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REVIEW ARTICLE

Enhanced recovery versus conventional care in gastric cancer surgery: a meta-analysis of randomized and non-randomized controlled trials

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Abstract

Introduction Enhanced recovery after surgery (ERAS) protocols have been successfully integrated into peri-operative management of different cancer surgeries such as colorectal cancer. Their value for gastric cancer surgery, however, remains uncertain.

Methods A search for randomized and observational studies comparing ERAS versus conventional care in gastric cancer surgery was performed according to PRISMA guidelines. Random-effects meta-analyses with inverse variance weighting were conducted, and quality of included studies was assessed using the Cochrane risk-of-bias tool and Newcastle-Ottawa scale (PROSPERO: CRD42017080888).

Results Twenty-three studies involving 2686 patients were included. ERAS was associated with reduced length of hospital stay (WMD—2.47 days, 95% CI − 3.06 to − 1.89, $P < 0.00001$), time to flatus (WMD—0.70 days, 95% CI − 1.02 to − 0.37, $P < 0.0001$), and hospitalization costs (WMD—USD$ 4400, 95% CI − USD$ 5580 to − USD$ 3210, $P < 0.00001$), with consistent results across open and laparoscopic surgery. Postoperative morbidity and 30-day mortality were similar, although a higher rate of readmission was observed in the ERAS group (RR = 1.95, 95% CI 1.03–3.67, $P = 0.04$). Patients in the ERAS arm had significantly attenuated C-reactive protein levels on days 3/4 and 7, interleukin-6 levels on days 1, and 3/4, and tumor necrosis factor-α levels on days 3/4 postoperatively.

Conclusion Compared to conventional care, ERAS reduces hospital stay, costs, surgical stress response and time to return of gut function, without increasing post-operative morbidity in gastric cancer surgery. However, precaution is necessary to reduce the increased risk of hospital readmission when adopting ERAS.

Keywords ERAS · Enhanced recovery after surgery · Gastric surgery · Gastric cancer

Introduction

Gastric cancer is the fourth leading cause of cancer-related mortality globally, accounting for over 750,000 deaths annually [1]. Surgical resection remains the pillar of gastric cancer management, but is associated with significant post-operative morbidity and healthcare costs [2], hence warranting improvements in surgical standards. First described by Bardram et al. in 1995 [3], the enhanced recovery after surgery (ERAS) pathway adopts a multidisciplinary approach to expedite recovery, alleviate surgical stress response, and reduce complication rates. The ERAS program amalgamates distinct key measures including preoperative counselling; provision of carbohydrate loading prior to surgery; perioperative management of body temperature; early removal of urinary catheters, early postoperative feeding and mobilization. Important procedures that are avoided include bowel

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preparation; premedication; preoperative fasting; perioperative fluid overload; use of drains and nasogastric decompression tubes [4, 5].

ERAS programs have long been established in colorectal cancer surgery, demonstrating improved complication rates, reduced length of hospital stay without compromising patient safety [4]. Recently, the enhanced recovery after surgery (ERAS®) Society published a consensus guideline on gastrectomy for cancer patients [6]. However, the measure of impact following the adoption of these guidelines is yet to be established. Nonetheless, reports evaluating ERAS programs for gastrectomy for gastric cancer are emerging, albeit few in numbers, small in sample sizes, and incongruent in conclusions [7–24]. A few meta-analyses [25–33] have also attempted to assess the impacts of ERAS for gastric cancer surgeries, reporting shorter length of stay, reduced hospital cost, and improved recovery of gut function in the ERAS arm, with no increased risk of post-operative complications. Although some studies demonstrated a trend towards an increased risk of readmission, this was not statistically significant and was hence something we were interested to explore. There was significant heterogeneity in the number of included studies (ranging from 6 to 14), attributable to methodological gaps and weaknesses, which we seek to address in this systematic review and meta-analysis.

The aim of this systematic review and meta-analysis is to review the latest body of literature comparing ERAS programs with conventional care in gastric cancer surgery. Unlike previously published meta-analyses, a comprehensive coverage of the literature will be achieved to provide the real-world evidence by including randomized and non-randomized studies in both published and unpublished forms.

Methods

The study method was conducted as per the guidelines of the Cochrane Handbook of systematic reviews and meta-analysis [25], and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [26]. An electronic search was performed on the following databases: Medline (via PubMed), Embase, OvidSP, Cochrane databases, and the ClinicalTrials.gov website to identify all published and indexed studies reporting gastrectomy outcomes in an enhanced recovery after surgery program. A repetitive and exhaustive combination of the following 'MeSH' search terms were used: "Stomach Neoplasms", "Stomach Diseases", "Stomach", "Gastrectomy", "Laparoscopy", "General Surgery". These were combined with non-MeSH terms including: fast track, ERAS, enhanced recovery after surgery, multimodal, accelerated rehabilitation. The reference lists of relevant studies were manually search to identify additional studies. The last date of search was 10th September 2018. The protocol was registered on PROSPERO prior to the commencement of this study (CRD42017080888).

Inclusion and exclusion criteria

Studies were included if comparative outcomes were reported for patients undergoing ERAS programs versus conventional care for gastric cancer surgery. There was no restriction on study type and language. However, non-English studies with no extractable data were excluded.

Selection of studies and data extraction

Two reviewers (IW, NS) independently screened and assessed the studies for inclusion. The studies were first screened by their titles and abstracts. We then retrieved the full-text articles for review if we could not confirm the relevance of the studies for inclusion. If disputed, JS or GK would be the arbiter to resolve differences of opinions regarding the studies' eligibility by discussion and consensus. Full-text articles were retrieved for review if we could not confirm the relevance of the studies for inclusion. The search strategy is shown in the PRISMA diagram (Fig. 1).

