Systematic Review and/or Meta-analysis

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Intracorporeal versus extracorporeal anastomosis in laparoscopic total gastrectomy: a systematic review and meta-analysis

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Background: To evaluate outcomes of intracorporeal (IOJ) versus extracorporeal (EOJ) oesophagojejunostomy following laparoscopic total gastrectomy (LTG) for the treatment of gastric cancer.

Methods: A comprehensive search of various electronic databases was conducted. Comparative studies of IOJ versus EOJ following LTG in patients with gastric malignancy were included. Primary outcomes were anastomotic leak, anastomotic bleeding, and anastomotic stricture formation. Secondary outcomes included operative time, length of hospital stay (LOS), volume of intra-operative haemorrhage, number of harvested lymph nodes, time to flatus, time to soft diet, intra-abdominal infection, pulmonary infection, surgical site infection (SSI), duodenal stump leak, pancreatic fistula occurrence, postoperative ileus, re-operation, and mortality. Combined overall effect sizes were calculated using the random-effects model, and the Newcastle-Ottawa Scale was used to assess risk of bias.

Results: Seventeen non-randomised studies enrolling 2,960 patients divided between an IOJ (n = 1430) and EOJ (n = 1530) group were included. IOJ was associated with significantly lower risk of anastomotic stricture (P = 0.01), volume of intra-operative bleeding (P = < 0.001), and SSI (P = 0.04) compared to EOJ. No difference was found in anastomotic leak (P = 0.93); anastomotic bleeding (P = 0.35); operative time (P = 0.63); LOS (P = 0.30); lymph node yield (P = 0.17); time to first flatus (P = 0.77); time to resumption of soft diet (P = 0.32); intra-abdominal infection (P = 0.22); pulmonary infection (P = 0.45); duodenal stump leak (P = 0.46); pancreatic fistula occurrence (P = 0.16); and paralytic ileus (P = 0.59), re-operation (P = 0.50), and mortality (P = 0.23) between the two groups.

Conclusions: LTG for gastric malignancy with IOJ may be associated with lower risk of anastomotic stricture and SSI compared to the extracorporeal approach. However, future adequately powered randomized studies are needed to compare the two techniques.

Keywords: extracorporeal, gastrectomy, gastric cancer, intracorporeal, oesophagojejunostomy

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HIGHLIGHTS

- Laparoscopic total gastrectomy is a technically demanding procedure, particularly in the presence of gastric malignancy.
- Methods of anastomosis could be intracorporeal or extracorporeal.
- Intracorporeal anastomosis is associated with a lower incidence of leak and surgical site infections.
- More robust controlled studies are needed on this topic.

Introduction

Gastric cancer is the fifth most common malignancy worldwide and the fourth leading cause of cancer-related mortality[1,2]. In the United Kingdom (UK), the incidence is approximately 6,500/year, accounting for 2% of all new malignant cases. Rates are highest amongst the elderly (85–89 years of age) and more common in males, although overall incidence and mortality have declined[3].

The most common anatomical location is the cardia, and risk factors include age, genetics, smoking, excess alcohol consumption, and low socio-economic status[3]. Distinct risk factors may also be associated with anatomical subsets, for instance, gastro-oesophageal reflux disease (GORD) and obesity in the development of lesions in the cardia, and 90% of non-cardia cancers being associated with *Helicobacter pylori* (*H. pylori*) infection[3].

Treatment options for gastric cancer include chemotherapy, radiotherapy, immunotherapy, surgical resection, and palliation. Surgical resection can be performed through open surgery or minimally invasive techniques. The benefits of laparoscopic surgery are well-documented and include reduced post-operative pain and analgesic requirement, earlier mobilisation, shorter length of hospital stay (LOS), and improved cosmesis[4].

Laparoscopic total gastrectomy (LTG) to treat disease in the upper or middle third of the stomach constitutes an increasing proportion of all gastric operations. A previous review reported superior short-term outcomes of LTG compared with open surgery[5]. The procedure involves the construction of an oesophagojejunostomy either through an intracorporeal or extracorporeal technique. A mixed review of distal and total gastrectomy found that intracorporeal anastomosis was safe and feasible[6]. However, the study called for further analysis comparing the two techniques to confirm the benefits of laparoscopic intracorporeal anastomosis.

We therefore performed an updated systematic review and meta-analysis, taking into account additional published studies to compare outcomes following intracorporeal versus extracorporeal anastomosis. We focused solely on LTG in the treatment of gastric cancer.

Methods

This systematic review and meta-analysis were performed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines[7] and the Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2) guidelines[8]. The protocol was registered on the international prospective register of systematic reviews (PROSPERO registration number: CRD42023455332)[9].

Search strategy

A bibliographic search was conducted on 30 May 2024 in the following sources: the National Library of Medicine through

