Systematic Review and/or Meta-analysis

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Extensive intraoperative peritoneal lavage with surgery, compared to surgery alone, for patients diagnosed with gastric cancer: a systematic review and meta-analysis of randomized controlled trials

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Background: Gastric cancer ranks as the fifth most frequently diagnosed cancer and the seventh most prevalent overall. The lifetime risk of developing gastric cancer is 1.87% for males and 0.79% for females worldwide.

Aim: This systematic review and meta-analysis aimed to determine whether extensive intraoperative peritoneal lavage (EIPL) provides short-term benefits or improved survival outcomes for patients undergoing gastrectomy.

Methods: A comprehensive search spanned PubMed, Embase, Cochrane Library, clinicaltrials.gov, and Web of Science, from their inception up to October 2023, adhering to predefined inclusion and exclusion criteria. The quality of the studies was analyzed using the Cochrane Collaboration Risk of Bias Tool. Data analysis was done using Review Manager 5.3, utilizing a random-effects model.

Results: Our analysis incorporated seven randomized controlled trials with 2602 patients. The follow-up time for all outcomes varied from 30–60 months. For our primary outcomes, EIPL demonstrated a significant benefit over surgery alone in terms of recurrence (RR = 0.73; 95% CI: 0.65–0.83, $P < 0.00001$) and postoperative complications (RR = 0.67; 95% CI: 0.51–0.87, $P = 0.003$). For our secondary outcomes, postoperative hospital stay (MD = −0.35; 95% CI: −1.11 to 0.41; $P = 0.37$), 3-year overall survival (OR = 1.44; 95% CI: 0.84–2.47; $P = 0.19$), 3-year disease-free survival (HR = 0.93; 95% CI: 0.78–1.13; $P = 0.48$), and time to first flatus (MD = −0.17; 95% CI: −0.35 to 0.01; $P = 0.06$), no statistically significant differences were observed between the EIPL and control groups.

Conclusion: While there is a marginal difference in survival outcomes, EIPL holds promise in significantly reducing overall cancer recurrence and suggests an enhancement in postoperative recovery.

Keywords: extensive intraoperative peritoneal lavage, gastrectomy, gastric cancer, meta-analysis

Introduction

Stomach cancer, also known as gastric cancer, originates from the stomach lining and remains a global health concern with[1] over one million cases are diagnosed annually worldwide. It ranks as the fifth most frequently diagnosed cancer and the seventh most prevalent overall. The lifetime risk of developing gastric cancer is 1.87% for males and 0.79% for females worldwide[2].

Conventional treatment for gastric cancer is gastrectomy followed by postoperative chemotherapy[3]. However, recurrence in the peritoneum often occurs postsurgery even with chemotherapy and typically carries a poor prognosis. Peritoneal dissemination may be caused by the shedding of cancer cells from the serosal

HIGHLIGHTS

- This meta-analysis incorporated seven randomized controlled trials involving 2602 patients and aimed to assess the comparative effectiveness of surgery alone versus surgery combined with extensive intraoperative peritoneal lavage (EIPL) in the treatment of gastric cancer.
- This analysis revealed a significant positive impact of EIPL when used in conjunction with surgery, particularly in reducing cancer recurrence and postoperative complications. However, EIPL did not demonstrate a statistically significant effect on 3-year overall survival, 3-year disease-free survival, postoperative hospital stay, or the time to first flatus.
- While there is a marginal difference in survival outcomes, EIPL holds promise in significantly reducing overall cancer recurrence and suggests an enhancement in postoperative recovery.

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surface of the stomach or their detachment during primary tumor manipulation or lymphadenectomy[4].

To prevent metastasis and recurrence, two primary approaches are employed: intraperitoneal chemotherapy (IPC) and extensive intraoperative peritoneal lavage (EIPL)[3]. Recently, EIPL has garnered substantial interest as a novel lavage method. EIPL is defined as repeatedly (up to 10 times) washing the peritoneal cavity with 1 l of physiological saline immediately after gastrectomy[3]. The physiological saline is usually first heated up to 37°C in an incubator, after which it is used to wash out the peritoneal layer of the stomach. While conventional peritoneal lavage uses no more than 3 l of warm physiological saline (2–3 times with 1 l), extensive intraperitoneal lavage uses 10 l or more of warm physiological saline (at least 10 times with 1 l) after curative gastrectomy. The fluid is then removed by aspiration[5].

EIPL offers several advantages over surgery alone. Cancer cells isolated from lavage fluid can aid us in predicting the recurrence and survival of cancer, as well as adjusting medication according to the extent and magnitude of metastasis[6]. For instance, a previous study consisted of patients receiving open curative gastrectomy and undergoing either conventional peritoneal lavage or surgery plus EIPL. Every time, the contents of the peritoneal cavity were stirred and washed sufficiently, and the fluid was aspirated entirely. After the operation, all participants were recommended medications according to the degree of metastasis, and adverse events recorded[5]. Another study noted that the presence of intraperitoneal free cancer cells in lavage fluid is cor related with a worse outcome in gastric cancer, and thus this biomarker can be used to determine therapy both before and after surgery[7]. Furthermore, EIPL helps in the control and reduction of bacterial load in the abdominal cavity and complements sur gical treatments by thoroughly cleaning and removing debris, and foreign material from the abdominal cavity, which provides a clean surgical field and lowers infection risk that can help in wound healing and tissue restoration as well as reduce post operative complications. Nevertheless, the outcomes and survival rates associated with EIPL treatment for gastric cancer remain controversial. Some previous studies[8–10] have suggested that EIPL can prolong overall survival and reduce complications while others[4,5,11,12] have found limited survival benefits and a sub stantial incidence of complications[13]. Therefore, the purpose of this systematic review and meta-analysis was to investigate whe ther EIPL can provide short-term benefits or improved survival outcomes.

