

# Enhanced Recovery After Surgery in Emergency Resection for Obstructive Colorectal Cancer: A Systematic Review and Meta-analysis

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## Research article

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# Abstract

**Background:** Enhanced recovery after surgery (ERAS) improves outcomes after elective colorectal operations. Whether it is beneficial for emergency colorectal surgery is unclear. This study aimed to systematically review and summarize evidence from all studies comparing ERAS versus conventional care in patients having emergency colectomy and/or proctectomy for obstructive colorectal cancer.

**Methods:** EMBASE and MEDLINE from inception to October 2019 were systematically searched. Any studies comparing our primary outcome of interest (length of hospitalization) among patients having emergency resection for obstructive colorectal cancer who received ERAS versus conventional care were selected. Primary outcome was length of hospitalization. Secondary outcomes were gastrointestinal recovery, postoperative complication, 30-day readmission and mortality, and time to start adjuvant therapy.

**Results:** Three cohort studies with 818 participants (418 received ERAS and 400 received conventional care) were included. Length of hospitalization (mean reduction 3.07 days; 95% CI, - 3.91 to -2.23) and risk of overall postoperative complication (risk ratio 0.78; 95% CI, 0.63 to 0.97) were significantly lower in ERAS than in conventional care. ERAS was also associated with quicker time to gastrointestinal recovery, a lower incidence of ileus, and a shorter interval between operation and commence of adjuvant chemotherapy. There was no significant difference in the rates of anastomotic leakage, re-operation, readmission and mortality within 30 days after an operation between groups.

**Conclusions:** ERAS had advantages over conventional care in patients undergoing emergency resection for obstructive colorectal cancer - including a shorter length of hospitalization, a lower incidence of complication and quicker gastrointestinal recovery.

## Background

Emergency colectomy and/or proctectomy are among the top three most common emergency laparotomies performed in the United Kingdom [1] and the United States [2] – with a high rate of 30-day postoperative morbidity (ranging from 26.8–69.2%) [2] and mortality (ranging from 8.8–31.6%) [1]. Acute colonic obstruction is a common manifestation of colorectal cancer (CRC) that is responsible for 15–30% of initial clinical presentation [3]. Emergency resection of the tumor with or without anastomosis remains the mainstay treatment for obstructive CRC - especially right-sided colon cancer, left-sided colonic obstruction that is not eligible for colonic stenting, and CRC with suspected bowel perforation [3]. However, postoperative morbidities and mortalities following surgical treatment for obstructive CRC are high [4] - even performed by colorectal surgeons [5].

Enhanced recovery after surgery (ERAS) minimizes patient's surgical stress responses, optimizes their function, and enables rapid recovery [6]. Several meta-analyses of randomized controlled trials of elective colorectal operations have consistently found the advantages of ERAS over perioperative conventional care - including shorter hospitalization and fewer complications [7–9]. However, only few studies

examining the benefits of ERAS in emergency colorectal surgery were available and their results were inconsistent [10–12].

To our knowledge, there is no meta-analysis evaluating the benefits of ERAS protocol for colorectal surgery in an emergency setting. Our study hypothesized that ERAS could facilitate patient's discharge and improves surgical outcomes after emergency colectomy and/or proctectomy for obstructive CRC.

## **Materials And Methods**

This systematic review and meta-analysis was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [13].

### **Search strategy**

Published literature indexed in EMBASE and MEDLINE from inception to October 2019 was independently searched by three investigators. Search terms for EMBASE were 'enhanced recovery after surgery'/exp OR 'enhanced recovery after surgery', and for MEDLINE were enhanced recovery after surgery.mp. OR exp enhanced recovery after surgery/. No language limitation was applied. References of the included studies were further reviewed to identify any additional suitable studies that may be missed by the aforementioned search strategy.

### **Inclusion criteria**

Studies that were eligible for this meta-analysis must be cohort studies that enrolled patients having emergency colectomy and/or proctectomy for obstructive CRC. One group of patients must follow ERAS pathway while the other group must receive conventional care. The eligible studies must report the primary outcome, which is the average length of hospital stay of both groups along with standard deviation (SD). Secondary outcomes, including time to pass stool, time to resume regular diet, time to start adjuvant chemotherapy, rate of postoperative ileus, rate of leakage, rate of complications, reoperation, readmission and mortality within 30 days after an operation, were extracted and analyzed but were not part of the inclusion criteria. Study eligibility was independently evaluated by the three investigators with differing opinions resolved by group discussion. The Newcastle-Ottawa quality assessment scale for cohort studies was used to determine the quality of each study [14].

### **Data extraction**

The three investigators independently extracted data using a standardized form containing the primary outcome, secondary outcomes and characteristics of the study which included, country where the study was conducted, study period, year of publication, number of cases, age and gender of participants, location of obstructive CRC and types of surgery performed in that study. Any discrepancies were reviewed and corrected according to the original reports.