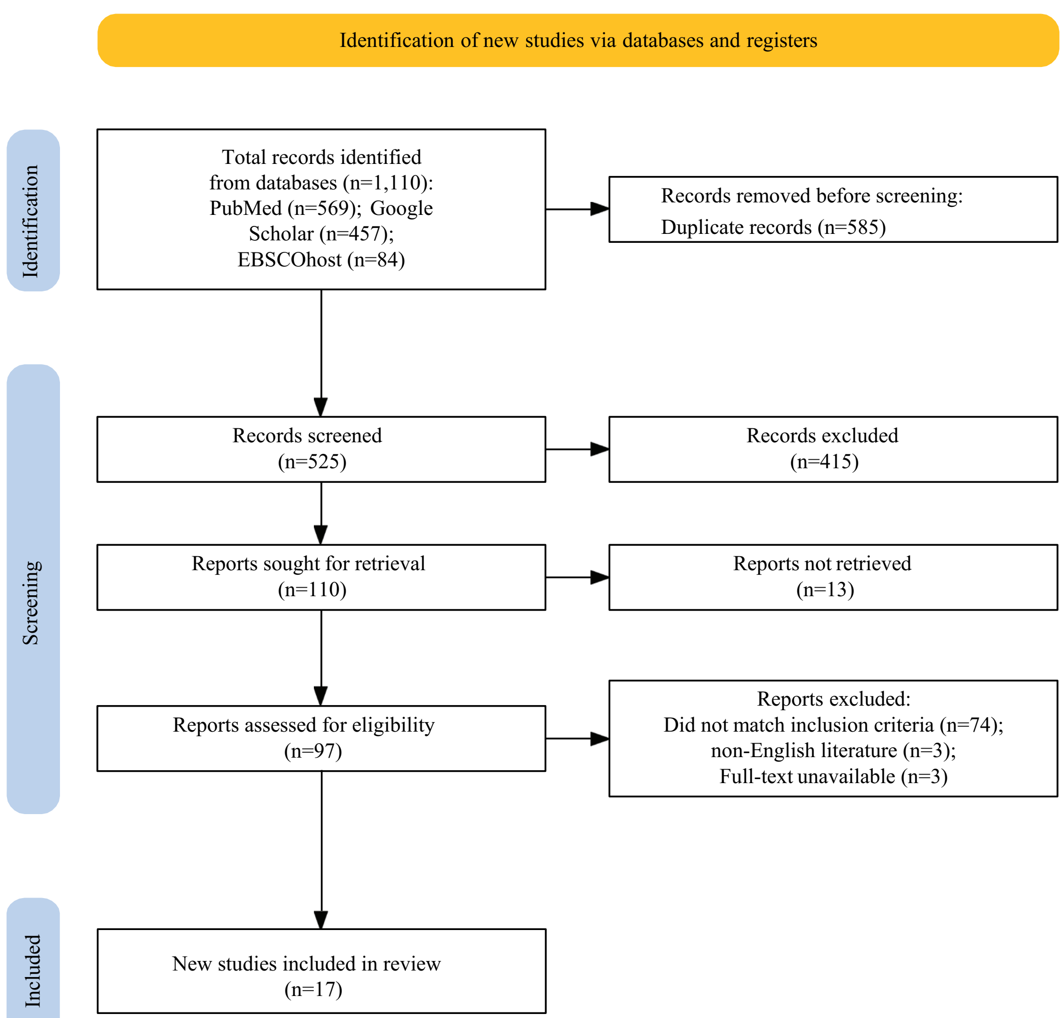

Figure 1. PRISMA flow chart.

Table 1

Characteristics of the included studies

Author	Year	Title	Journal	Country	Study Type	Indication	Comparison
Chen et al[14].	2020	The safety of esophagojejunostomy via a transorally inserted-anvil method vs extracorporeal anastomosis using a circular stapler during total gastrectomy for Siewert type 2 adenocarcinoma of the esophagogastric junction	Gastroenterology Report (Oxford)	China	PSM	GEJ cancer	EOJ (circular stapler) vs IOJ (TIAM)
Chen et al[15].	2023	Effectiveness and safety of self-pulling and latter transected reconstruction in totally laparoscopic total gastrectomy: a comparison with laparoscopic-assisted total gastrectomy	BMC Surgery	China	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (SPLT-TLTG)
Gong et al[16].	2017	Comparison of totally laparoscopic total gastrectomy using an endoscopic linear stapler with laparoscopic-assisted total gastrectomy using a circular stapler in patients with gastric cancer: a single-center experience	World Journal of Gastroenterology	South Korea	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (linear stapler)
Han et al[17].	2021	A comparative study of the short-term operative outcome between intracorporeal and extracorporeal anastomoses during laparoscopic total gastrectomy	Surgical Endoscopy	South Korea	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (linear stapler)
Huang et al[18].	2017	Digestive tract reconstruction using isoperistaltic jejunum-later-cut overlap method after totally laparoscopic total gastrectomy for gastric cancer: Short-term outcomes and impact on quality of life	World Journal of Gastroenterology	China	PSM	Gastric cancer	EOJ (circular stapler) vs IOJ (linear stapler (IJOM))
Ito et al[19].	2014	Evaluation of the safety and efficacy of esophagojejunostomy after totally laparoscopic total gastrectomy using a trans-orally inserted anvil: a single-center comparative study	Surgical Endoscopy	Japan	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (circular stapler (TIAM))
Jeong et al[20].	2020	Reduced anastomotic complications with intracorporeal esophagojejunostomy using endoscopic linear staplers (overlap method) in laparoscopic total gastrectomy for gastric carcinoma	Surgical Endoscopy	South Korea	RCS	Gastric cancer	EOJ (circular) vs IOJ (linear stapler (overlap method))
Jung et al[21].	2013	Safety of intracorporeal circular stapling esophagojejunostomy using trans-orally inserted anvil (OrVil™) following laparoscopic total or proximal gastrectomy – comparison with extracorporeal anastomosis	World Journal of Surgical Oncology	South Korea	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (circular stapler (TIAM))
Kim et al[22].	2013	Comparison of totally laparoscopic total gastrectomy and laparoscopic-assisted total gastrectomy methods for the surgical treatment of early gastric cancer near the gastroesophageal junction	Journal of Laparoendoscopic and Advanced Surgical Techniques	South Korea	RCS	GEJ cancer (defined as one for which the upper margin of the tumor was located within 3 cm of the GEJ on postoperative pathologic examination)	EOJ (circular stapler) vs IOJ (linear stapler)
Kim et al[23].	2016	Totally laparoscopic total gastrectomy versus laparoscopically assisted total gastrectomy for gastric cancer	Anticancer Research	South Korea	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (linear stapler)
Kim HB et al[24].	2016	Comparison of reduced port totally laparoscopic-assisted total gastrectomy (duet TLTG) and conventional laparoscopic-assisted total gastrectomy	Surgical Laparoscopy Endoscopy and Percutaneous Techniques	South Korea	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (linear stapler (duet TLTG))
Park et al[25].	2021	Postoperative morbidity and quality of life between totally laparoscopic total gastrectomy and laparoscopy-assisted total gastrectomy: a propensity-score matched analysis	BMC Cancer	South Korea	PSM	Gastric cancer	EOJ (circular stapler) vs IOJ (circular stapler (hemi-double stapling technique))
Qiu et al[26].	2022	Totally laparoscopic total gastrectomy using the “enjoyable space” approach coupled with self-pulling and latter transection reconstruction versus laparoscopic-assisted total gastrectomy for upper gastric cancer: short-term outcomes	Wideochir Inne Tech Maloinwazyjne	China	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (linear stapler (SPLT))

(*Continued*)

Table 1
(Continued)

Author	Year	Title	Journal	Country	Study Type	Indication	Comparison
Wang et al.(A)[27]	2021	Digestive tract reconstruction of laparoscopic total gastrectomy for gastric cancer: a comparison of the intracorporeal overlap, intracorporeal hand-sewn anastomosis, and extracorporeal anastomosis	Journal of Gastrointestinal Oncology	China	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (liner stapler (overlap))
Wang et al. (B)[27]	2021	Digestive tract reconstruction of laparoscopic total gastrectomy for gastric cancer: a comparison of the intracorporeal overlap, intracorporeal hand-sewn anastomosis, and extracorporeal anastomosis	Journal of Gastrointestinal Oncology	China	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (hand-sewn)
Wei et al[28].	2021	Short-term and quality of life outcomes of patients using linear or circular stapling in esophagojejunostomy after laparoscopic total gastrectomy	Journal of Gastrointestinal Surgery	China	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (linear stapler)
Lu et al[29].	2016	Short-term outcomes of intracorporeal esophagojejunostomy using the transorally inserted anvil versus extracorporeal circular anastomosis during laparoscopic total gastrectomy for gastric cancer: a propensity score matching analysis	Journal of Surgical Research	China	PSM	Gastric cancer	EOJ (circular stapler) vs IOJ (circular stapler (TIAM))
Yan et al[30].	2023	Different methods of minimally invasive esophagojejunostomy after total gastrectomy for gastric cancer: outcomes from two experienced centers	Annals of Surgical Oncology	USA/China	RCS	Gastric cancer	EOJ (circular stapler) vs IOJ (linear stapler, overlap & TIAM)

PSM, propensity score matching; RCS, retrospective cohort study; GEJ, gastro-oesophageal junction; EOJ, extracorporeal oesophagojejunostomy; IOJ, intra-corporeal oesophagojejunostomy; TIAM, trans-orally inserted-anvil method; SPLT, self-pulling and later transection; IJOM, isoperistaltic jejunum-later-cut overlap method; TLTG, totally laparoscopic total gastrectomy.