Methods

The work has been reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplemental Digital Content 1, http://links.lww.com/JS9/D478, Supplemental Digital Content 2, http://links.lww.com/JS9/D479)[14] and assessing the methodological quality of systematic reviews (AMSTAR) (Supplemental Digital Content 3, http://links.lww.com/JS9/D480)[15] Guidelines. The study protocol has been registered in PROSPERO.

Search strategy

Two independent researchers (D.G. and M.T.H.M.) comprehensively searched PubMed, Embase, Cochrane Library, clinicaltrials.gov, and Web of Science from their inception till October 2023, with no restrictions placed. In addition, they screened the references of studies of interest for additional trials that satisfied the inclusion criteria. The search terms employed included 'extensive intraoperative peritoneal lavage' and 'gastric cancer' along with words analogous to them and the Boolean operators, 'AND' and 'OR'. Our search was then limited to randomized controlled trials (details of the search strategy employed are available in Supplementary Information Table S1, Supplemental Digital Content 4, http://links.lww.com/JS9/D481).

Study criteria and selection

Studies were included for this review and a meta-analysis of the following predetermined inclusion criteria was fulfilled: 1) participants were enrolled regardless of age, sex, and ethnicity, 2) participants were diagnosed with gastric cancer, 3) there was an experimental group present including patients who underwent extensive intraoperative peritoneal lavage with surgery, 4) there was a control group present, including patients who underwent surgery alone, 5) at least one of the primary or secondary outcomes of interest was mentioned, and 6) the study design was interventional randomized controlled trials. The population from the shortlisted RCTs included patients who were (1) booked for gastrectomy, (2) were considered to have T3 (subserosal) or T4 (serosal) disease identified by CT scan and intraoperative examination with N staging and M0 stomach cancer (in contrast to surgical or pathological staging methods, CT scans provide comprehensive benefits including preoperative planning, risk assessment, minimally invasive evaluation, cost-effectiveness, and time efficiency in oncological management)[16], (3) were able to authorize informed consent, (4) were over the age of 18. Our exclusion criteria were as follows: cohort studies, studies with animal models, narrative reviews, systematic reviews, meta-analyses, commentaries, protocols, editorials, letters, and case studies or studies where at least one of the primary outcomes was not reported.

Two reviewers (R.E. and E.A.) independently screened the short-listed articles to identify relevant studies. The selected studies were then imported into Endnote X7[17] (Clarivate Analytics, Thomson Reuters Corporation), which was used to find and eradicate duplicates. A third reviewer (K.A.S.) was consulted to resolve any differences. Details of the study selection process are available in the PRISMA diagram Figure 1.

Data extraction

Data extraction was performed by two independent researchers (M.T.H.M. and H.A.). The first author's name, publication year, study design, sample size, as well as raw and adjusted data for associated characteristics, including age, sex ratio, and the types of control, were retrieved from all eligible papers and entered into a predesigned extraction sheet. Primary outcomes of interest included: recurrence, and postoperative complications (till latest follow-up). Secondary outcomes included: postoperative hospital stay, 3-year overall survival (OS), 3-year disease-free survival (DFS), and time to first flatus. Time to first flatus was used to determine the restoration of gastric and other intestinal functions after surgery, with a shorter time signifying faster recovery. After extracting the data, it was inspected for shortcomings, and subsequently organized into a table.

Risk of bias assessment

The reliability of the included studies was assessed using the Cochrane Collaboration Risk of Bias Tool[18] by two reviewers (D.G. and M.S.). The scale consisted of seven fields: random sequence generation (to check for selected bias), allocation concealment (to check for selected bias), participant and employee blinding (checking for performance bias), blinding of outcome assessment (checking for detection bias), incomplete outcome data (checking for attribution bias), selecting reporting (checking for reporting bias), and other bias. In case of any disagreements, a third reviewer (D.A.M.) was consulted.

Certainty of evidence

To evaluate the certainty of evidence, Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Guidelines[19] were used. The results of this assessment can be accessed in Supplementary Information Table S2 (Supplemental Digital Content 4, http://links.lww.com/JS9/D481).

Statistical analysis

Trials were aggregated using a random-effects model. We extracted event counts over the total population to calculate risk ratios (RR) for recurrence and postoperative complications. Odds ratios (OR) were computed for 3-year overall survival, while hazard ratios (HR) were obtained for 3-year disease-free survival. Postoperative hospital stay and time to flatus were quantified as mean differences (MD). The statistical heterogeneity between studies was evaluated using I^2 statistics. Significant heterogeneity was determined when the I^2 value was $\geq 50\%$. Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration) was used to conduct analyses. A P-value of less than or equal to 0.05 was regarded as significant in every setting. Subgroup analyses were performed to evaluate the effect of EIPL on individual postoperative complications and recurrence in specific locations. Sensitivity analyses were performed for 3-year OS. A funnel plot was generated for inspection of publication bias in the primary outcomes of interest.

Results

Study selection

A total of 53 articles were identified through an extensive literature search, of which 37 were selected through database searching, while 16 additional records were determined through other means such as trial registries. After the removal of duplicates and excluding articles based on title and abstract relevance, a total of 11 articles were fully assessed. Consequently, seven randomized control trials[4,5,8–12] were determined to be eligible, with four articles failing to meet the inclusion criteria (refer to the PRISMA flow diagram Fig. 1).