### **Statistical analysis**

Mean length of hospital stay, time to first bowel movement, time to tolerate solid food, and time to start adjuvant chemotherapy along with SD of participants in both groups were extracted from each study and the mean difference (MD) was calculated. Pooled MD was then calculated by combining MDs of each study using random-effects model. If the study provided median and interquartile range, median would be used as an estimate for mean and SD would be estimated from interquartile range divided by 1.35.

Relative risk (RR) of postoperative ileus, leakage, complications, reoperation, readmission and mortality were calculated using rate of that event in each group. RRs from all studies included were added together to calculate pooled RR using the DerSimonian and Laird random-effect model [15].

The heterogeneity of the MDs and RRs across studies was calculated using the Q statistic ( $I^2$  statistics) where  $I^2$  value of 0–25%, 26-50%, 51-75% and 76-100% means insignificant, low, moderate and high heterogeneity, respectively [16]. Visual inspection of funnel plots would be used to determine publication bias if enough eligible studies were identified. Statistical analysis was done using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom).

## Results

Some 4236 potentially relevant articles (2646 from EMBASE and 1590 from MEDLINE) were identified. After removal of 1104 duplicated articles, 3132 articles underwent title and abstract review. At this stage, 3098 articles were excluded because they did not meet our inclusion criteria – leaving the remaining 34 articles retrieved for a complete review. After reviewing full-length articles, 31 articles were excluded because of no emergency cases included (n=11), duplication (n=8), conference abstract (n=8), and no report of the outcome of interest (n=4). Details of the last four studies are as follows; one study compared outcome between patients underwent ERAS after emergency colorectal surgery who did and did not have complicated intraabdominal infection [17], one examined whether ERAS improved outcomes following emergency major abdominal surgery [18], one evaluated the feasibility of early postoperative mobilization after colorectal surgery under an ERAS protocol [19], and one determined predictors of nasogastric tube reinsertion following emergency operations for obstructive CRC [20]. Finally, three cohort studies [10-12] with 818 participants (418 underwent ERAS and 400 underwent conventional care) fulfilled the inclusion criteria and were included into the meta-analysis. Study flow is shown in **Figure 1**. Characteristics of the included studies are summarized in **Table 1**.

### *Length of hospital stay*

Length of hospital stay was significantly shorter in patients receiving ERAS than that of those receiving conventional care with the pooled MD of -3.07 days (95% CI, -3.91 to -2.23). Heterogeneity among studies was negligible ( $I^2$  of 0%) (**Figure 2a**).

### *Complications*

The rate of postoperative complication was significantly lower in patients receiving ERAS than that of those receiving conventional care with the pooled RR of 0.78 (95% CI, 0.63 to 0.97). Heterogeneity among studies was negligible ( $I^2$  of 0%) (**Figure 2b**).

### ***30-day readmission and mortality***

Rates of 30-day readmission and mortality were comparable between the two groups - with the pooled RR of 0.91 (95% CI, 0.54 to 1.51) and 0.79 (95% CI, 0.11 to 5.38), respectively. Heterogeneity among studies was negligible ( $I^2$  of 0% and 24%, respectively) (**Figure 2c and Figure 2d**).

### ***Time to gastrointestinal recovery***

Time to pass flatus was significantly shorter in patients receiving ERAS than that of those receiving conventional care with the pooled MD of -1.39 days (95% CI, -1.52 to -1.25). The between-study heterogeneity was negligible ( $I^2$  of 0%) (**Figure 3a**). Time to first defecation was also significantly shorter in patients receiving ERAS - with the pooled MD of -0.73 days (95% CI, -1.40 to -0.06), but heterogeneity between studies was moderate ( $I^2$  of 73%) (**Figure 3b**). A significantly shorter time to resume regular diet was found in the ERAS group with the pooled MD of -2.39 days (95% CI, -2.62 to -2.15), and the between-study heterogeneity was negligible ( $I^2$  of 0%) (**Figure 3c**).

### ***Postoperative ileus***

The rate of postoperative ileus was significantly lower in patients receiving ERAS than that of those receiving conventional care with the pooled RR of 0.55 (95% CI, 0.33 to 0.91). Heterogeneity among studies was negligible ( $I^2$  of 0%) (**Figure 4a**).

### ***Anastomotic leakage***

Rate of anastomotic leakage was comparable between the two groups - with the pooled RR of 0.96 (95% CI, 0.25 to 3.65). The between-study heterogeneity was negligible ( $I^2$  of 0%) (**Figure 4b**).

### ***Re-operation***

Rate of 30-day re-operation was comparable between the two groups - with the pooled RR of 0.78 (95% CI, 0.32 to 1.92). The between-study heterogeneity was negligible ( $I^2$  of 0%) (**Figure 4c**).