PubMed, Cochrane database, Web of Science, and Google Scholar. The keywords used were "laparoscopy" AND "laparoscopic" AND "laparoscopic-assisted total gastrectomy" AND "totally laparoscopic total gastrectomy" AND "gastric carcinoma" AND "gastric neoplasms," AND "stomach carcinoma," AND "stomach neoplasms," AND "gastrectomy," AND "total gastrectomy," "intracorporeal anastomosis" AND "extracorporeal anastomosis." We checked the reference list of relevant reviews manually for additional citations.

Inclusion and exclusion criteria

All peer-reviewed studies published in English and including adult patients who had undergone LTG followed by intracorporeal oesophagojejunostomy (IOJ) or extracorporeal oesophagojejunostomy (EOJ) were considered. EOJ was defined based on the included studies' descriptions of the exteriorisation of gastric and oesophageal segments to perform anastomosis extracorporeally. This may include extending the surgical incision and/or the use of adjuncts to aid exteriorisation. To ensure high-quality and reliable data, we included only comparative studies in our analysis. Data from robotic-assisted, non-comparative studies, case reports, case series, review articles, editorials, letters to the editor, abstracts, conference posters, and comments were excluded.

Outcomes measures

The primary outcome measures were anastomotic leak, anastomotic bleeding, and anastomotic stricture occurrence. The evaluated secondary outcome measures were operative time, LOS, volume of intraoperative blood loss, number of harvested lymph nodes, time to first flatus and first soft diet, and postoperative complications such as intraabdominal infection, pulmonary infection, surgical site infection (SSI), duodenal stump leak, pancreatic fistula occurrence, postoperative ileus, reoperation, and mortality.

Data extraction

Two authors extracted the data independently, and a third author settled any disagreements following discussion. Studies included were fully matched for the patient's anthropometric parameters, indications for surgery, postoperative outcomes, functional outcomes, and oncological data.

Risk of bias assessment

Observational studies were assessed independently by two authors for their methodological quality and risk of bias using the Newcastle-Ottawa Scale[10] (star-based scoring system with a maximum score of 9). The studies included in our analysis were rigorously evaluated based on the selection of study groups, comparability between groups, and the determination of the outcome of interest. Only studies that scored nine stars were deemed to have a negligible risk of bias, while those that scored seven or eight stars were considered to have a medium risk. Any study that scored six or less was considered high risk of bias.

Any disagreements during the assessment were resolved through discussion between the assessing authors, and in case of unresolved discrepancies, a third reviewer was consulted.

Table 2

Inclusion and exclusion criteria of the included studies

Author	Year	Inclusion Criteria	Exclusion Criteria
Chen et al[14].	2020	NR	NR
Chen et al[15].	2023	gastric adenocarcinoma confirmed by pathological biopsy; contrast-enhanced CT performed prior to surgery to confirm T1–4a; no distant metastasis (M0); and tumor located in the gastric body, fundus, entire stomach, or cardia, and if there was any invasion of intra-abdominal esophagus, no more than 2 cm above the cardia	NR
Gong et al[16].	2017	NR	NR
Han et al[17].	2021	NR	patients with synchronous other organ malignancy and a history of preoperative chemotherapy
Huang et al[18].	2017	pathologically proved gastric cancer by endoscopic biopsy specimen analysis; aforementioned examination indicated no evidence of distant metastasis; and postoperative pathological diagnosis was curative R0	intraoperatively proved distant metastasis; T4b stage; missing pathological data; neoadjuvant therapy; and comorbidities that could influence QoL (e.g., previous or combined malignancies; cardiovascular disease; cerebrovascular disease; neurological conditions, such as dementia and seizure; and severe chronic obstructive pulmonary disease requiring persistent medical aid)
Ito et al[19].	2014	patients with histologically proven carcinoma who underwent total gastrectomy, followed by esophagojejunostomy with Roux-en-Y reconstruction using a circular stapler	patients with carcinoma of the remnant stomach and those who underwent surgery via a hand-assisted laparoscopic approach
Jeong et al[20].	2020	NR	NR
Jung et al[21].	2013	NR	NR
Kim et al[22].	2013	NR	NR
Kim et al[23].	2016	NR	NR
Kim HB et al[24].	2016	NR	patients with another cancer or previously treated patients
Park et al[25].	2021	NR	TLTGs with intracorporeal esophagojejunostomy other than hDST or reduced port laparoscopic total gastrectomies
Qiu et al[26].	2022	preoperative examinations confirming UGC; no preoperative evidence of distant metastasis; invasion of the lower esophagus no more than 2 cm above the cardia; surgery performed by the same surgeon; and curative resection (R0) according to the postoperative pathological diagnosis	prior abdominal surgery or preoperative chemoradiation therapy; preoperatively or intraoperatively proven distant metastasis; stage T4b disease; esophageal invasion more than 2 cm above the cardia; combined resection; and missing pathological data; patients with preoperative or intraoperative severe LN metastases or peripheral organ involvement who underwent open surgery
Wang et al.(A)[27]	2021	confirmation of gastric cancer by preoperative pathological diagnosis; clinical stage I–III; and operation performed by the same group of doctors	history of stomach surgery; other malignant tumors; comorbid serious systemic diseases such as hypertension and diabetes; and history of preoperative radiotherapy and chemotherapy
Wang et al. (B)[27]	2021	confirmation of gastric cancer by preoperative pathological diagnosis; clinical stage I–III; and operation performed by the same group of doctors	history of stomach surgery; other malignant tumors; comorbid serious systemic diseases such as hypertension and diabetes; and history of preoperative radiotherapy and chemotherapy
Wei et al[28].	2021	under 75 years of age and diagnosed with gastric carcinoma located in the fundus, upper body, or entire stomach were included	previous history of upper abdominal surgery (except laparoscopic cholecystectomy), adenocarcinoma of the esophagogastric junction, neoadjuvant therapy, combined resection during the gastrectomy, comorbidities that could influence the QoL (e.g. previous or combined malignancies, cardiovascular disease, cerebrovascular disease, neurologic conditions such as dementia and seizure, and severe chronic obstructive pulmonary disease, requiring persistent medical aid), and recurrent gastric cancer within 1 year of surgery and those who died within 1 year after their surgery
Lu et al[29].	2016	NR	NR
Yan et al[30].	2023	NR	diagnoses other than adenocarcinoma, and those with open gastrectomy, remnant, or stage IV GC

NR, not recorded; CT, computed tomography; QoL, quality of life; TLTG, totally laparoscopic total gastrectomy; hDST, hemi-double stapling technique; UGC, upper gastric cancer; LN, lymph nodes; GC, gastric cancer.

Handling continuous data

Continuous data were analyzed using the Review Manager Web statistical package from Cochrane collaboration for meta-analysis[11]. When the mean and standard deviation (SD) were not reported, they were estimated from the provided interquartile range (IQR) and median based on the formula described by Hozo *et al*[12].