Risk of bias assessment and publication bias

For each of the seven articles included for quantitative synthesis, the Cochrane RoB 2 Tool was utilized to assess the associated risk of bias. The cumulative analysis of each RCT revealed three studies[5,9,10] at some risk of bias, with the other four[4,8,11,12] at low risk (refer to Supplementary Information Figure 1, Supplemental Digital Content 4, http://links.lww.com/JS9/D481).

Publication bias was inspected using funnel plots, generated for two major outcomes: recurrence and postoperative complications (refer to Supplementary Information Figures 2–3, Supplemental Digital Content 4, http://links.lww.com/JS9/D481).

Study characteristics

A total of 2602 patients were studied from all seven RCTs combined, of which 1294 belonged to the control group undergoing surgery alone, and the remaining 1308 received the intervention of EIPL and surgery. All studies met the criteria of EIPL, which is the washing of the peritoneum 10 times with 1 l of normal saline followed by complete aspiration. Five[5,8–10,12] of these studies were multicenter and the other two[4,11] were multi-institutional. Additionally, three studies[4,5,12] were open-blinded, that is, both participants and researchers were fully aware of the treatment being admi nistered, while three studies[8,10,11] were single-blinded, with par ticipants who were unaware of the intervention being received. Lastly, only one RCT[9] was found to be double-blinded, with masking of both researchers and patients. Furthermore, the mean age of the control group varied from 60.7 to 67.9 compared to the mean age of individuals in the intervention group which varied between 60.6 and 66.6. Of the entire patient pool, 29.9% con sisted of females; a proportion of 30% was calculated for the female population amongst the control group and 29.8% within the intervention group. Details of the study characteristics are available in baseline characteristics Table 1.

Primary outcomes

Recurrence

In five studies[4,5,9–11], data regarding the recurrence of gastric cancer following surgical intervention were reported. An overall risk ratio of

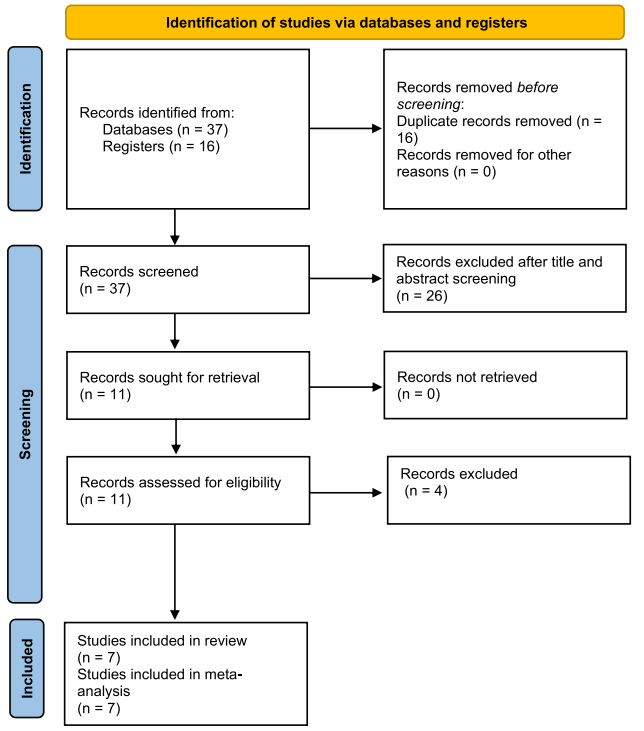

Figure 1. PRISMA flow diagram.

Table 1

Baseline characteristics.

Author, year of study	Type of study	Masking	Mean age (control group)	Mean age (intervention group)	Male/ Female (control)	Male/Female (intervention)	Fluid volume/ type (control)	Fluid volume/ type (intervention)	Median follow-up	Control	Sample size (control group/ intervention group)
Guo *et al.*, 2019[8]	Randomized, multicenter, parallel group trial	Single-blinded	60.8 (10.7)	60.6 (10.8)	196/75	194/85	< 3 l, 0·9% saline	10 l, 0·9% saline	N/A	Surgery	271/279
Guo *et al.*, 2021[5]	Prospective, randomized, multicenter, phase III trial	Open label	60.7 (10.7)	60.7 (10.6)	245/84	233/100	< 3 l, 0·9% saline	10 l, 0·9% saline	47.8 months	Surgery	329/333
Kuramoto *et al.*, 2009[9]	Prospective, randomized, multicenter study	Double-blinded	65.2 (7.3), 66.3 (8.3)	63.4 (10.6)	13/16,14/ 15	13/17	3 l, 0·9% saline	10 l, 0·9% saline	60 months	Surgery, surgery and intraperitoneal chemotherapy	29/30
Misawa *et al.*, 2019[4]	Randomized, multi-institutional, phase III trial	Open label	66·8 (8·7)	66·6 (9·5)	91/54	101/49	< 3 l, 0·9% saline	10 l, 0·9% saline	39·3 months	Surgery	145/150
Santiago *et al.*, 2021[11]	Prospective, randomized, multi-institutional, phase III trial	Single-blinded	67.9 (11.2)	66.4 (12.6)	25/18	29/14	< 2 l, 0·9% saline	10 l, 0·9% saline	45 months	Surgery and standard lavage	43/43
Song *et al.*, 2023[10]	Prospective, randomized, multicenter study	Single-blinded	66.93 (9.38)	64.55 (8.22)	51/24	58/17	≤ 3 l, 0·9% saline	10 l, 0·9% saline	30 months	Surgery and standard lavage	75/75
Yang *et al.*, 2020	Randomized, multicenter, phase III trial	Open label	N/A	N/A	285/117	290/108	≤ 2 l, 0·9% saline	10 l, 0·9% saline	28.8 months	Surgery	402/398

0.73 was observed, indicating a significantly reduced risk of relapse among patients who underwent combined treatment with EIPL [RR = 0.73; 95% CI: 0.65–0.83; $P < 0.00001$; $I^2 = 2\%$, Fig. 2].