### ***Time to start adjuvant chemotherapy***

Patient receiving ERAS had a significantly shorter time to start adjuvant chemotherapy, with the pooled MD of -12.05 days (95% CI, -14.76 to -9.35) and negligible between-study heterogeneity ( $I^2$  of 0%) (**Figure 5**).

### ***Evaluation for publication bias***

Due to a limited number of eligible studies, funnel plot was not created for evaluating publication bias.

## Discussion

This systematic review and meta-analysis of ERAS in emergency resection for obstructive CRC incorporated 3 cohort studies that included 418 cases with ERAS and 400 cases with conventional care. This meta-analysis indicated that patients receiving ERAS had a significantly shorter length of hospital stay, quicker time to gastrointestinal recovery, lower incidence of postoperative ileus and overall complications, and shorter time to initiate adjuvant chemotherapy.

The approximately 3-day reduction in hospital stay and a 22% decreased risk of overall complications observed in this study are comparable to the benefit of ERAS in the setting of elective colorectal operation. A systematic review and meta-analysis of 13 randomized controlled trials including 1,910 patients undergoing elective major colorectal operations showed that ERAS decreased length of hospitalization by 2.4 days and decreased risk of overall complications by 29% compared with conventional care [8]. Another systematic review and meta-analysis of 25 trials including 3,787 patients undergoing elective laparoscopic or open surgery for malignant and benign colorectal diseases [9] found a 2.6 days reduction of hospital stay and a 34% decrease in risk of perioperative complications compared with conventional care. All of these suggest that benefit of ERAS is seen across different surgical approaches and indications.

There was no significant difference in the rate of anastomotic leakage and re-operation. Therefore, the benefit of early resumption of solid food and accelerated gastrointestinal recovery by ERAS does not come at the expense of increased anastomotic leakage. In fact, it has been shown that implementation of ERAS [21] and early consumption of solid food [22] can facilitate the return of bowel function and minimize the rate of prolonged ileus following elective colorectal operation.

The current study also demonstrated that patients in ERAS pathway had an approximately 2 weeks shorter time interval between operation and starting date of adjuvant chemotherapy (which is usually indicated in patients with obstructive CRC [23]). Time to adjuvant therapy is a potential mid-term outcome measure that could be used to determine patient's overall recovery and performance [24], as it has been shown that delayed commencement of adjuvant chemotherapy (especially > 8 week) is linked to a worse overall survival in patients with CRC. One possible explanation of this is that early initiation of postoperative chemotherapy may prevent tumor growth or recurrence [25]. Since postoperative complications are one of the major reasons for delayed adjuvant chemotherapy [26], the benefits of ERAS, therefore, may go beyond just the immediate postoperative period.

It is worth noting that all three cohort studies included in this meta-analysis used their 'modified' ERAS pathway [10–12] as there is still no standard ERAS Society guideline or recommendation for emergency colorectal surgery. Thus, it remains unknown which interventions of ERAS pathway are beneficial and should be recommended in clinical practice. Obviously, some interventions, such as preoperative nutritional support and carbohydrate loading, are not advisable for patients with acute malignant colonic

obstruction. However, most ERAS interventions recommended for elective colorectal operation appear to be applicable to emergency surgery as well [27].

It should also be noted that patients with obstructive CRC with colonic perforation were not included in any of the included studies. In fact, a recent study of ERAS in emergency colorectal resection for various colorectal conditions, including obstructive CRC and fecal peritonitis, suggested that patients with bowel perforation had a lower rate of ERAS compliance and a higher rate of complications than those without [17]. Further investigations are still needed to determine whether ERAS could provide similar benefits to these patients.

A major strength of this study is the unique advantage of the systematic review and meta-analysis technique that offers comprehensive evaluation of all available evidence. The study was conducted in accordance to the PRISMA guideline to ensure the highest standard of the analyses and data on several outcomes were analyzed. Nonetheless, there are some limitations that should be acknowledged.

First, only three cohort studies were included and they were all retrospective in nature. This may increase the risk for both performance and measurement bias – although a matching analysis was performed in two of the three studies [10, 12] and one study was a relatively large multicenter trial [12]. It is noteworthy that, to date, there is no published or registered randomized controlled trial that compares outcomes between ERAS versus conventional care in emergency setting for malignant colonic obstruction (<http://www.clinicaltrials.gov/ClinicalTrials.gov>; accessed on 25 March 2020). It may be difficult, or even ethical [27], to conduct such randomized controlled trials because ERAS has increasingly become a standard of surgical care [6]. As a result, the present study might be the best available evidence to support that ERAS can be applied effectively and safely in the setting of emergency resection for obstructive CRC - similar to elective colorectal operations [7–9].