Assessment of study heterogeneity

To assess for between-study heterogeneity, the Cochran Chi[2] test (Q-test) was used. The Tau[2] which is the variance of true effects and 95% predictive interval (index of dispersion) were used to estimate the degree of heterogeneity. We calculated the predictive interval using a comprehensive meta-analysis prediction interval.

Table 3

Baseline demographics of the included studies

Author	Year	Sample size (number)	Age (years)	Gender (Male: Female)	BMI	Smokers N(%)	DMN (%)	IHDN (%)	Respiratory disease (N (%)	Hypertension N (%)	Hepatic disease N (%)	Previous abdominal surgery N (%)	Neo-adjuvant chemotherapy N (%)	Tumour Size cm (SD/ Range)
Chen et al[14].	2020	EOJ: 26	EOJ: 61.3 ± 7.9	EOJ: 21:5	EOJ: 21.6 ± 3.3	EOJ: NR	EOJ: 3(11.5%)	EOJ: 2(7.7%)	EOJ: 1(3.8%)	EOJ: 4(15.4%)	EOJ: 5	EOJ: 2(7.7%)	EOJ: 5(19.2%)	EOJ: 4.71 ± 1.41
		IOJ: 26	IOJ: 61.8 ± 9.1	IOJ: 22:04	IOJ: 22.5 ± 3.4	IOJ:NR	IOJ: 2(7.6%)	IOJ: 0(0%)	IOJ: 2(7.7%)	IOJ: 5(19.2%)	IOJ: 1	IOJ: 0(0%)	IOJ: 2(7.7%)	IOJ: 4.60 ± 1.41
Chen et al[15].	2023	EOJ: 43	EOJ: 57.95 ± 14.02	EOJ: 31:12	EOJ: 22.32 ± 3.64	EOJ: 20(46%)	EOJ: 5(11.6%)	EOJ: NR	EOJ: 0(0%)	EOJ: 6(13.9%)	EOJ:NR	EOJ:6 (14%)	EOJ: 14 (32.6%)	EOJ: 3.34 ± 2.15
		IOJ: 40	IOJ: 60.30 ± 11.8	IOJ: 31:9	IOJ: 22.01 ± 2.42	IOJ: 20(50%)	IOJ: 1(2.5%)	IOJ: NR	IOJ: 4(10%)	IOJ: 2(5%)	IOJ: NR	IOJ: 7 (17.5%)	IOJ: 13 (32.5%)	IOJ: 3.46 ± 1.94
Gong et al[16].	2017	EOJ: 266	EOJ: 55.69 ± 11.96	EOJ: 167:99	EOJ: < 23: 119>23— < 25:70>25— < 30:69; >30: 8	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: 3.72 ± 2.47
		IOJ: 421	IOJ: 57.78 ± 11.2	IOJ: 273:148	IOJ: < 23: 198>23— < 25: 103>25— < 30: 110>30:10	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: 3.95 ± 2.90
Han et al[17].	2021	EOJ: 110	EOJ: 59.6 ± 11.8	EOJ: 68:42	EOJ: 23.5 ± 2.9	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: NR
		IOJ: 92	IOJ: 62 ± 11.2	IOJ: 68:24	IOJ: 23.7 ± 3.3	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: NR
Huang et al[18].	2017	EOJ: 102	EOJ: 55.9 ± 11	EOJ: 68:34	EOJ: 22.6 ± 12.8	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: 4.7 ± 1.7
		IOJ: 51	IOJ: 55.5 ± 12.1	IOJ: 34:17	IOJ: 22.5 ± 13.1	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: 4.5 ± 1.5
Ito et al[19].	2014	EOJ: 46	EOJ: NR	EOJ: NR	EOJ:NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: NR
		IOJ: 117	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: NR
Jeong et al[20].	2020	EOJ: 292	EOJ: 62.1 ± 11	EOJ: 206:86	EOJ: 23.4 ± 3.2	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: NR
		IOJ: 118	IOJ: 61.8 ± 11.9	IOJ: 87:31:00	IOJ: 24.6 ± 3.4	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: NR
Jung et al[21].	2013	EOJ: 47	EOJ: 61.2 ± 12.1	EOJ: 37:10	EOJ: 23.4 ± 4.3	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: 5.3 ± 3.6
		IOJ: 40	IOJ: 63.4 ± 12.1	IOJ: 31:09:00	IOJ: 24±4.8	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: 4.5 ± 3.2
Kim et al[22].	2013	EOJ: 23	EOJ: 56.8 ± 14.2	EOJ: 19:6	EOJ: 22.2 ± 1.8	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: 5.5 ± 3.3
		IOJ: 90	IOJ: 58 ± 10.8	IOJ: 61:29	IOJ: 23.2 ± 2.9	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: 4.4 ± 3.2
Kim et al[23].	2016	EOJ: 29	EOJ: 59.3 ± 13.1	EOJ: 20:9	EOJ: 23.3 ± 3.2	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: 5.1 ± 3.5
		IOJ: 27	IOJ: 60.8 ± 9.1	IOJ:22:05	IOJ: 24 ± 2.9	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: 2.9 ± 1.4
Kim HB et al[24].	2016	EOJ: 24	EOJ: 53(34–79)	EOJ: 14:10	EOJ: 22.7 (18.6 – 30.4)	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: 2.9 (1.2–9.5)
		IOJ: 30	IOJ: 51(25–74)	IOJ: 16:14	IOJ: 22.2 (17.2–28)	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: 3 (0.9–12.7)
Park et al[25].	2021	EOJ: 111	EOJ: 59.8 ± 10.7	EOJ: 76:35	EOJ: 24.1 ± 3.3	EOJ: NR	EOJ: 16(14.4%)	EOJ: 4(3.6%)	EOJ: 4(3.6%)	EOJ: 41(36.9%)	EOJ: 0(0%)	EOJ:NR	EOJ: NR	EOJ: 3.2 ± 1.9
		IOJ: 213	IOJ: 61.4 ± 10.7	IOJ: 158:55	IOJ: 24.2 ± 2.9	IOJ: NR	IOJ: 41(19.2%)	IOJ: 19(8.9%)	IOJ: 13(6.1%)	IOJ: 81(38%)	IOJ: 7(3.3%)	IOJ: NR	IOJ: NR	IOJ: 3.3 ± 1.7
Qiu et al[26].	2022	EOJ: 51	EOJ: 63.9 ± 8.2	EOJ: 36:15	EOJ: 23.07 ± 4.18	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: 4.3 ± 2.4
		IOJ: 46	IOJ: 63.3 ± 9.1	IOJ: 31:15	IOJ: 23.74±3.98	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: NR	IOJ:3.6 ± 1.8
Wang et al.(A) [27]	2021	EOJ: 74	EOJ: 53.7±10.7	EOJ: 55:19	EOJ: 22.7 ± 3.4	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: NR
		IOJ: 36	IOJ: 53.7 ± 10.7	IOJ: 25:11	IOJ: 23.6 ± 3.8	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: NR	IOJ: NR
Wang et al.(B) [27]	2021	EOJ: 74	EOJ: 53.07 ± 10.7	EOJ: 55:19	EOJ: 22.7 ± 3.4	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: NR
		IOJ: 20	IOJ: 56.3 ± 7.8	IOJ:14:06	IOJ: 23.9±3	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: NR	IOJ: NR
Wei et al[28].	2021	EOJ: 42	EOJ: 54.9 ± 10.6	EOJ: 36:6	EOJ: 22.3 ± 2.9	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: NR	EOJ: NR
		IOJ: 78	IOJ: 55.2 ± 9.9	IOJ: 61:17	IOJ: 23.4 ± 3.3	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ: NR	IOJ: NR
Lu et al[29].	2016	EOJ: 25	EOJ: 58.4±7.7	EOJ: 21:4	EOJ: 22.9 ± 3.7	EOJ: NR	EOJ: 3(12%)	EOJ: 0(0%)	EOJ: 0(0%)	EOJ: 6(24%)	EOJ: 1(4%)	EOJ:NR	EOJ: NR	EOJ: 4.6 ± 1.8
		IOJ: 25	IOJ: 59 ± 8.9	IOJ:22:03	IOJ: 22.5 ± 2.5	IOJ: NR	IOJ: 1(4%)	IOJ: 1(4%)	IOJ: 1(4%)	IOJ: 4(16%)	IOJ: 2(8%)	IOJ: NR	IOJ: NR	IOJ: 4.8 ± 2.0
Yan et al[30].	2023	EOJ: 45	EOJ: 64.5 ± 9.2	EOJ: 31:14	EOJ: 22.8 ± 3.4	EOJ: NR	EOJ: 12(26.6%)	EOJ: 18(40%)	EOJ: NR	EOJ: NR	EOJ:NR	EOJ:NR	EOJ: 2	EOJ: 5.8 ± 2.3
		IOJ: 60	IOJ: 61.4 ± 12.6	IOJ: 38:22	IOJ: 25.6 ± 4.1	IOJ: NR	IOJ: 10(16.6%)	IOJ: 20(33%)	IOJ: NR	IOJ: NR	IOJ:NR	IOJ: NR	IOJ:13	IOJ: 4.5 ± 2.6