When analyzing individual recurrence sites, a significantly lower risk of peritoneal recurrence was noted in the EIPL group [RR = 0.66; 95% CI: 0.47–0.93; $P = 0.02$; $I^2 = 43\%$], as well as a lower risk of overall recurrence (all sites) [RR = 0.71; 95% CI: 0.57–0.88; $P = 0.002$; $I^2 = 44\%$]. However, no significant difference was observed between the experimental and control groups for recurrence in lymph nodes [RR = 0.63; 95% CI: 0.36–1.10; $P = 0.10$; $I^2 = 0\%$], the liver [RR = 0.96; 95% CI: 0.62–1.49; $P = 0.86$; $I^2 = 0\%$], the lung [RR = 1.09; 95% CI: 0.51–2.34; $P = 0.82$; $I^2 = 0\%$], local recurrence [RR = 0.74; 95% CI: 0.37–1.49; $P = 0.40$; $I^2 = 0\%$], or other sites [RR = 1.11; 95% CI: 0.51–2.38; $P = 0.80$; $I^2 = 0\%$].

Postoperative complications

This meta-analysis incorporated a total of five studies[4,8,10–12] examining multiple postoperative complications, namely, abdominal pain, abdominal abscess, anastomotic leakage, intra-abdominal bleeding, abdominal ileus, and pancreatic fistula, between the two groups of patients. The summary effect size represented as risk ratio was calculated to assess the impact of each intervention on the aforementioned adverse events. A statistically significant difference was observed [RR = 0.67; 95% CI: 0.51–0.87; $P = 0.003$; $I^2 = 8\%$] with the pooled effect size estimate favoring surgery with EIPL over surgery alone.

Abdominal pain was reported in two studies[8,10], with a significantly lower incidence in EIPL and surgery patients [RR = 0.59; 95% CI: 0.40–0.87; $P = 0.008$; $I^2 = 0$]. No in-study heterogeneity was observed[4,8,10–12].

Abdominal abscess and anastomotic leakage were reported in five studies[4,8,10–12], the pooled analysis for the former ranked surgery with EIPL superior [RR = 0.55; 95% CI: 0.21–1.50; $P = 0.24$; $I^2 = 50\%$] whilst the latter favored none of the approaches over the other [RR = 1.08; 95% CI: 0.57–2.05; $P = 0.81$; $I^2 = 0\%$].

No significant difference, deduced from three studies[8,10,12], was indicated in terms of intra-abdominal bleeding [RR = 0.65; 95% CI: 0.31–1.33; $P = 0.24$; $I^2 = 0$].

Abdominal ileus was documented in two studies[8,10]. Patients who received surgery with EIPL showed a trend towards lower abdominal ileus rates compared to those who had surgery alone. However, the difference was statistically not significant, though notable heterogeneity was observed among the studies [RR = 0.44; 95% CI: 0.11–1.68; $P = 0.23$; $I^2 = 74\%$].

Two studies[4,12] provided data on pancreatic fistula, and as indicated by the forest plot, pooled results esteemed surgery with EIPL pre-eminent compared to surgery alone. Nevertheless, the difference proved to not be statistically significant with no in-study heterogeneity [RR = 0.55; 95% CI: 0.24–1.27; $P = 0.16$; $I^2 = 0\%$] (Fig. 3).

Secondary outcome

Postoperative hospital stay

Postoperative hospital stay, in days, was reported in three RCTS[8,10,11]. Quantitative analysis revealed a mean difference of −0.35, implying a shorter stay for patients who experienced surgery plus EIPL compared to surgery alone. Nonetheless, a statistically nonsignificant difference was measured with low in-study heterogeneity [MD = −0.35; 95% CI: −1.11 to 0.41; $P = 0.37$; $I^2 = 19\%$, Fig. 4].

Three year overall survival and 3-year disease-free survival

Three-year overall survival was noted in five studies[4,5,10–12], with their pooled analysis suggesting no significant differences between the two interventions [OR = 1.44; 95% CI: 0.84–2.47; $P = 0.19$; $I^2 = 83\%$, Fig. 5] with substantial study heterogeneity. Sensitivity analysis for this outcome was performed yielding nonsignificant results [OR = 1.06; 95% CI: 0.85–1.30, $P = 0.62$, $I^2 = 0\%$, Supplementary Information Fig. 4, Supplemental Digital Content 4, http://links.lww.com/JS9/D481].

The analysis of the 3-year disease-free survival endpoint disclosed no statistically significant difference between the two groups, as recorded by three studies[4,5,12] encompassed within this meta-analysis [HR = 0.93; 95% CI: 0.78–1.13; $P = 0.48$; $I^2 = 25\%$, Fig. 6]. Low in-study heterogeneity was observed.

The time to first flatus

Interval until the occurrence of the first expulsion of flatus, measured in days, was documented in two studies[8,10]. Upon reviewing the forest plot, outcomes tended to favor the combination of the surgical procedure with EIPL over surgery in isolation, suggesting that surgery and EIPL allow for a shorter duration of recovery; however, according to the quantitative analysis, no statistical difference amongst the procedures was suggested [MD = −0.17; 95% CI: −0.35 to 0.01; $P = 0.06$; $I^2 = 0\%$, Fig. 7] with no significant heterogeneity amongst the studies.