Primary outcomes of interest included length of hospital stay (LOS), postoperative morbidity, rates of readmission, time to return of gut function, and total costs. Secondary outcomes of interest included inflammatory markers [C-reactive protein (CRP), interleukin 6 (IL6), tumour necrosis factor alpha (TNFα)]. We abstracted the following data from each study: first author, year, type of publication, age, gender, ERAS measures, length of hospital stay (LOS) in days, rates of postoperative morbidity, rates of readmission, inflammatory markers at postoperative days 1, 3/4, and 7 (CRP, IL6, TNFα), time to return of gut function, and total costs.

Data analysis

All statistical analyses were conducted using RevMan 5.1 software (The Nordic Cochrane Centre, Copenhagen, Denmark). A meta-analysis was conducted to pool weighted mean difference (WMD) or standardized mean difference (SMD) as the summary statistic for continuous variables, and risk ratio (RR) for dichotomous variables. Statistical heterogeneity was assessed using the I^2 statistic. A fixed-effects model was chosen when the I^2 statistic value was less than or equal to 50%, and a random-effects model otherwise. Results were reported with 95 percent confidence intervals (95% CI), and a P value of less than 0.05 was considered to be statistically significant. When outcomes were reported as median and range, methods described by Hozo et al. [27] were utilized to convert the values to the mean and standard deviation (SD). In brief, SD was calculated as range/6 and

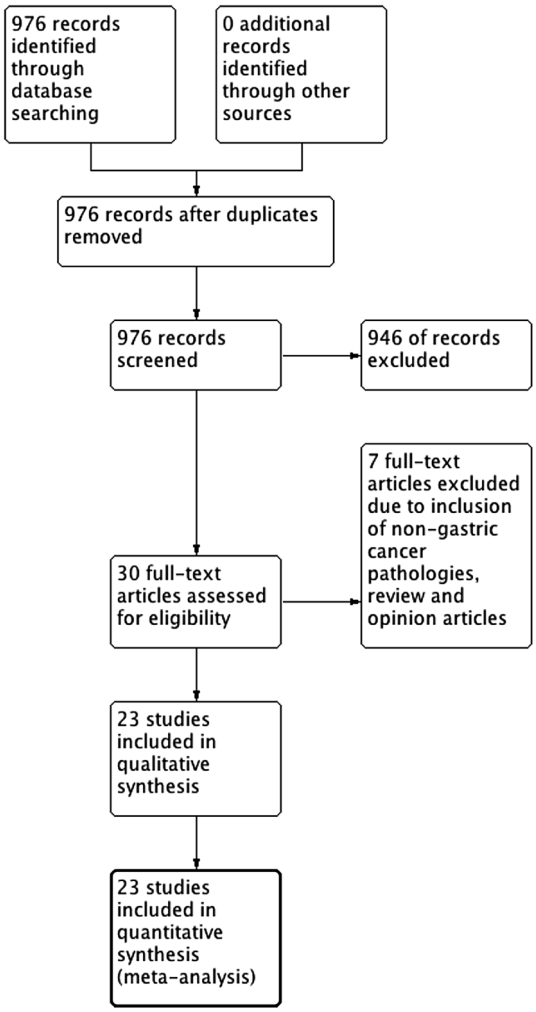

Fig. 1 PRISMA flow diagram

range/4 when the sample sizes were either greater than 70 or between 15 and 59, respectively.

Assessment of bias

Assessment of study quality and risk of bias for randomized controlled trials was conducted using the Cochrane Risk of Bias tool [25], which included aspects of selection, performance, detection, attrition, reporting and other bias. The Newcastle-Ottawa scale [28] was used to assess quality of non-randomized studies, which included domains of patient selection, comparability of study groups, and outcome assessment. With respect to all aforementioned outcomes of interest, several pooled analyses were conducted and stratified based on the surgical techniques used in the intervention arms. Two subgroup analyses were performed for each endpoint: (1) open versus laparoscopic surgery, (2) high versus low number of items in the ERAS protocol. Based on a published Cochrane review [29] that defined a minimum of 7 out of 17 items in the ERAS protocol as a benchmark, we applied this standard to our study using the consensus guidelines published by the ERAS® Society for gastrectomy [6]. Publication bias was evaluated based on visual inspection for extent of symmetry on the funnel plot, as well as using Egger's regression test if there were more than ten studies.

Results

Systematic search

The systematic search revealed a total of 976 publications for possible inclusion. Based on title and abstract review, irrelevant publications, duplicate publications or those not fitting our inclusion criteria were excluded. Thirty publications were reviewed in their entirety and seven were excluded based on the full text, leaving 23 studies included in the final analysis (Fig. 1). This included 14 randomized controlled trials (RCTs) [7–12, 14, 15, 17, 19–21, 23, 30, 31], 5 prospective cohort studies [16, 18, 22, 32, 33], one of which was a conference abstract [34], and 3 retrospective cohort studies [13, 24].

Study characteristics

The 23 studies comprised a total of 2686 patients, of which 1391 received ERAS program, and 1295 received conventional care. Six studies [15, 18, 20, 23, 30, 31] reported only the laparoscopic approach, while three studies [14, 16, 23] reported both. For the latter, outcomes were extracted in a stratified manner according to open or laparoscopic, except for one study [16] that did not stratify the outcomes based on surgical technique. Across the studies, the mean age ranged from 52.6 to 80.1 years in the ERAS arm, and 54.5 to 79.6 years in the conventional care arm. The proportion of males ranged from 42.9 to 74% in the ERAS arm, and 45.5–80% in the conventional arm. One study [21] stratified the outcomes according to age groups (45–74 years; 75–89 years), and hence was included in the meta-analysis as two separate studies. The characteristics of the included studies are shown in Table 1.

Supplementary table 1 details the ERAS program technical measures reported in all, except for seven studies due to insufficient information in full-text [7–9, 19, 23, 34]. The average number of items reported was 9.7/17. As only one study registered below the benchmark number of ERAS items, we could not perform subgroup analysis assessing high versus low number of ERAS protocol items [13]. None of the studies reported patient adherence rates, hence subgroup analysis investigating patient adherence could not be performed (Supplementary table 1).