Second, the role of compliance on the benefit of ERAS is not known as none of the included studies investigated the impact of compliance on surgical outcomes although a large international registry of patients undergoing elective CRC resection [28] and a small cohort of patients undergoing emergency surgery for obstructive CRC and colonic perforation [17] have demonstrated that higher compliance to ERAS was associated with better outcomes. Similarly, the impact of laparoscopy is not known because only one study in this meta-analysis included patients who underwent laparoscopic surgery in their ‘modified’ ERAS protocol (and only 4 patients were included) [11]. Although studies of elective colorectal surgery found a significant benefit of laparoscopy combined with ERAS with markedly improved surgical outcomes and patient recovery [28, 29], the benefit of laparoscopy may not be translated into emergency setting as the conversion rate is still relatively high [27].

## Conclusions

This systematic review and meta-analysis of 3 non-randomized observational studies incorporating 818 patients undergoing emergency resection for obstructive CRC found that, in comparison with conventional care, ERAS pathway was associated with a shorter length of hospital stay, quicker time to

bowel function recovery, a lower incidence of postoperative ileus and overall complications, and a shorter time to start adjuvant chemotherapy. Anastomotic leakage, re-operation, 30-day readmission and mortality were comparable between the groups.

## Declarations

### Ethics approval and consent to participation

Not applicable. (The identity of the subjects under this systematic review and meta-analysis was omitted and anonymized.)

### Consent for publication

Not applicable.

### Availability of data and materials

All data analyzed during this study are included in this published article.

### Completing interests

The authors declare that they have no completing interests.

### Funding

None

### Authors' contribution

VL and PU outlined the content. VL, RJ and WC reviewed literature and collected data. VL and PU analyzed data and wrote the manuscript. RJ and WC critically reviewed the manuscript. All authors read and approved the final manuscript.

### Acknowledgements

Not applicable.

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## Tables

Table 1 Main characteristics of the cohort studies included in the meta-analysis

	Lohsiriwat [10]	Shida et al. [11]	Shang et al. [12]
Country	Thailand	Japan	China
Study design	Retrospective cohort (matched-case control)	Retrospective cohort (Pre vs Post-ERAS)	Retrospective cohort (propensity score matching)
Period of study conducted	2011- 2013	2008 - 2012	2010 - 2017
Year of publication	2014	2017	2018
Total number of patients (ERAS vs non-ERAS)	60 (20 vs 40)	122 (80 vs 42)	636 (318 vs 318)
Inclusion criteria	Obstructive CRC	Obstructive CRC	Obstructive CRC
Exclusion criteria	No bowel resection, concomitant bowel perforation, recurrent tumor, neoadjuvant therapy	No bowel resection, concomitant bowel perforation	No bowel resection, concomitant bowel perforation, recurrent tumor, gastrointestinal bleeding, neoadjuvant therapy, colonic stent utilization
Outcome(s)	LOHS, 30-day morbidity, 30-day mortality, 30-day readmission, GI recovery time, interval between surgery and chemotherapy	LOHS, 30-day morbidity, 30-day mortality, 30-day readmission	LOHS, 30-day morbidity, GI recovery time, interval between surgery and chemotherapy
Average age (years)	ERAS: 58 Non-ERAS: 62	ERAS: 69 Non-ERAS: 68	ERAS: 66 Non-ERAS: 65
Male (%)	ERAS: 70 Non-ERAS: 60	ERAS: 65 Non-ERAS: 60	ERAS: 60 Non-ERAS: 63
Average BMI (kg/m <sup>2</sup> )	ERAS: 21.7 Non-ERAS: 22.8	n/a	ERAS: 25.1 Non-ERAS: 24.9
ASA class ≥ 3 (%)	ERAS: 20 Non-ERAS: 10	n/a	ERAS: 32 Non-ERAS: 31
Tumor location: right colon, left colon, rectum (%)	ERAS: 50, 40, 10 Non-ERAS: 47, 40, 13	ERAS: 34, 50, 16 Non-ERAS: 41, 45, 14	ERAS: 43, 45, 12 Non-ERAS: 45, 41, 14
Pathological staging ≥ 3 (%)	ERAS: 70 Non-ERAS: 65	ERAS: 60 Non-ERAS: 74	ERAS: 69 Non-ERAS: 71
Newcastle-Ottawa score	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 1 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3