Discussion

This meta-analysis, comprising seven randomized controlled trials[4,5,8–12] and involving 2602 patients, aimed to assess the comparative effectiveness of surgery alone versus surgery combined with extensive intraoperative peritoneal lavage (EIPL) in the treatment of gastric cancer. This analysis revealed a significant positive impact of EIPL when used in conjunction with surgery, particularly in reducing cancer recurrence and postoperative complications. However, EIPL did not demonstrate a statistically significant effect on 3-year overall survival, 3-year disease-free survival, postoperative hospital stay, or the time to first flatus. There is reduced cancer recurrence but no improvement in overall survival because survival is influenced by many other factors and comorbidities, which may have led to overall decreased survival. In the examination of individual postoperative complications, a significantly lower incidence of abdominal pain was observed when EIPL was integrated into the surgical approach. This reduction in abdominal pain might be explained by the decrease in the inflammatory response, which involves the release of inflammatory cells and cytokines that induce pain. Using EIPL and 1 l of saline for 10 rounds of washing of the peritoneal cavity is likely to eliminate bacterial materials and tissue debris and, hence, reduce local inflammation and pain[8]. Additionally, while there were fewer occurrences of abdominal abscess, abdominal ileus, and pancreatic fistula in the EIPL group, these differences did not attain statistical significance. The reduction in the fre quency of abdominal ileus can be explained by the decrease in the inflammatory response, which can avoid the adhesion formation that results in ileus[8].

Furthermore, when individual subgroups were evaluated for recurrence, the EIPL group exhibited a significantly reduced risk of recurrence, both at peritoneal and overall sites.

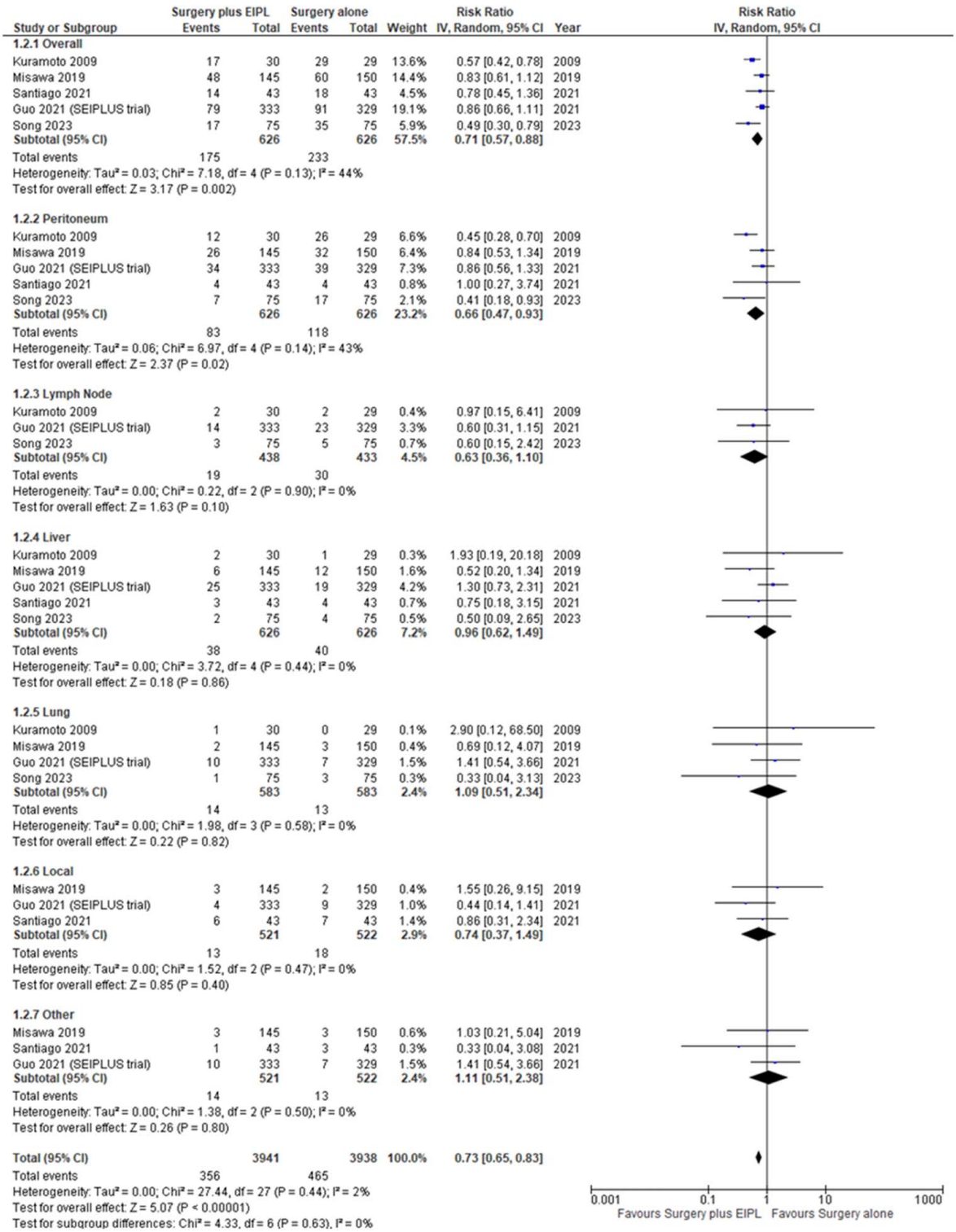

Figure 2. Forest plot for recurrence.