Table 1 Baseline characteristics of included studies

First author, year	Study design	Outcomes reported	Open or laparoscopic	Treatment arm	Number of patients	Mean age ± SD	Gender (Male/%)	Surgery: distal/subtotal gastrectomy (%)	Surgery: total gastrectomy (%)	Surgery: function preserving (%)	Surgery: others (%)
Kiyama, 2003	RCT	1, 2, 9	Open	ERAS	47	NR	NR	NR	NR	NR	NR
				Conventional	38	NR	NR	NR	NR	NR	NR
Jiang, 2007	RCT	1, 8, 9	Open	ERAS	40	NR	NR	NR	NR	NR	NR
				Conventional	40	NR	NR	NR	NR	NR	NR
So, 2008	ReC	1, 2, 3, 4, 9	Open	ERAS	61	66.3	70.5	74.0	NR	23.0	3.0
				Conventional	54	63.7	68.5	74.1	NR	25.9	0.0
Wang, 2009	RCT	5, 6, 7, 8, 9	Open	ERAS	46	NR	NR	NR	NR	NR	NR
				Conventional	46	NR	NR	NR	NR	NR	NR
He, 2010	RCT	1, 2, 8, 9	Open	ERAS	59	NR	NR	NR	NR	NR	NR
				Conventional	41	NR	NR	NR	NR	NR	NR
Liu, 2010	RCT	1, 2, 3, 4, 5, 6, 7, 8	Open	ERAS	33	60.7 ± 9.7	54.5	60.6	39.4	NR	NR
				Conventional	30	61.9 ± 8.3	50.0	63.3	36.7	NR	NR
Wang, 2010	RCT	1, 2, 3, 4, 5, 6, 7, 8, 9	Open	ERAS	45	58.8 ± 9.7	71.1	84.4	15.6	NR	NR
				Conventional	47	56.9 ± 9.2	61.7	89.4	10.6	NR	NR
Tang, 2010	ReC	1, 2, 8, 9		ERAS	21	NR	NR	NR	NR	NR	NR
				Conventional	21	NR	NR	NR	NR	NR	NR
Hu, 2012 (open)	RCT	1, 2, 5, 8, 9	Open	ERAS	21	59.8 ± 8.9	42.9	100	NR	NR	NR
				Conventional	20	63.3 ± 7.5	60.0	100	NR	NR	NR
Hu, 2012 (laparoscopic)	RCT	1, 2, 5, 8, 9	Laparoscopic	ERAS	19	59.5 ± 6.4	52.6	100	NR	NR	NR
				Conventional	22	60.5 ± 7.8	45.5	100	NR	NR	NR
Kim, 2012	RCT	1, 2, 4, 5, 8, 9	Laparoscopic	ERAS	22	52.6 ± 11.6	59.1	100	NR	NR	NR
				Conventional	22	57.5 ± 14.5	68.2	100	NR	NR	NR
Yamada, 2012	PC	1, 2	Open/laparoscopic – 43/48 in ERA; 57/43 in conventional	ERAS	91	65 ± 12.1	68.1	37.4	62.6	NR	NR
				Conventional	100	61 ± 15.9	72.0	48.0	52.0	NR	NR
Feng, 2013	RCT	1, 2, 3, 4, 8, 9	Open	ERAS	59	55 ± 11.4	69.5	NR	100.0	NR	NR
				Conventional	60	56.8 ± 10.1	73.3	NR	100.0	NR	NR
Sahoo, 2014	PC	1, 5, 8	Laparoscopic	ERAS	22	61.8 ± 10.7	59.1	NR	100.0	NR	NR
				Conventional	25	66.3 ± 6.1	52.0	NR	100.0	NR	NR
Wang, 2014	RCT	1, 8, 9	Open	ERAS	71	NR	NR	NR	NR	NR	NR
				Conventional	71	NR	NR	NR	NR	NR	NR
Abdikarim, 2015	RCT	1, 2, 8	Laparoscopic	ERAS	30	63 ± 12	70.0	70.0	30.0	NR	NR
				Conventional	31	62 ± 11	64.5	74.2	25.8	NR	NR

Table 1 (continued)

First author, year	Study design	Outcomes reported	Open or laparoscopic	Treatment arm	Number of patients	Mean age ± SD	Gender (Male/%)	Surgery: distal/subtotal gastrectomy (%)	Surgery: total gastrectomy (%)	Surgery: function preserving (%)	Surgery: others (%)
Bu, 2015 (45–74 years)	RCT	1, 2, 4, 8, 9	Open	ERAS	64	62.4 ± 7.8	48.4	76.0	24.0	NR	NR
				Conventional	64	63 ± 7.4	54.7	66.0	34.0	NR	NR
Bu, 2015 (75–89 years)	RCT	1, 2, 4, 8, 9	Open	ERAS	64	80.1 ± 4	57.8	66.0	34.0	NR	NR
				Conventional	64	79.6 ± 3.5	62.5	74.0	26.0	NR	NR
Karran, 2016	PC	1, 2, 3, 4	Open	ERAS	160	60.5 ± 17.9	74.0	NR	NR	NR	NR
				Conventional	92	65.5 ± 13.6	80.0	NR	NR	NR	NR
Liu, 2016 (Open)	RCT	1, 2, 5, 6, 8, 9	Open	ERAS	21	67.8 ± 3.9	42.9	71.4	28.6	NR	NR
				Conventional	21	68.6 ± 4.9	52.4	76.2	23.8	NR	NR
Liu, 2016 (Laparoscopic)	RCT	1, 2, 5, 6, 8, 9	Laparoscopic	ERAS	21	69.2 ± 5.1	47.6	57.1	42.9	NR	NR
				Conventional	21	70.3 ± 5.8	57.1	42.8	57.2	NR	NR
Meng, 2016	Conference abstract	1, 2, 4, 5, 6, 7, 8, 9	Open	ERAS	70	NR	NR	NR	NR	NR	NR
				Conventional	70	NR	NR	NR	NR	NR	NR
Li, 2016	PC	1, 2, 8	Laparoscopic	ERAS	67	NR	NR	NR	NR	NR	NR
				Conventional	60	NR	NR	NR	NR	NR	NR
Mingjie, 2016	RCT	1, 2, 5, 8	Open	ERAS	73	61 (40–75)	65.8	NR	NR	NR	NR
				Conventional	76	63 (35–75)	65.8	NR	NR	NR	NR
Makuuchi, 2017	ReC	1, 2, 4	Open	ERAS	108	59.5 ± 11.2	65.7	67.6	7.4	25.0	NR
				Conventional	108	60.3 ± 10.7	65.7	57.4	1.9	40.7	NR
Kang, 2018	RCT	1, 2, 3, 4, 8	Laparoscopic	ERAS	46	56.3 ± 10.4	28.8	100.0	0.0	0.0	0.0
				Conventional	51	54.5 ± 12.6	25.5	100.0	0.0	0.0	0.0