## Figures

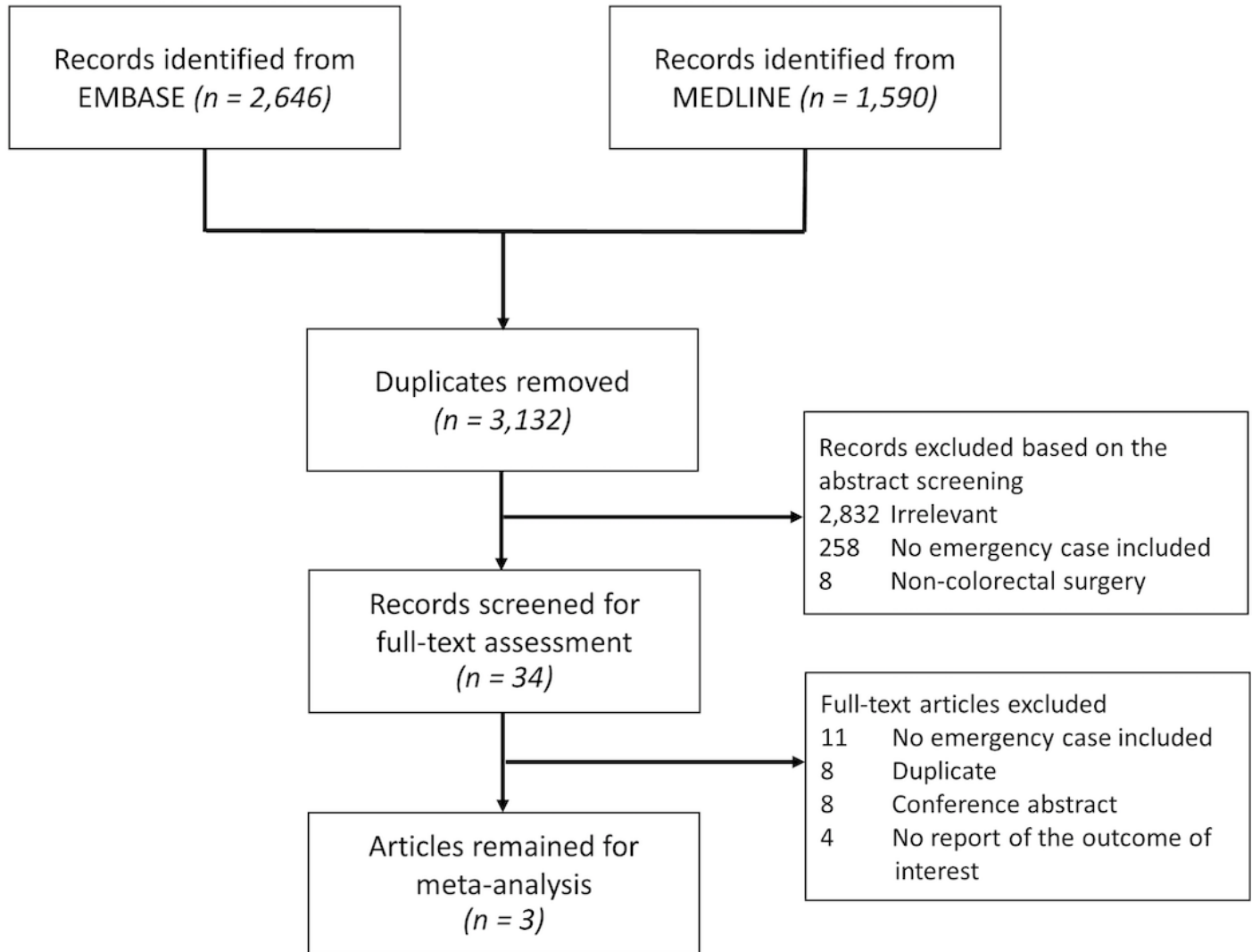
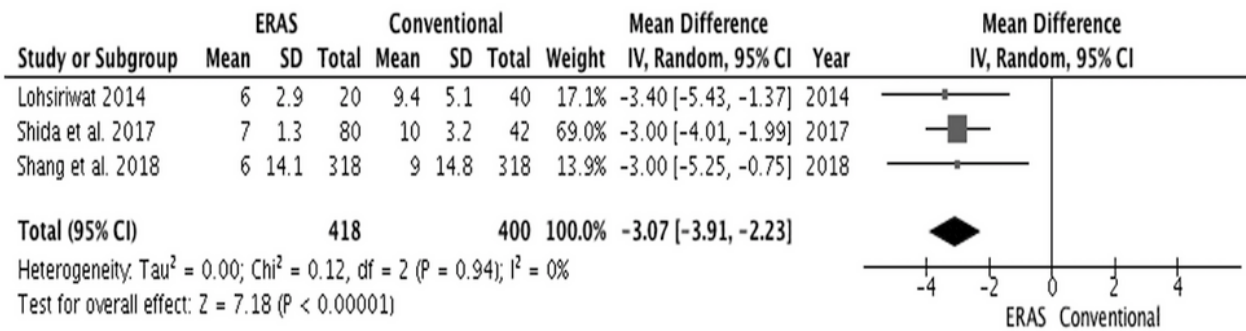