Several theories may explain why the combination of extensive intraoperative peritoneal lavage with surgery yields more favorable outcomes when compared to surgery alone. One plausible mechanism could be attributed to the efficacy of the limiting dilution method employed in EIPL, which reduces the bacterial load, thereby diminishing the risk of infection and other postoperative complications, such as abdominal abscesses and adhesions. Additionally, this method facilitates the removal of metabolic waste and tissue debris, mitigating excessive postoperative inflammation that might otherwise trigger the production of cytokines responsible for inducing pain[20]. Chronic inflammation can also create an environment conducive to cancer

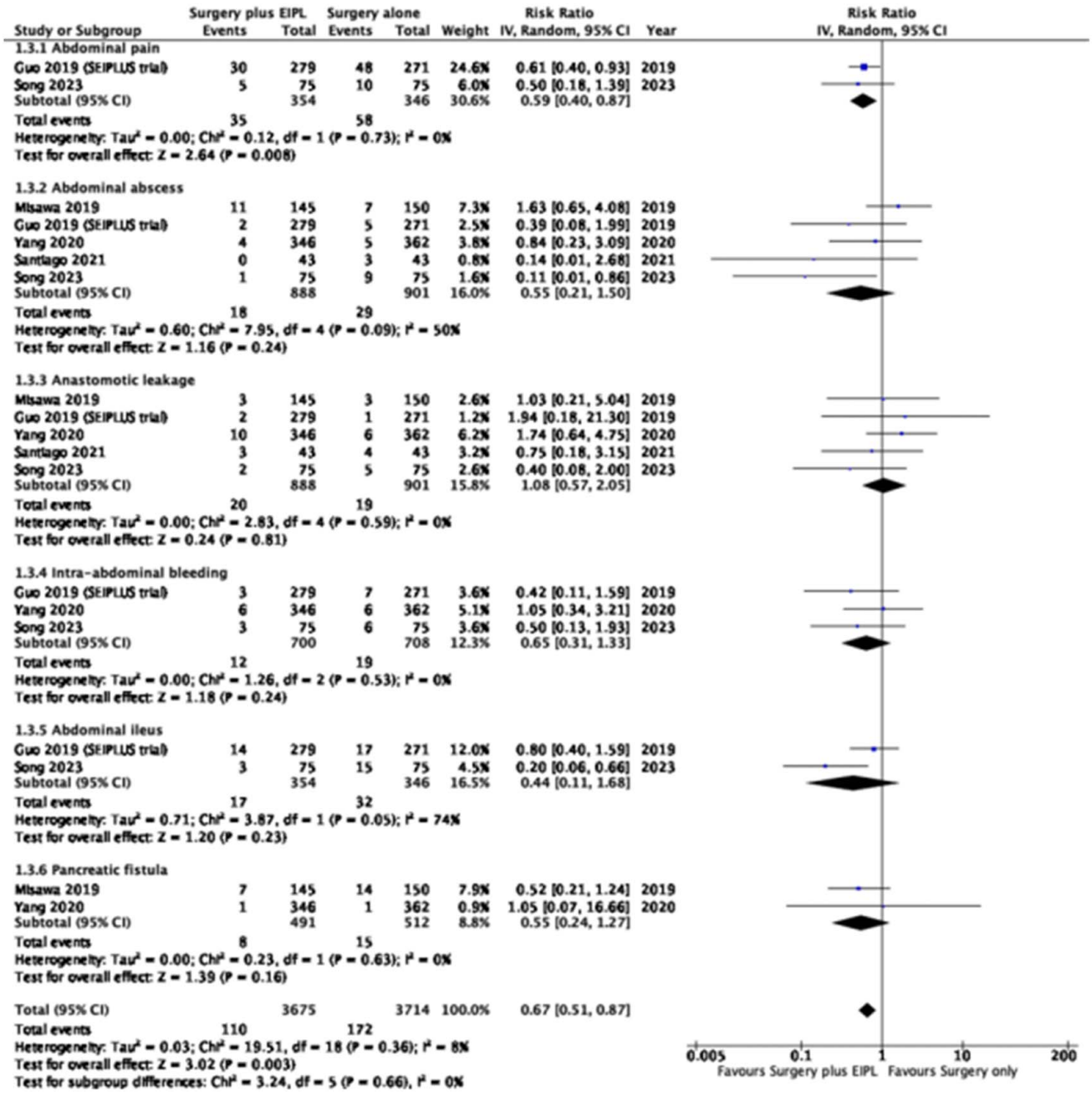

Figure 3. Forest plot for postoperative complications.

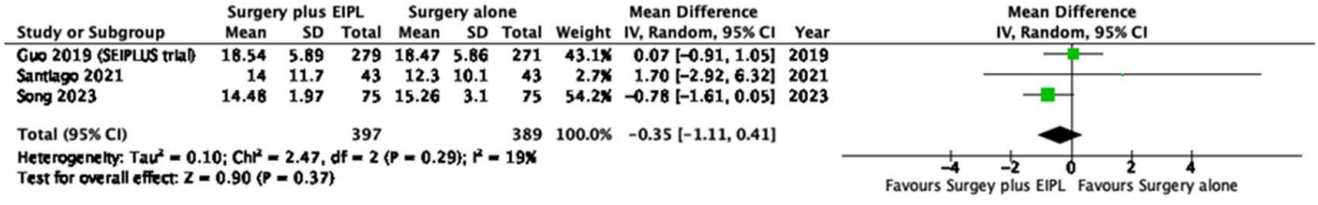

Figure 4. Forest plot for postoperative hospital stay.