RCT randomized controlled trial, *ReC* retrospective cohort study, *PC* prospective cohort study, *NR* not reported

[a]Outcomes reported: 1—length of postoperative stay; 2—postoperative morbidity; 3—postoperative mortality; 4—rates of readmission;5—CRP levels; 6—IL6 level; 7—TNF-a levels; 8—time to return to gut function; 9—total hospital cost

Study quality

Of the eight cohort studies assessed using the Newcastle-Ottawa scale [28], five studies [13, 16, 18, 22, 24] had a score above 7 out of the maximum 9, and were deemed to be robust with regards to bias arising from patient selection, comparability of study groups, and outcome assessment. One study scored 5 [23], and one was not assessed due to the limited information in the conference abstract (Supplementary table 2). The risk-of-bias for randomized trials was assessed using the Cochrane Risk-of-Bias tool [25], where all studies had high risk for performance and detection bias as blinding of participants, personnel and/or outcome assessors was not performed in any trial. However, the authors concede that this is an inherent limitation in surgical interventions.

Length of hospital stay (LOS)

All except one study [9] reported LOS, involving 2469 participants, which yielded a statistically significant shorter LOS in the ERAS arm in the overall analysis (WMD—2.47 days, 95% CI −3.06 to −1.89, $P<0.00001$), with significant heterogeneity between the studies ($I^2=91\%$, $P<0.00001$). It was evident graphically from the forest plot that the LOS consistently favored the ERAS arm across individual studies. Subgroup analysis likewise recapitulated the aforementioned advantages, with both open (WMD—2.89 days 95% CI −3.66 to −2.12, $P<0.00001$) and laparoscopic (WMD—1.70 days, 95% CI −2.63 to −0.76, $P<0.00001$) approaches demonstrating shorter LOS in the ERAS arm (Fig. 2). There was a moderate risk of publication bias based on the funnel plot (Figure S1), and Egger's test was significant ($P=0.047$).

Postoperative morbidity

Seventeen studies involving 4348 participants evaluated the rate of post-operative morbidity. There were no statistically significant differences in postoperative morbidity between ERAS and conventional care in the overall analysis (RR = 0.96, 95% CI 0.75–1.23, $P=0.73$), with a low level of heterogeneity between the studies ($I^2=45\%$, $P=0.01$). In subgroup analysis, the laparoscopic approach reported significantly higher morbidity rates in the ERAS arm (RR = 1.49, 95% CI 1.04–2.13, $P=0.009$) (Fig. 3). Although the slight asymmetry in the funnel plot points toward a possible influence of publication bias, Egger's test was not significant for the risk of small-study effects ($P=0.083$) (Figure S2).