EOJ, extracorporeal oesophagojejunostomy; IOJ, intra-corporeal oesophagojejunostomy; BMI, body mass index; DM, diabetes mellitus; IHD, ischaemic heart disease; NR, not recorded.
Age – expressed in mean (standard deviation) or median (range).
BMI – expressed in mean (standard deviation), median (range), or number.

Summary of findings

Two authors independently assessed the evidence for the primary outcomes. We used The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)[13]. We considered the study limitations constancy of effect, imprecision, indirectness, and publication bias. We assessed the certainty of evidence as high, moderate, low, or very low. If appropriate, we considered the following criteria for upgrading the evidence: large effect, dose-response gradient, and plausible confounding effect. We used the methods and recommendations described in sections 8.5 and 8.7 and chapters 11 and 12 of the Cochrane Handbook for Systematic Reviews of Interventions[13]. We used GRADEpro GDT software to prepare the Summary of Findings table. We explain the reasons for downgrading or upgrading the included studies using footnotes with comments.

Evaluation of effect size

We used RevMan Web statistical package from the Cochrane collaboration for meta-analysis. We selected the mean difference (MD) as an effective measure for continuous data. For dichotomous variables, odds ratios (OR) or risk difference (RD) with 95% confidence intervals (95% CI) were calculated. The random-effects model was used for all analyses, and a threshold of significance was set at 0.05.

Results

Literature search

A total of 1,110 articles were detected following the literature search of which 97 studies were short-listed for further assessment. Another 74 articles were excluded as they did not meet the eligibility criteria, three were not-English literature, and three did not have full-text available. We retained seventeen eligible studies[14-30] (Fig. 1). These articles were published between 2013 and 2023, and all were from the Far East: eight studies[16,17,20-25] from South Korea, eight studies[14,15,18,26-30] from China, and one study[19] from Japan. These studies involved a total of 2,960 patients: 1,430 patients in the EOJ group and 1,530 patients in the IOJ group.

Characteristics of the included studies and their inclusion/exclusion criteria are outlined in Tables 1 and 2. The baseline demographic data of the included studies are summarized in Table 3. Results of our analyzed secondary outcome measures are presented in Table 4.

Table 4

Results of measured secondary outcomes

Outcome	Number of studies reporting outcome	Number of patients	MD; OR; RD and 95% CI	*P* value	Cochran's Q test (I^2 statistic)	Level of between study heterogeneity	GRADE certainty of evidence
Total operative time (minutes)	17[14-30]	EOJ: 1356 IOJ: 1519	MD: 1.79; [−5.60, 9.19]	0.63	71%	High	High
LOS	15[14-18,20-29]	EOJ: 1265 IOJ: 1342	MD: 0.43; [−0.39, 1.26]	0.30	85%	High	High
Intra-operative blood loss (mls)	13[14,15,17-20,23,24,26-30]	EOJ: 909 IOJ: 746	MD: 37.22; [19.52, 54.92]	<0.0001	86%	High	High
Harvested lymph nodes	12[14-18,21-26,30]	EOJ: 877 IOJ: 1145	MD: − 1.56; [−3.77, 0.66]	0.17	60%	Moderate	Moderate
Time to pass first flatus	13[14-18,20-23,26-29]	EOJ: 1130 IOJ: 1101	MD: − 0.02; [−0.17, 0.12]	0.77	65%	Moderate	High
Time to first soft diet	7[14,16,20,22,26,28,29]	EOJ: 725 IOJ: 804	MD: 0.14; [−0.14, 0.42]	0.32	0%	Low	High
Intra-abdominal infection	10[14-17,20,26-30]	EOJ: 974 IOJ: 942	OR: 0.74; [0.45, 1.20]	0.22	0%	Low	Very low
Pulmonary infection	10[14,15,17,22,23,26-30]	EOJ: 468 IOJ: 520	OR: 1.20; [0.74, 1.95]	0.45	0%	Low	Very low
SSI	8[14,16,17,20,22,27,29,30]	EOJ: 861 IOJ: 868	OR: 2.10; [1.03, 4.27]	0.04	12%	Low	High
Duodenal stump leak	5[15,20,22,27,28]	EOJ: 474 IOJ: 362	OR: 1.61; [0.45, 5.73]	0.46	0%	Low	Low
Pancreatic fistula	7[14,15,20,27-30]	EOJ: 547 IOJ: 383	OR: 1.82; [0.79, 4.19]	0.16	0%	Low	Low
Post-operative ileus	9[14-17,20,22,23,26,30]	EOJ: 885 IOJ: 920	OR: 1.19; [0.62, 2.28]	0.59	26%	Low	Low
Re-operation rate	3[15,20,27]	EOJ: 409 IOJ: 194	OR: 0.71; [0.27, 1.91]	0.50	0%	Low	Very low
Mortality	5[15,18,20,23,30]	EOJ: 511 IOJ: 296	RD: 0.01; [−0.01, 0.02]	0.23	0%	Low	High

MD, mean difference; OR, odds ratio; RD, risk difference; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; EOJ, extracorporeal oesophagojejunostomy; IOJ, intracorporeal oesophagojejunostomy; LOS, length of hospital stay; SSI, surgical site infection.