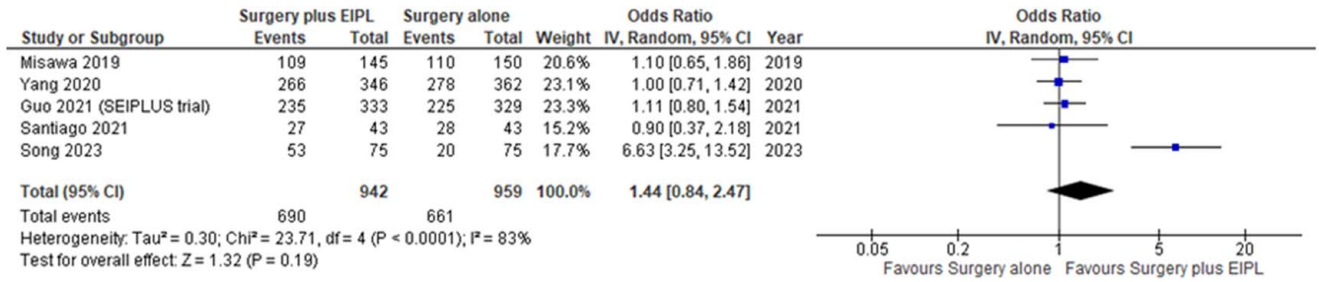

Figure 5. Forest plot for 3-year overall survival.

cell proliferation, thereby increasing the likelihood of recurrence[21].

The occurrence of recurrence, particularly within the peritoneal cavity, after curative surgical resection of gastric cancer, is relatively frequent and represents a substantial contributor to mortality[22]. The presence of free cancer cells, either shed from the surface of serosa-invading primary tumors or disseminated during surgery and lymph node dissection, within the peritoneal cavity plays a pivotal role in the development of peritoneal metastasis[23–25]. Extensive intraperitoneal lavage (EIPL) has been proposed as a prophylactic strategy against peritoneal recurrence, employing a limiting dilution therapy approach by washing the peritoneal cavity ten times with 1 l of normal saline each time, followed by complete aspiration. This rigorous regimen sub stantially reduces the number of free cancer cells, lowering the risk of their implantation into the peritoneum[26]. Furthermore, certain studies have revealed a significantly lower postoperative neutrophil-to-lymphocyte ratio (NLR), a parameter used to assess inflammatory status, in the EIPL group compared to the non-EIPL group[10]. These findings underscore how EIPL can effectively mitigate complications associated with excessive inflammation and contribute to a reduction in recurrence risk.

Intriguingly, repeated washes of the peritoneal cavity with warm normal saline in EIPL may play a role in promoting intestinal motility and functional recovery after surgery and each wash is followed by complete drainage of the fluid, it may also help locate any potential postoperative bleeding. Additionally, rigorous cleaning of the peritoneal cavity via EIPL has been proposed to help in optimum wound healing due to sterile conditions[10]. However, there has also been conflicting evidence that a decrease in normal inflammatory cells can occur by repeated peritoneal washing and can impair the peritoneal integrity and the natural healing environment of the peritoneal cavity. A study reveals how resident peritoneal macrophages contribute to decreasing the risk of postoperative adhesion formations by acting as a cellular barrier and, therefore, reducing the exposure of fibrin clots[27]. The depletion of these macrophages can occur due to repeated peritoneal lavage and could, therefore, exacer bate postoperative adhesions[28]. Certain studies also suggest that repeated irrigation of the peritoneal cavity can damage mesothe lial cells and affect their regrowth thus affecting the healing of the peritoneal cavity after surgery[29]. However, one study states that the concern of depletion of macrophages and other immune cells is more likely theoretical than practical[30].

While previous meta-analyses[3,13,31] have attempted to investigate the effect of EIPL on gastric cancer, but they have produced heterogeneous results. In contrast to our findings, Tao *et al.*[13] and Li *et al.*[3] reported no significant impact of EIPL on post operative complications, with odds ratios (OR) of 0.88 (95% CI: 0.51–1.53) and hazard ratios (HR) of 0.774 (95% CI: 0.376–1.592), respectively. Moreover, unlike our results, Tao *et al.*[13] and Li *et al.*[3] found no positive effect of EIPL on reducing peritoneal cancer recurrence. However, in line with our findings, Tao *et al.*[13] found no significant association of EIPL with disease-free survival, while Li *et al.*[3] also found no correlation between EIPL and 3-year overall survival. Consistent with our study, a recent meta-analysis conducted by Najah *et al.*[31] showed no significant difference between EIPL and non-EIPL groups regarding length of hospital stay. However, it found no significant impact of EIPL on peritoneal recurrence and postoperative complications. The conflicting results of these studies may not necessarily be due to the effect of EIPL on outcomes after surgery, but rather to pre-existing comorbidities such as hypertension and diabetes mellitus. Due to the unavail ability of sufficient data, we were unable to perform an analysis separating groups according to existing comorbidities that may cause increased mortality and adverse events.

Our analysis extends beyond previous meta-analyses by including several outcomes that were not investigated in some prior studies. In comparison to a recent meta-analysis[31], this analysis incorporates additional postoperative complications, including abdominal pain, abdominal abscess, as well as both abdominal

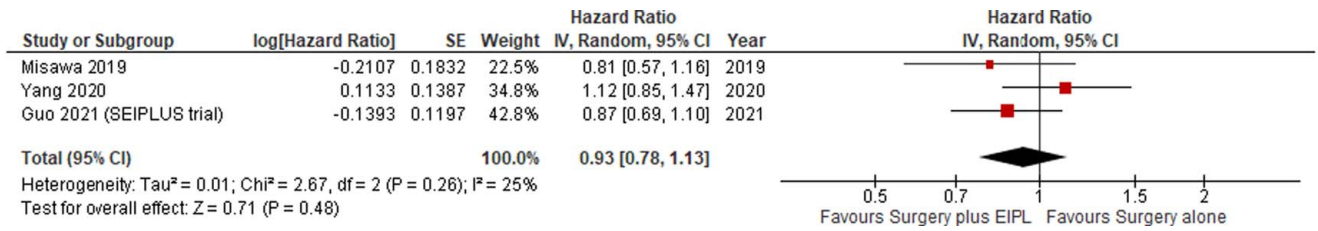

Figure 6. Forest plot for 3-year disease-free survival.