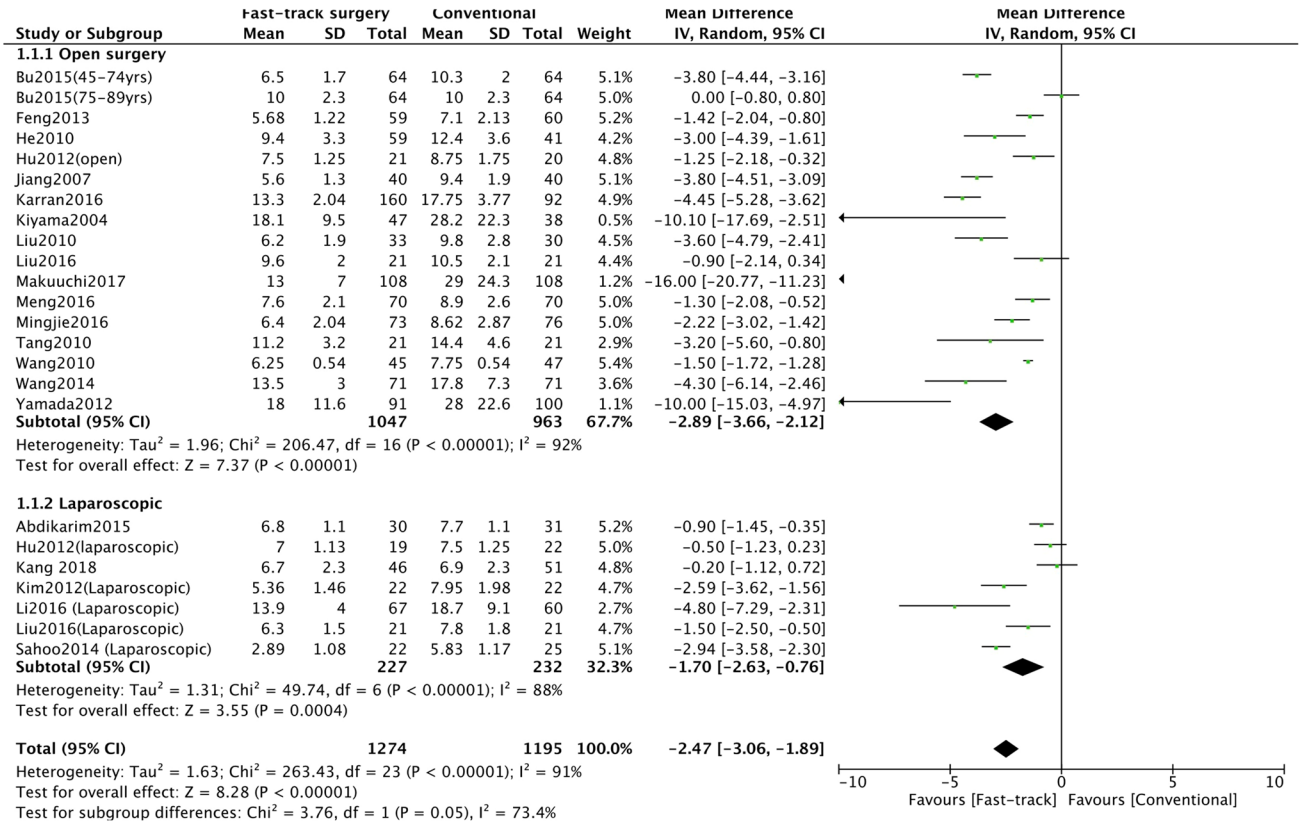

Fig. 2 Length of hospital stay (LOS)

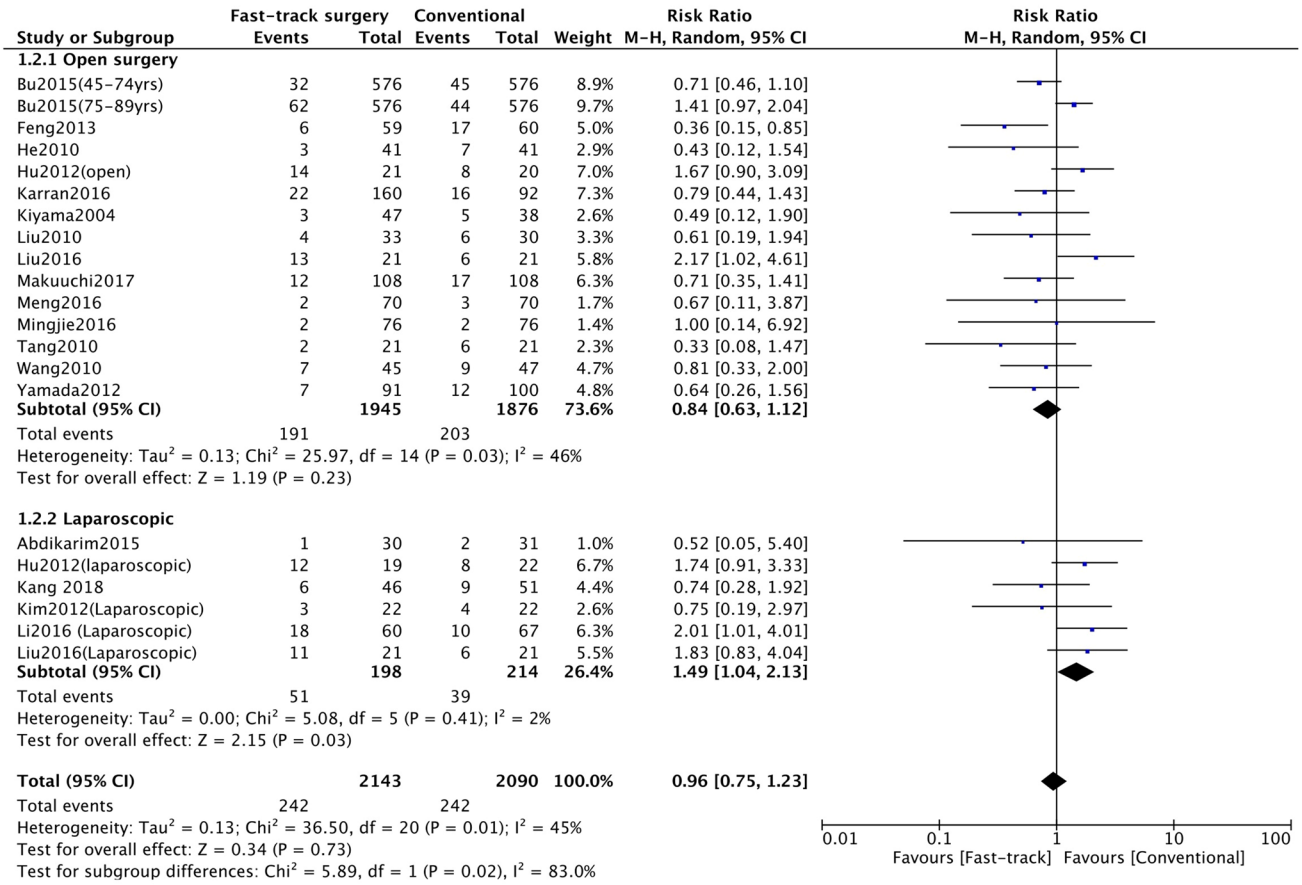

Fig. 3 Postoperative morbidity

Readmission rates

Nine studies involving 1273 participants reported readmission rates. Intriguingly, there was a statistically significant increase in readmission rates in the ERAS arm than in the conventional arm (RR = 1.95, 95% CI 1.03–3.67, $P = 0.04$), with no heterogeneity between the studies ($I^2 = 0\%$, $P = 0.70$). This was likewise corroborated in subgroup analysis, where the open approach reported significantly increased readmission rates in the ERAS arm (RR = 1.92, 95% CI 1.00–3.67, $P = 0.05$) (Fig. 4). There was no evidence of publication bias, evident from the high degree of symmetry in the funnel plot, and Egger' test ($P = 0.288$) (Figure S3).

