studies ( $I^2 = 0\%$ ,  $P = 0.48$ ). The amount of patients in the GDFT group readmitted was significantly less than the control group [OR = 1.67, 95% CI (1.05, 2.65),  $P = 0.03$ ] (Fig. 3).

#### 3.3.2 LOHS

A total of 10 RCTs were included [22–31]. There was statistical heterogeneity between the studies ( $I^2 = 96\%$ ,  $P < 0.00001$ ). The GDFT group had no significant difference in shortening LOHS compared with the control group [MD = -0.11, 95% CI (-1.22, 1.00),  $P = 0.85$ ] (Fig. 4).

#### 3.3.3 Postoperative morbidity

A total of 10 RCTs were included [22–31]. There was statistical heterogeneity between the studies ( $I^2 = 49\%$ ,  $P = 0.04$ ). There was no significant difference in postoperative morbidity between groups [OR = 0.78, 95% CI (0.55, 1.11),  $P = 0.17$ ] (Fig. 5).

#### 3.3.4 Postoperative mortality

A total of 7 RCTs were included [23–26, 29–31]. There was no statistical heterogeneity between the studies ( $I^2 = 0\%$ ,  $P = 0.78$ ). There was no significant difference in postoperative mortality between groups [OR = 0.86, 95% CI (0.30, 2.49),  $P = 0.78$ ] (Fig. 6).

#### 3.3.5 Postoperative ileus

A total of 5 RCTs were included [25, 26, 28–30]. There was no statistical heterogeneity between the studies ( $I^2 = 0\%$ ,  $P = 0.56$ ). There was no significant difference in postoperative ileus between groups [OR = 1.24, 95% CI (0.70, 2.19),  $P = 0.45$ ] (Fig. 7).

#### 3.3.6 Anastomotic leak

A total of 6 RCTs were included [25, 26, 28–31]. There was no statistical heterogeneity between the studies ( $I^2 = 8\%$ ,  $P = 0.37$ ). There was no significant difference in anastomotic leakage between groups [OR = 0.66, 95% CI (0.29, 1.49),  $P = 0.31$ ] (Fig. 8).

**TABLE 1. Basic characteristics of included studies 1.**

Included Publications	Number of cases		ASA rating 1 : 2 : 3/4		Number of laparoscopic operations	
	GDFT	Control	GDFT	Control	GDFT	Control
Wakeling <i>et al.</i> , 2005 [22]	64	64	Median 2	Median 2	Not mentioned	Not mentioned
Noblett <i>et al.</i> , 2006 [23]	51	52	Median 2.1	Median 2.2	13	13
Challand <i>et al.</i> , 2012 [24]	89	90	11 : 51 : 27	11 : 52 : 27	28	37
Zakhaleva <i>et al.</i> , 2012 [25]	32	42	0 : 6 : 26	0 : 10 : 32	32	42
Brandstrup <i>et al.</i> , 2012 [26]	71	79	26 : 37 : 08	20 : 43 : 16	21	26
Srinivasa <i>et al.</i> , 2013 [27]	37	37	5 : 20 : 12	5 : 15 : 17	5	6
Zheng <i>et al.</i> , 2013 [28]	30	30	0 : 11 : 19	0 : 13 : 17	0	0
Phan <i>et al.</i> , 2014 [29]	50	50	Median 2	Median 2	23	20
Juan <i>et al.</i> , 2017 [30]	64	64	6 : 42 : 16	8 : 38 : 18	56	59
Lai <i>et al.</i> , 2015 [31]	109	111	16 :76 : 17	15 : 77 : 19	29	31

**TABLE 1. Basic characteristics of included studies 2.**

Included Publications	The intervention indicators of GDFT	The intervention measures of GDFT
Wakeling <i>et al.</i> , 2005 [22]	SV change > 10% or CVP rise < 3 mmHg	200 mL colloid impact in 2.5 minutes
Noblett <i>et al.</i> , 2006 [23]	FTc < 350 ms or SV change > 10%	first 7 mL/kg, followed by 3 ml/kg colloid impact
Challand <i>et al.</i> , 2012 [24]	SV change > 10%	200 mL colloid impact in 5 minutes
Zakhaleva <i>et al.</i> , 2012 [25]	FTc < 350 ms or SV change > 10%	first 7 mL/kg, followed by 3 ml/kg colloid impact
Brandstrup <i>et al.</i> , 2012 [26]	Horizontal position SV change > 10%	200 mL colloid impact
Srinivasa <i>et al.</i> , 2013 [27]	FTc < 350 ms or SV change > 10%	first 7 mL/kg, followed by 3 mL/kg colloid impact
Zheng <i>et al.</i> , 2013 [28]	CI < 2.5 L/min/m <sup>2</sup> and SVI < 35 mL/m <sup>2</sup> , SVV < 12%	dopamine 10 mL/h + 200 mL colloidal impact
	CI < 2.5 L/min/m <sup>2</sup> and SVI < 35 mL/m <sup>2</sup> , SVV > 12%	500 mL Ringer test solution impact
Phan <i>et al.</i> , 2014 [29]	FTc < 350 ms, SVI < 35 mL/m <sup>2</sup> or low blood pressure	250 mL colloidal impact in 2 minutes
Juan <i>et al.</i> , 2017 [30]	SV change > 10%	200 mL colloid impact in 5 minutes
Lai <i>et al.</i> , 2015 [31]	SVV > 10%	200 mL colloid impact