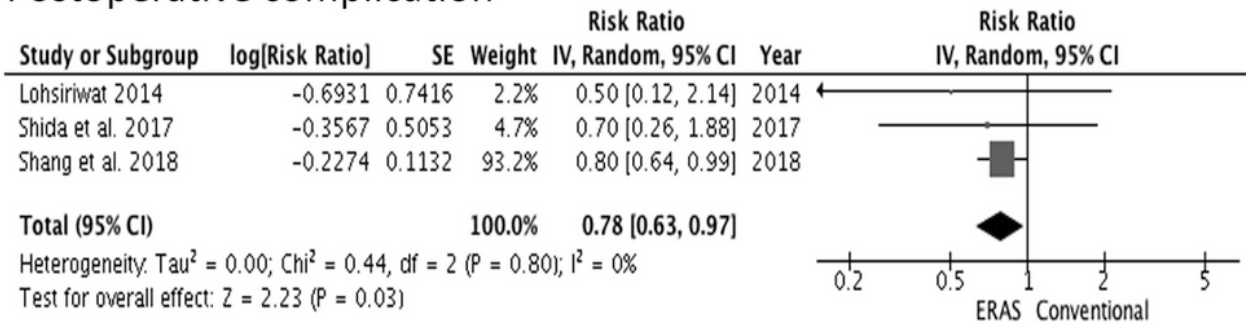
Figure 1

PRISMA flow diagram

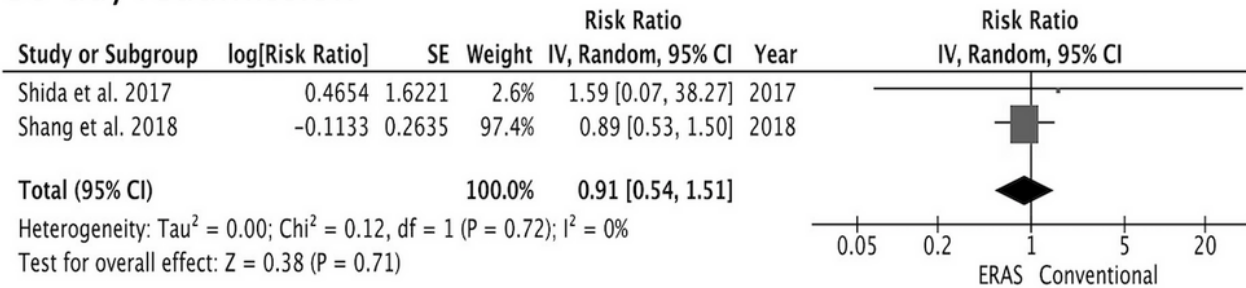
### (a) Length of hospital stay



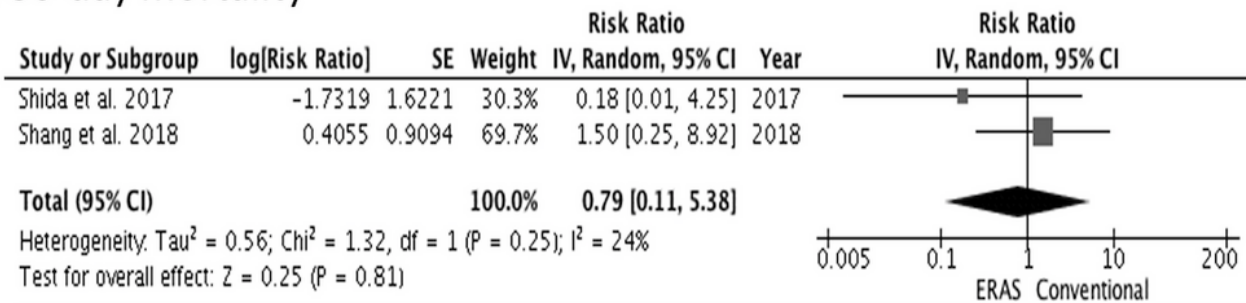
### (b) Postoperative complication



### (c) 30-day readmission



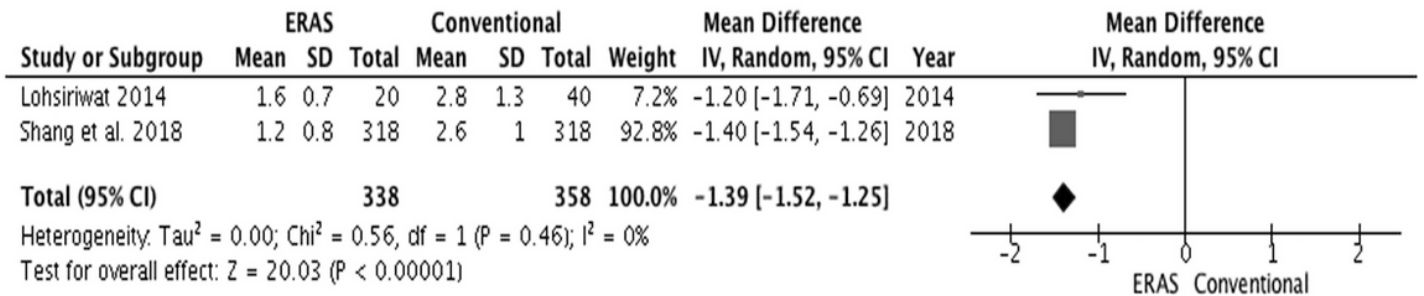
### (d) 30-day mortality



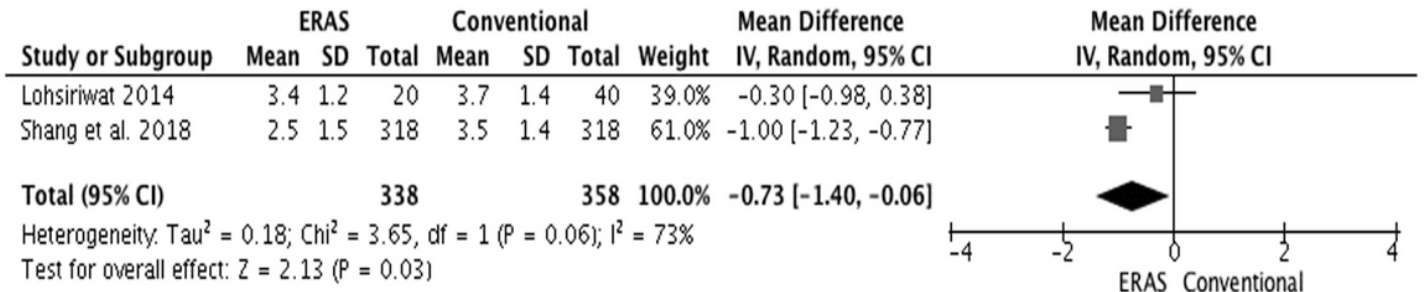
**Figure 2**

Forest plots of the comparisons of main surgical outcomes between ERAS and conventional care: (a) length of hospital stay, (b) postoperative complication, (c) 30-day readmission and (d) 30-day mortality. ERAS = enhanced recovery after surgery