Table 5

Risk of bias assessment for observational studies using the Newcastle-Ottawa Scale.

		Selection				Comparability	Outcome			
Study	Year	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow-Up of Cohorts	Total
Chen et al[14].	2020	*	*	*	*	*	*	*	*	******** (8)
Chen et al[15].	2023	*	*	*	*	*	*	*	*	******** (8)
Gong et al[16].	2017	*	*	*	*	*	*	*	*	******** (8)
Han et al[17].	2021	*	*	*	*	**	*	*	*	********* (9)
Huang et al[18].	2017	*	*	*	*	**	*	*	*	********* (9)
Ito et al[19].	2014	*	*	*	*	*	*	*	*	******** (8)
Jeong et al[20].	2020	*	*	*	*	*	*	*	*	******** (8)
Jung et al[21].	2013	*	*		*	*	*	*	*	******** (8)
Kim et al[22].	2013	*	*	*	*	*	*	*	*	******** (8)
Kim et al[23].	2016	*	*	*	*	*	*	*	*	******** (8)
Kim HB et al[24].	2016	*	*	*	*	*	*	*	*	******** (8)
Park et al[25].	2021	*	*	*	*	**	*	*	*	********* (9)
Qiu et al[26].	2022	*	*	*	*	*	*	*	*	******** (8)
Wang et al[27].	2021	*	*	*	*	*	*	*	*	******** (8)
Wei et al[28].	2021	*	*	*	*	*	*	*	*	******** (8)
Lu et al[29].	2016	*	*	*	*	*	*	*	*	******** (8)
Yan et al[30].	2023	*	*	*	*	*	*	*	*	******** (8)

Risk of bias assessment

Table 5 outlines the outcome of the risk of bias assessment of the included observational studies. The risk of bias was judged to be low in three studies[17,18,25] and moderate in fourteen studies[14–16,19–24,26-30].

Outcome synthesis

Figure 2 presents the results of outcome syntheses.

Table 6 provides a summary of evidence as per the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework.

Primary Outcomes

Anastomotic leak

Sixteen studies[14-25,27-30] reported anastomotic leak as an outcome and included a total of 1,305 patients in the EOJ group and 1,473 patients in the IOJ group. There was no significant difference between the two groups (3.8% vs. 4.2%); OR: 0.86; 95% CI [0.55, 1.36], $P = 0.53$. The Cochran Q test revealed a low level of heterogeneity between the included studies ($I^2 = 9\%$). The certainty of evidence was moderate (Table 6).

Anastomotic bleeding

Nine studies[14,17,18,20,23,26,27,29,30] with 754 patients (EOJ group) and 481 patients (IOJ group) reported anastomotic bleeding. There was no statistically significant difference between the two groups (3.1% vs. 0.8%); OR: 1.91; 95% CI [0.49, 7.37], $P = 0.35$. The Cochran Q test revealed a low level of heterogeneity between the included studies ($I^2 = 31\%$). The certainty of evidence was moderate (Table 6).

Anastomotic stricture

Sixteen studies[15-30] with a total of 2,823 patients reported anastomotic stricture as an outcome (1,330 EOJ group; 1,493 IOJ group), with a statistically significant difference between the two groups (3.7% vs. 1.8%); OR: 2.00; 95% CI [1.16, 3.44], $P = 0.01$. The Cochran Q test revealed a low level of heterogeneity between the included studies ($I^2 = 0\%$). The certainty of evidence was moderate (Table 6).

Sub-group analysis demonstrated that the observed difference between the two groups was due to the use of linear stapling devices in anastomosis formation; OR: 2.84; 95% CI [1.28, 6.28], $P = 0.01$ (Fig. 2).

Secondary Outcomes

The results of our secondary outcomes are summarized and presented in Table 4.

Discussion

Advancements in minimally-invasive techniques have facilitated performing an intracorporeal anastomosis in total gastrectomy[31]. This updated systematic review and meta-analysis of observational studies reports results of various certainty of evidence and significance following evaluation of post-operative outcomes of LTG with intracorporeal versus extracorporeal approach to oesophagojejunostomy.