SV: Stroke Volume; CVP: Central Venous Pressure; FTc: descending aortic corrected flow time; CI: Cardiac Index; SVV: Stroke Volume Variability; SVI: Stroke Volume Index.

### 3.3.7 First postoperative gastrointestinal motility time

A total of 4 RCTs were included [22–24, 30]. There was statistical heterogeneity between the studies ( $I^2 = 60\%$ ,  $P = 0.06$ ). There was no decrease in the first gastrointestinal motility time between groups [MD = - 0.37, 95% CI (-1.07, 0.33),  $P = 0.30$ ] (Fig. 9).

## 4. Discussion

Intraoperative fluid therapy may affect the patient’s intraoperative stability and postoperative recovery [32]. Several studies [7, 15] confirmed that GDFT used measurements of SV to meliorate blood flow during operation, further reduce LOHS and related complications by combining the use of fluids and inotropic drugs. ERAS pathways are being increasingly implemented in surgical practices. ERAS has been shown to significantly accelerate the patient’s postoperative recovery, reduce LOHS and decrease medical costs [33].

The results of this meta-analysis has demonstrated that in

gastrointestinal surgery within ERAS, GDFT only decreased the rate of readmission compared with traditional fluid therapy. However, it did not significantly reduce LOHS, postoperative morbidity, mortality, ileus, anastomotic leaks, and first gastrointestinal motility time. This was similar to a previous meta-analysis [20]. GDFT may not further improve outcomes in patients who are already on ERAS protocols in the gastrointestinal surgery.

Rollins *et al.* [34] demonstrated that the rate of incisional wound infection was decreasing and the rate of acute kidney injury was increasing when patients obtained GDFT management, although this trend was not statistically significant. And Benes *et al.* [6] demonstrated that GDFT significantly reduced wound infections, postoperative hypotension, and cardiovascular complications. It may be that GDFT reduced non-gastrointestinal complications, therefore GDFT did reduce the incidence of readmission but not any other outcomes variables in this study.

Moore *et al.* [35] determined that the inappropriate fluid management could delay the recovery of gastrointestinal function, and excessive fluids could cause intestinal edema and gastrointestinal mucosal damage which affects the healing of the anastomosis. In contrast, restrictive infusions could accelerate the recovery of intestinal function and facilitate feeding. However, Myles *et al.* [36] suggested that restrictive fluid management might cause kidney damage. All patients in this present study were enrolled in the ERAS program. This avoids fluid overload or deficit, so the distinction in postoperative outcomes between groups may not be easily noticeable. By the combination of GDFT and ERAS, the clinical benefits of GDFT may be weakened [20].

The present study only focused on RCTs where ERAS had been used, which improved the homogeneity of this study, to a certain extent. But, in fact, due to the variable number and type of interventions included in the ERAS, it is difficult to make clear the specific impact of each intervention on outcome indicators. Moreover, our study included different methods for the implementation of GDFT such as transesophageal Doppler and pulse power wave analysis which are not interchangeable [34], and may have affected the heterogeneity of this study.

In this study, the overall level of heterogeneity within the analyses was low. There were four analyses with low heterogeneity, two analyses with moderate heterogeneity, and just one analyses with high heterogeneity. The study quality is relatively high, and it increases the credibility of the conclusions that were drawn.

In addition to important intraoperative fluid management, we should note that preoperative and postoperative fluid management are also critical [15]. In the included studies, the preoperative and intraoperative fluid management were well documented, however, the specific measures of postoperative fluid management were poorly documented. This may have impacted some clinical outcomes that cannot be accounted for.

1216 patients were included in this study, but more than half of the patients were low and medium-risk. But compared with these patients, high-risk patients can obtain more clinical benefits of GDFT [37]. Due to the limitation of the quality and quantity of studies included, further research with standardized, unbiased methods and larger sample sizes, specifically including high-risk patients, are required to further elucidate the benefits of GDFT in patients undergoing gastrointestinal surgery already enrolled in the ERAS program.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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