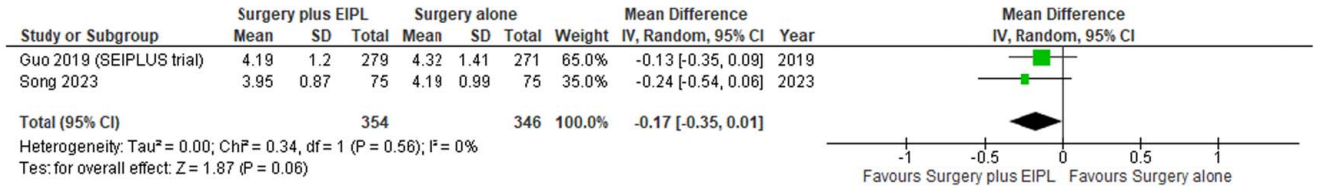

Figure 7. Forest plot for time to first flatus.

ileus and pancreatic fistula. In addition, we carried out subgroup analyses about postoperative complications, allowing us to investigate the impact of EIPL on the reduction of both general postoperative complications and those specifically associated with advanced gastric cancer patients following gastrectomy. Furthermore, we conducted subgroup analyses concerning cancer recurrence, thereby enabling us to assess the influence of EIPL on specific sites of recurrence. Given the significant heterogeneity observed for survival, we performed sensitivity analyses for 3-year survival. Notably, upon excluding Song's study[10] during the sensitivity analysis of 3-year survival, the heterogeneity decreased considerably. Additionally, we evaluated the time to the first flatus as an outcome to investigate the effect of EIPL on the return of bowel function after gastrointestinal surgery, with a shorter time indicating a more favorable prognosis[32].

Two recent meta-analyses[3,31] on the effectiveness of EIPL in patients undergoing surgery for gastric cancer have been published, with one also addressing short-term outcomes similar to our study. However, our analysis builds on these by including a slightly larger number of RCTs and offering a comprehensive evaluation of both short-term and long-term outcomes. Our findings suggest that while EIPL does not significantly improve survival, it can enhance certain short-term outcomes, providing valuable insights into its potential benefits postsurgery. Notably, the short-term benefits of intraperitoneal lavage have also been reported in other carcinomas during hepatobiliary and pancreatic surgeries[33].

Limitations of the study

While our study possesses notable strengths, it is important to acknowledge its limitations. Notably, some of the postoperative complications we analyzed, such as abdominal pain, ileus[8,10], and pancreatic fistula[4,12], were only assessed by two of the included studies. Consequently, future clinical trials should prioritize the investigation of these specific outcomes. Additionally, we were unable to perform a subgroup analysis on postoperative adjuvant chemotherapy due to the limited availability of data. Although some studies[4,5,11] mentioned patients who received adjuvant chemotherapy, the scarcity of data prevented us from conducting a subgroup analysis. Three of our studies also had a moderate risk of bias[5,9,10], which may have contributed to high heterogeneity or insignificant results. Moreover, by only including RCTs, we may have possibly missed out on valuable insights from existing observational studies. Although this approach reduces the risk of bias, it could potentially limit our perspectives. Another limitation is the regional bias in our study, with six[4,5,8–10,12] out of the seven included studies conducted in eastern countries. This geographic concentration restricts the diversity of patients included in our analysis. Furthermore, significant heterogeneity was observed in our meta-analysis of 3-year overall survival. This heterogeneity may be attributed to variations in surgical approaches and the use of chemotherapy, which can influence the effects of EIPL, in both the control and intervention groups. Consequently, another limitation of our study is the differences in surgical approaches employed in each trial, which can also be evaluated to reach a more certain result. Moreover, the period recorded for recurrence is not homogenous and specific across studies, which may thus affect the results of that outcome. Additionally, three[5,8,10] of the included studies exclusively enrolled patients at T3 or T4 and M0 disease stages, while the remaining studies encompassed patients at different stages of the disease. To enhance the reliability of results, future clinical trials should aim for larger, more heterogeneous patient populations. Lastly, conducting a cost-effectiveness analysis (CEA) could provide valuable insights into the economic impact of incorporating EIPL into standard clinical practice. Such an analysis can assist both researchers and patients in making informed decisions.

Conclusion

Our findings indicate that, overall, there is minimal difference in survival outcomes when utilizing EIPL with surgery compared to surgery alone in advanced gastric carcinoma patients. Nevertheless, EIPL does appear to have an impact on reducing the recurrence of cancer, suggesting the potential benefit for gastric cancer patients. Moreover, the significant reduction in combined postoperative complications and abdominal pain observed in the surgery plus EIPL group implies a potential improvement in the quality of postoperative recovery. Given the limitations of this study, future research and clinical exploration must be conducted to thoroughly elucidate the clinical implications of these findings and guide treatment decisions effectively.

Ethical approval

The authors affirm the integrity and impartiality of our work in compliance with ethical standards.

Consent

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Author contribution

M.O.O.: writing, reviewing, editing, and funding acquisition; M.A.: supervision; D.G.: data curation. All the authors

contributed in writing the initial draft, conceptualization of ideas, critical review and comments, administrative support, and final approval of manuscript for publication.

Conflicts of interest disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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