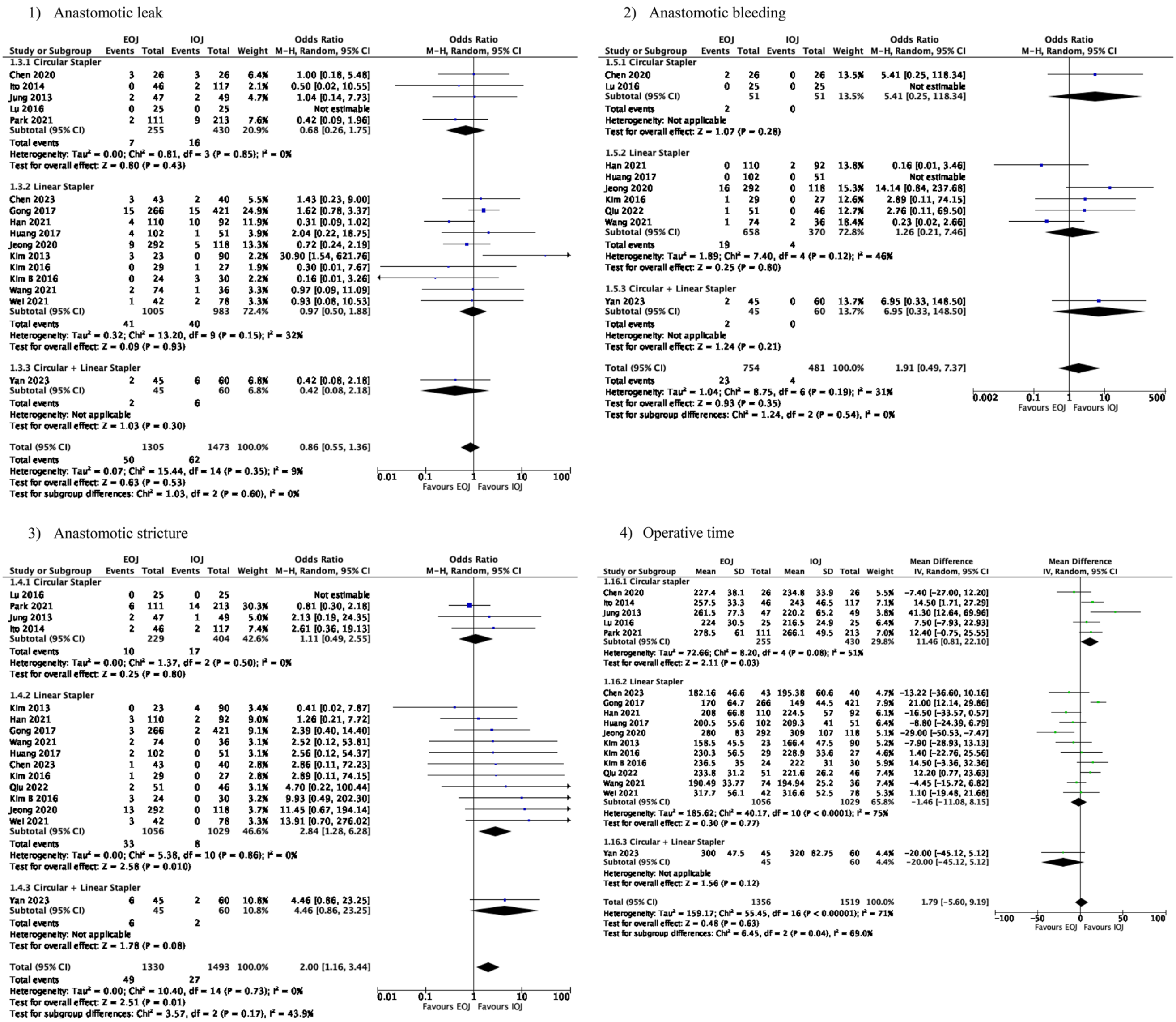

Figure 2. Forest plots of comparison of (1) anastomotic leak, (2) anastomotic bleeding, (3) anastomotic stricture, (4) operative time, (5) length of hospital stay, (6) volume of intraoperative haemorrhage, (7) number of harvested lymph nodes, (8) time to first flatus, (9) time to soft diet, (10) intraabdominal infection, (11) pulmonary infection, (12) surgical site infection, (13) duodenal stump leak, (14) pancreatic fistula, (15) postoperative ileus, (16) reoperation, and (17) mortality. The solid squares denote the mean difference, risk difference, or odds ratio. The horizontal lines represent the 95% confidence intervals (CIs), and the diamond denotes the pooled effect size. IOJ, intra-corporeal oesophagojejunostomy; EOJ, extracorporeal oesophagojejunostomy; M–H, Mantel–Haenszel test.

We included seventeen non-randomized studies with a total of 2,960 patients divided into an EOJ group (n = 1,430) and an IOJ group (n = 1,530). The incidence of anastomotic stricture formation was significantly higher in the EOJ group compared with the IOJ group. Anastomotic strictures were almost half as likely to occur in patients undergoing an intracorporeal anastomosis compared with EOJ. This important and potentially clinically relevant finding could be explained by the use of circular staplers in the EOJ group which are associated with an increased risk of stenosis compared with linear staplers. Anastomotic bleeding was also lower in the IOJ group compared with EOJ, although this difference did not reach statistical significance. The anastomotic leak rate was approximately the same in both groups.

Milone *et al*[6]. included six studies in patients undergoing total gastrectomy and found no significant difference in intraluminal bleeding and anastomotic leaks between the two groups. In an earlier study, Chen *et al*[32]. also reported similar anastomosis-related complications between the groups. The meta-analysis conducted by Nguyen *et al*[33]. included nine comparative studies and reported no statistically significant difference in anastomosis-related complication profile (leak, stricture, bleeding) after LTG with IOJ and EOJ. This was also reported in the study by Zheng *et al*[34]. including seven non-randomized studies and 785 patients. However, IOJ was associated with reduced blood loss compared with EOJ.

Our larger cohort size has demonstrated superior anastomosis-related outcomes including reduced risk of stricture formation

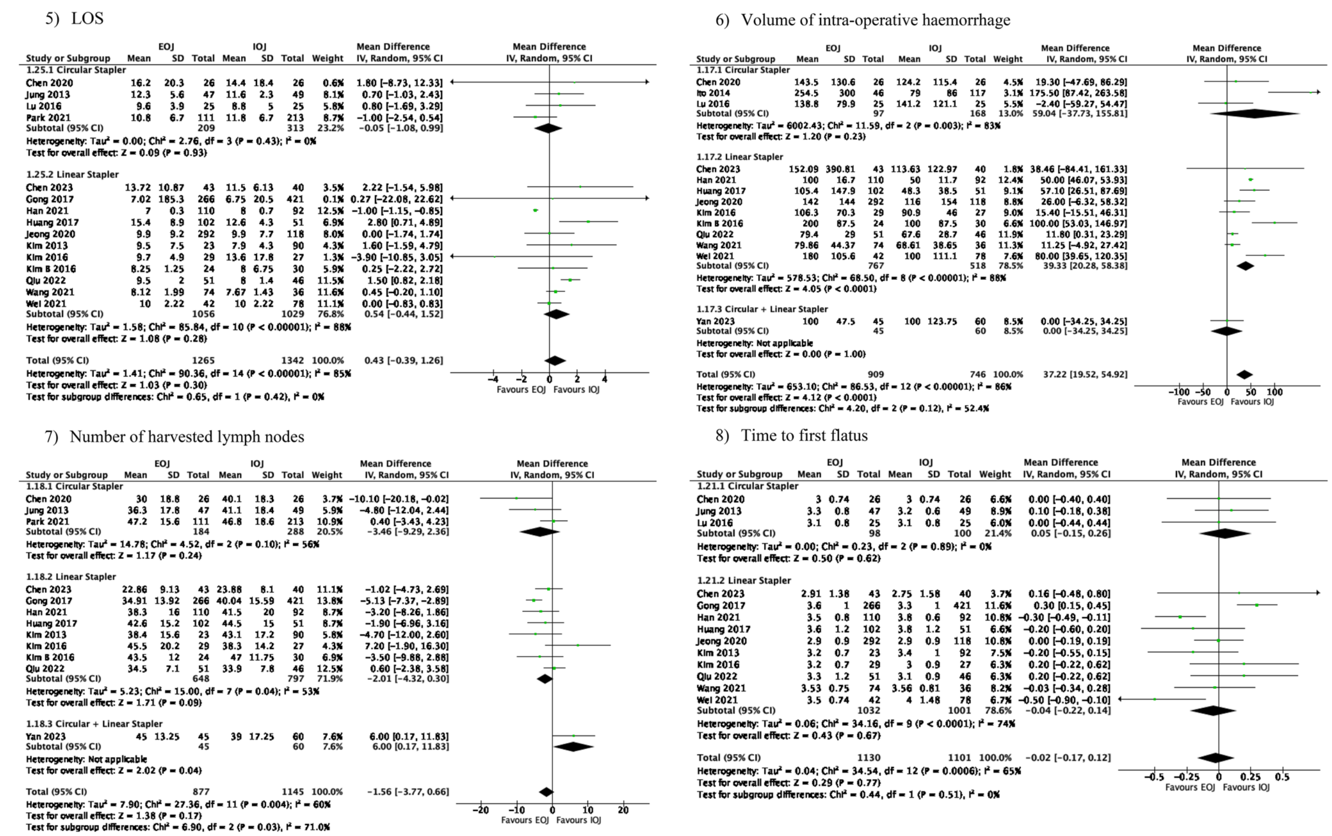

Figure 2. Continued.

(particularly with the use of linear staplers) and a tendency toward less anastomotic bleeding in patients undergoing totally laparoscopic total gastrectomies (TLTG) for gastric malignancy with similar leak rates. However, there is a need for rigorous, well-powered, randomized control trials (RCTs) to eliminate heterogeneity and provide more robust results.

We also investigated a number of secondary post-operative outcomes and found no significant difference in total operative time and LOS between the groups. However, intracorporeal anastomosis was associated with significantly lower volume of intra-operative bleeding and risk of SSI. For oncological outcomes, there was no significant difference for lymph node yield between the two groups.