Time to return of gut function

Fourteen studies involving 1643 participants reported time to return of gut function. The pooled analysis demonstrated that gut function recovered quicker in the ERAS arm, as evident from the significantly shorter time to return to flatus (WMD—0.70 days, 95% CI − 1.02 to − 0.37, $P < 0.0001$), although statistical heterogeneity across studies was significantly high ($I^2 = 96\%$, $P < 0.00001$). This was reiterated in the subgroup analysis, where both the open (WMD—0.73 days, 95% CI − 1.21 to − 0.24, $P = 0.003$), and laparoscopic arms (WMD—0.65 days, 95% CI − 0.97 to − 0.33, $P < 0.0001$) reported an improved recovery time in the ERAS arm (Fig. 5). There was no evidence of publication bias, given the high degree of symmetry in the funnel plot, and Egger's test ($P = 0.903$) (Figure S4).

Total cost

Thirteen studies involving 1358 participants provided data on total cost, yielding a significantly lower cost in the ERAS arm (WMD—4.40, 95% CI − 5.58 to − 3.21, $P < 0.00001$), although statistical heterogeneity was high across studies ($I^2 = 83\%$, $P < 0.00001$). Subgroup analyses recapitulated the aforementioned (Fig. 6). Again, there was no evidence of publication bias, as seen from the high degree of symmetry in the funnel plot, and Egger's test ($P = 0.157$) (Figure S5).

Additional outcomes

The meta-analysis also examined post-operative inflammatory markers and 30-day mortality. CRP levels were