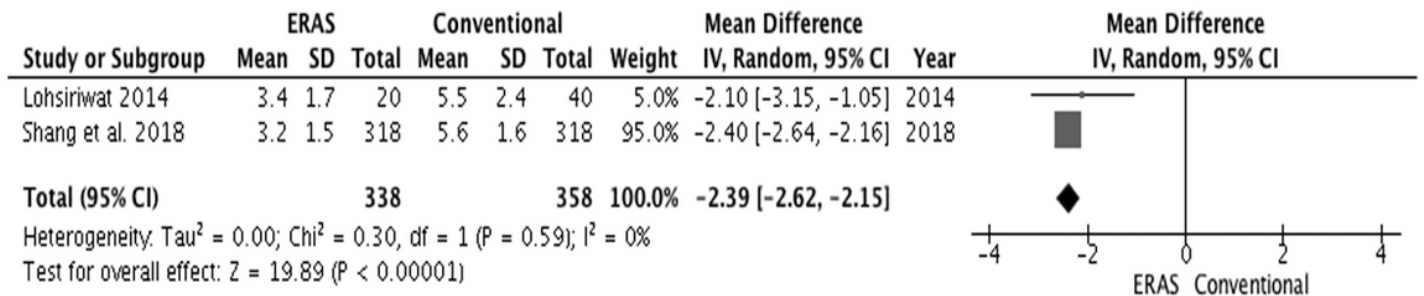
### (a) Time to pass flatus



### (b) Time to first defecation



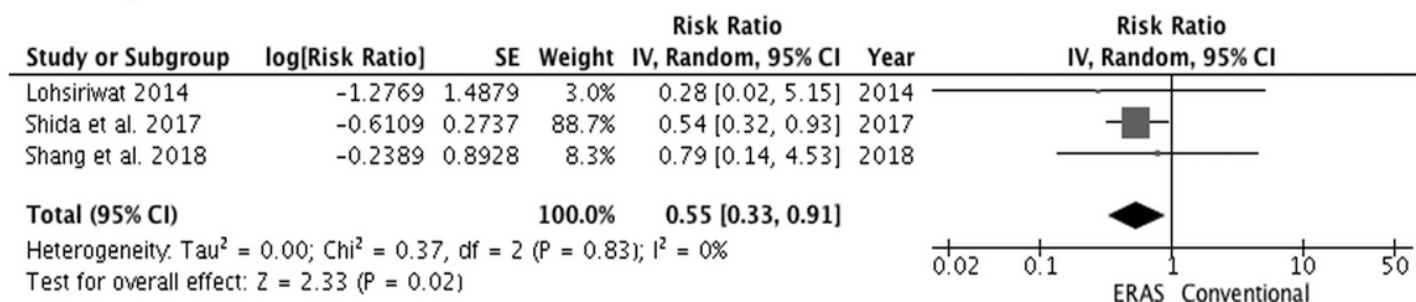
### (c) Time to resume solid food



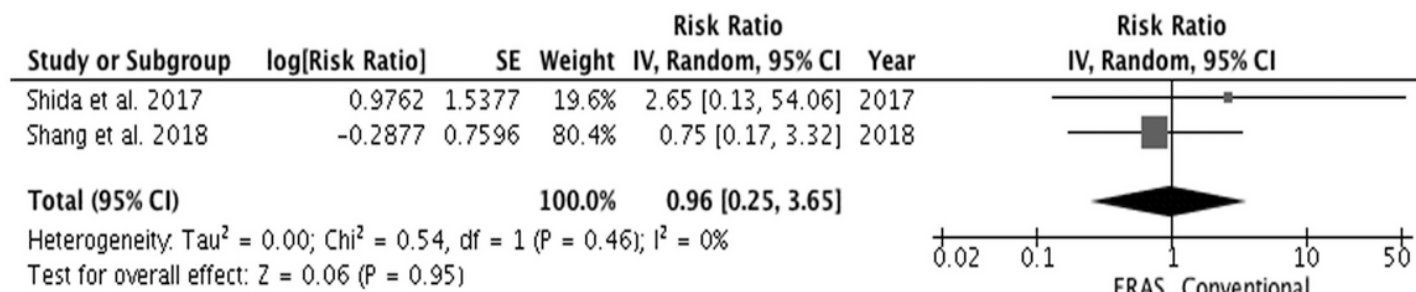
**Figure 3**

Forest plots of the comparisons of gastrointestinal recovery between ERAS and conventional care: (a) time to pass flatus, (b) time to first defecation and (c) time to resume solid food. ERAS = enhanced recovery after surgery

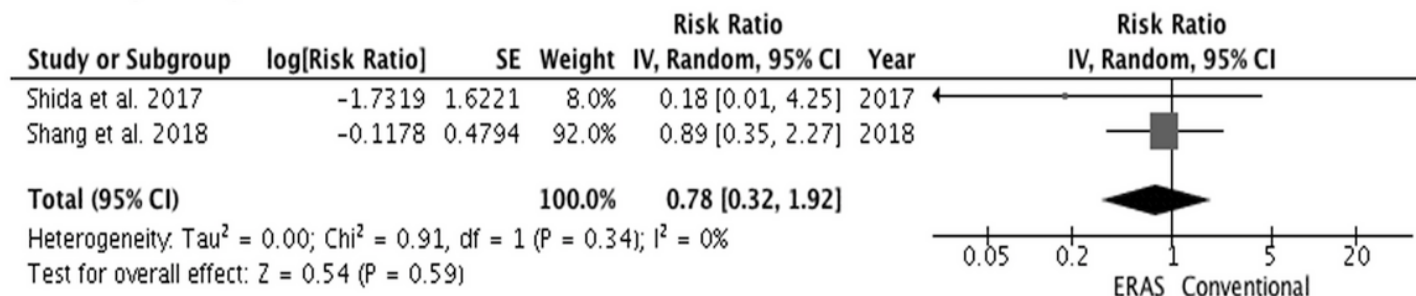