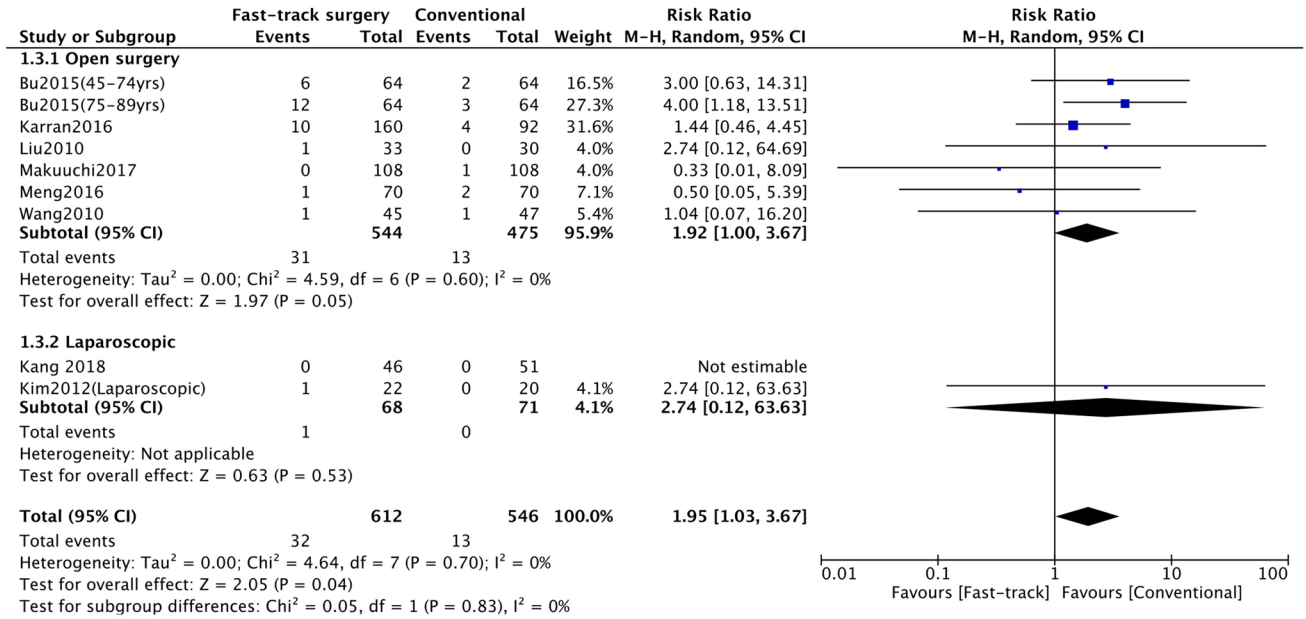

Fig. 4 Readmission rates

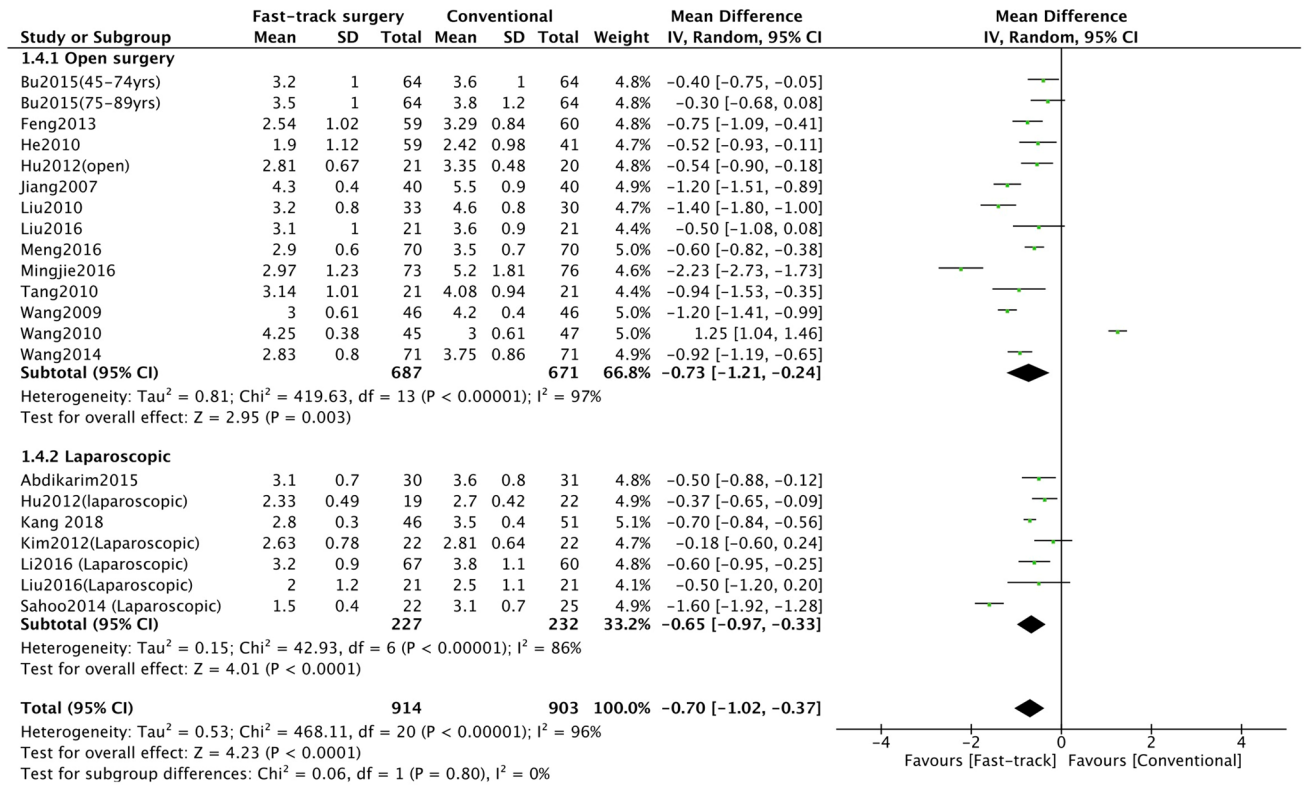

Fig. 5 Time to return of gut function

significantly lower in the ERAS arm on post operative days 3/4 (WMD—22.05 mg/L 95% CI − 28.32 to − 15.78 mg/L, $P < 0.00001$, $N = 8$ studies) and 7 (WMD—18.14 mg/L 95% CI − 24.21 to − 12.07 mg/L, $P < 0.00001$, $N = 6$ studies), but not on day 1 (WMD—11.46 mg/L 95%CI − 28.26 to − 5.34 mg/L, $P = 0.18$, $N = 8$ studies). IL6 levels were

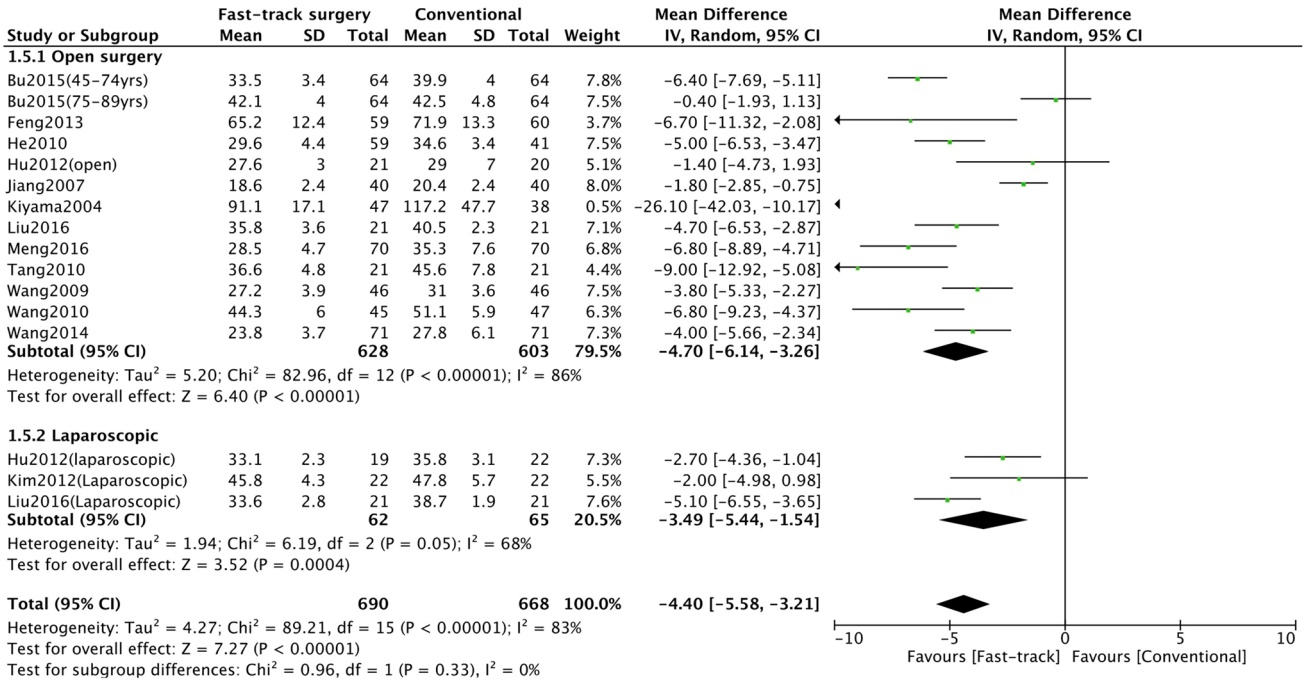

Fig. 6 Total cost

significantly lower in the ERAS arm on post operative days 1 (SMD—1.57, 95% CI − 2.39 to − 075, $P = 0.0002$, $N = 5$ studies), 3/4 (SMD—1.02, 95% CI − 2.00 to − 0.04, $P = 0.04$, $N = 4$ studies), but not 7 (SMD—4.29, 95% CI − 8.99 to 0.40, $P = 0.07$, $N = 2$ studies). Lastly, TNFα levels was significantly lower in the ERAS arm on days 3/4 (SMD—0.36, 95% CI − 0.61 to − 0.11, $P = 0.005$, $N = 3$ studies), but not on day 1 (SMD—0.49, 95% CI − 1.20 to 0.23, $P = 0.18$, $N = 4$ studies) (Figures S6–S13). A pooled analysis of 12 studies ($n = 1313$) revealed no significant difference in 30-day mortality between both arms (RR = 0.58, 95% CI 0.06–6.10, $P = 0.65$) (Figure S14).