## (a) Postoperative ileus



## (b) Anastomotic leakage

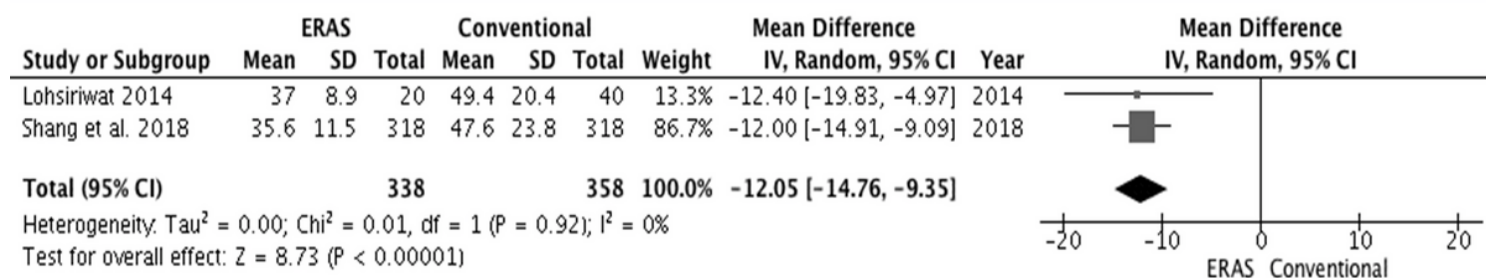


## (c) 30-day reoperation



**Figure 4**

Forest plots of the comparisons of postoperative morbidities between ERAS and conventional care: (a) postoperative ileus, (b) anastomotic leakage and (c) 30-day reoperation. ERAS = enhanced recovery after surgery



**Figure 5**

Forest plots of the comparisons of time to start adjuvant chemotherapy between ERAS and conventional care. ERAS = enhanced recovery after surgery