Discussion

We summarized the total body of evidence comparing ERAS program versus conventional care for patients undergoing gastric cancer surgery. Our findings demonstrate that the ERAS program resulted in shorter length of hospital stay (LOS), reduced hospital costs, reduced time to return of gut function, without compromising on risks of morbidity and mortality; however, an increased rate of readmission was observed in the ERAS arm, a finding not demonstrated in previous meta-analyses. Furthermore, there were weaknesses in these studies [35–43]. All except one meta-analysis [38] included only randomized controlled trials (RCTs); Li et al. [37] only examined laparoscopic gastrectomy; Ding et al. [36] limited their analysis to English language articles. In another study, all surgeries of the gastrointestinal tract were included which portends significant heterogeneity [32]. In addition, there are newer studies that have been published recently. Hence, our study serves as the latest and most comprehensive review of the literature on ERAS for gastric cancer surgery.

Our analysis demonstrated an increased rate of readmission in the ERAS arm, a contentious finding that was also shown by Ding et al. [36]. This trend, albeit non-significant, was also seen in other meta-analyses [37, 38, 41]. As this is contrariwise to the goals of ERAS to attenuate surgical stress and promote recovery, further research is warranted to investigate this antithetical phenomenon. ERAS programs have previously been scrutinized due to the increased risk of readmission particularly in colorectal cancer surgery [44], possibly due to early discharge [45]. However, this concern has not been realized in urological [46], gynaecological [47], and lung surgery [48]. This observed difference could be because gastric cancer surgery is intrinsically a higher-risk surgery, with complication rates reported in the literature to be as high as 45% [49, 50]. Late complications, in particular, may have been missed during the initial admission and hence could be the cause of readmission. In addition, gastric cancer patients are generally older, more malnourished and more advanced in stage compared to other cancer patients. Hence, they may have higher risk of readmission after discharge from surgery [2, 41, 44].

Readmissions may be unpredictable [49], however, measures can be employed early to identify postoperative

complications to mitigate this. For instance, a telephone interview and home-visit can be conducted post-discharge by a nurse clinician; patients can also be reviewed early—within a week—at outpatient clinics [32, 50, 51]. Individualized-patient education has also shown benefits compared to a standard education booklet [53–55].

Although risks of post-operative morbidity were similar between both groups, subgroup analysis of patients who underwent laparoscopic surgery revealed an increased risk of morbidity in the ERAS arm. This observation could be attributed to the effects of a learning curve or adaptation phase in some of these studies. Nevertheless, visual inspection of the forest plot suggests inconsistencies between studies, as half were in favor of the ERAS arm whilst the other half were in favor of the conventional care arm.

Nonetheless, the findings from this study should be interpreted in the context of known limitations. Significant statistical heterogeneity was observed in the various outcomes, with the accompaniment of qualitative heterogeneity which we cannot eliminate completely, such as surgeon competency and definition of inclusion criteria. Since the ERAS consensus guidelines for gastrectomy was only published recently [6], a major limitation is the significant heterogeneity of the ERAS protocol in included studies, as these were likely to have been developed from pre-existing ERAS protocols employed in colorectal [4], gynaecology [52], and hepatobiliary [53] surgery. Aside, poor or varied compliance to protocol, as reported in the literature [54], may exacerbate heterogeneity. Next, the findings from this review may not apply to patients who have received neoadjuvant radiotherapy or chemotherapy since they were excluded from most studies. Although these treatment regimens can potentiate malnutrition hence making them unsuitable for ERAS [10, 12, 13, 17, 55], ERAS actually involves key preoperative measures that aim to get patients in the best possible condition for surgery. In this regard, one might advocate that patients who received neoadjuvant treatment might actually benefit more from an ERAS regimen and it is therefore questionable whether these patients deserve to be excluded. Furthermore, neoadjuvant or perioperative chemotherapy is the standard of care prior to gastrectomy for cancer in many Asian and Western countries [56–58]. Lastly, as all studies included were from Asia, it may limit the application to Western populations. However, this might be attributed to the skewed global distribution of gastric cancers, where incidence in East Asia is 3–5 times greater than that in Western Europe and North America [59].

Our meta-analysis carries a few other implications for future studies. Firstly, it is notable that ERAS protocols of included studies did not mandate the use of laparoscopic approach, which is otherwise regarded a key constituent in ERAS for colorectal surgery. However, despite encouraging evidence of laparoscopic gastrectomy showing superior short-term outcomes for early gastric cancer and with emerging evidence for advanced gastric cancer [60, 61], it is still important for their effects to be studied methodically in an ERAS setting given the higher morbidity rate in the laparoscopic group. Secondly, the association between ERAS and inflammatory markers is still not well understood. Hence, future trials should attempt to investigate this relationship including TNFα to better inform clinicians and researchers. Thirdly, early initiation of oral feeding maybe controversial in the gastric cancer surgery, which is based on concerns regarding gastric distention and anastomotic leakage. However, most studies in the ERAS arm employed early oral feeding [11, 12, 15, 17, 21, 23], and our analysis showed that ERAS was associated with faster recovery of gut without increase in morbidity. Finally, future studies should standardize the reporting of outcomes, as well as compliance to the items in the protocol.

Conclusions

This meta-analysis is the most up-to-date and comprehensive review of the literature. Enhanced recovery after gastric cancer surgery reduces hospital stay, costs, surgical stress response and time to return of gut function as compared to conventional care. However, it may be associated with increased risk of readmission. Caution is necessary when adopting ERAS for gastric cancer surgery.

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Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest.

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