Time to resumption of a soft diet post-operatively and pass flatus was similar for IOJ and EOJ. Other outcomes including intra-abdominal and pulmonary infections, duodenal stump leak, development of pancreatic fistulas, paralytic ileus, re-operation rate, and mortality were comparable. Two studies reported post-operative mortality during the period of hospitalisation[15,18], one study assessed this at 30-days[23], and in the remaining two[20,30], this parameter was not defined.

No significant difference in operative time was also reported in the reviews by Milone *et al*[6]. and Zheng *et al*[34]. Fashioning of anastomosis is a critical step in any gastrointestinal procedure. Improvements in minimally invasive techniques and associated technologies have made totally laparoscopic procedures with intracorporeal anastomosis possible and more widely performed, especially in high-volume, specialist centers. It is anticipated that with increased surgical experience and further improvements in laparoscopic instruments and devices, totally laparoscopic procedures including gastrectomies will become more routine.

The results of this meta-analysis from the available literature seem to favor intra-corporeal anastomosis, especially with regard to anastomosis-related complications. Stricture formation is lower, and the use of a linear stapling device may be more favorable compared with a circular stapler. Stricture formation/stenosis at the site of an anastomosis can have significant associated morbidity and adversely impair quality of life. Therefore, continual refinements in techniques may help to improve post-operative outcomes. IOJ provides a tension-free joint while avoiding injury to surrounding structures and preserving blood supply[34]. These factors may account for the observed differences.

Moreover, other analyzed outcomes also seem to be at least comparable in patients undergoing IOJ compared with EOJ. The advantages of laparoscopic surgery generally are now well-recognized, and it has become the gold standard for many intra-abdominal procedures across specialties. Abdominal incisions in TLTG are smaller compared with those required for extracorporeal anastomosis. These may be beneficial in helping to reduce post-operative pain, wound infection, better cosmesis, and tissue handling. The risk of longer-term incisional hernia occurrence may also be minimised. However, further well-designed studies are needed to draw more robust conclusions.

Various intracorporeal techniques for anastomosis formation have been described. These include purse-string sutures, trans-

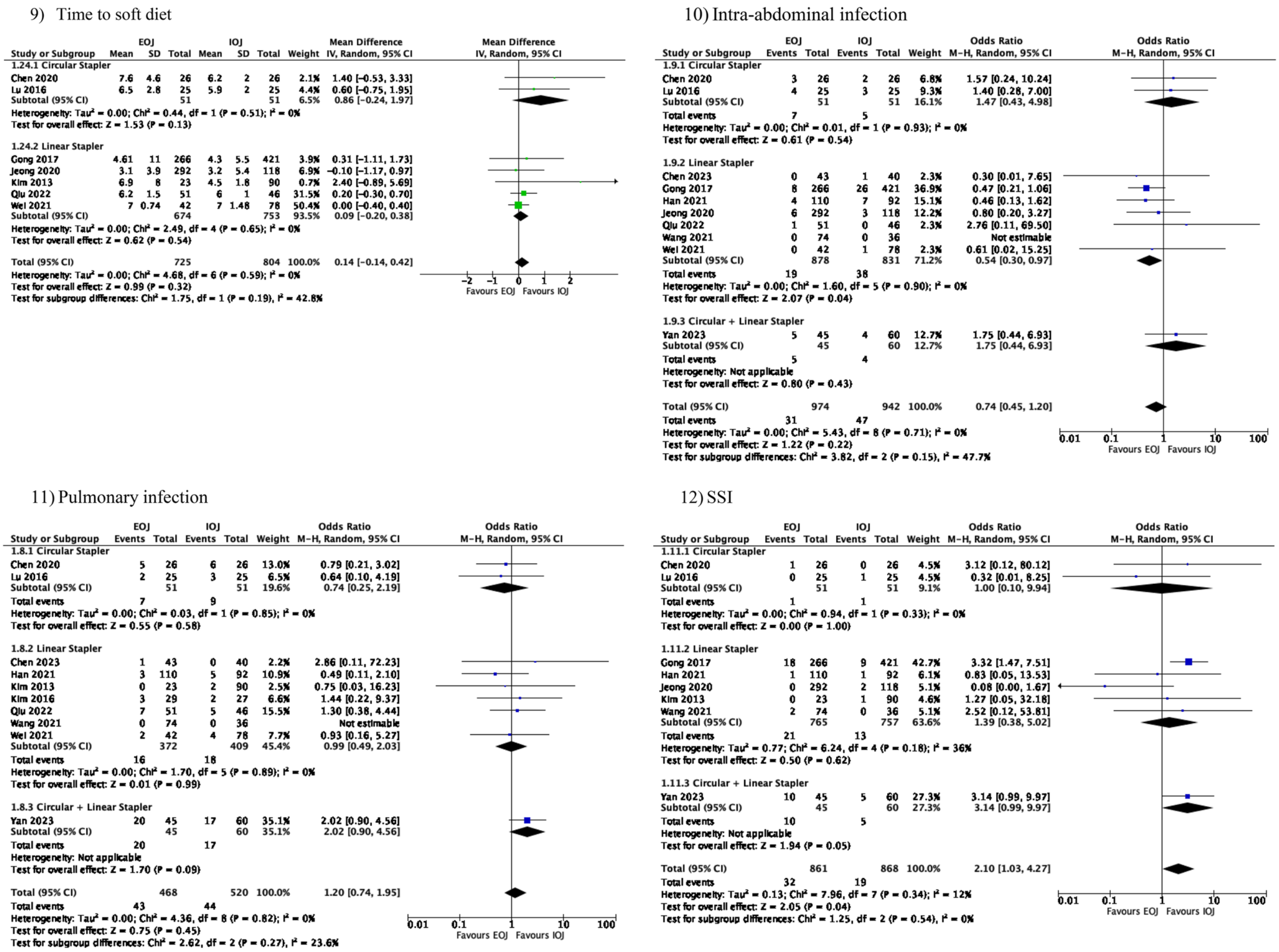

Figure 2. Continued.

orally inserted anvil (OrVil™)[35] for end-to-side oesophagojejunostomy, or side-to-side anastomosis with linear staplers[36]. Each of these methods have their own limitations for instance the risk of oesophageal injury with the trans-orally inserted device, and the need for adequate oesophageal length for application of the linear stapler. Hand-sewn methods can overcome some of these limitations, but are technically challenging and require skilled operators[32]. Consequently, future high-quality studies are needed to assess the optimal method for intracorporeal anastomosis.

In addition to peri-operative outcomes, oncological outcomes are also important in procedures performed for malignant conditions. Our study found no difference in lymph node yields between the two techniques. However, we did not assess for differences in specimen resection margins.

The present study has identified a lack of systematic assessment of evidence in previous meta-analyses on this topic; no previous analysis or review has considered the certainty of evidence when reporting outcomes. The lack of high-level evidence in the literature encouraged the authors of this review to assess the robustness of studies included by reporting GRADE scoring for each study outcome[37,38]. Only Milone *et al*[6]. considered the risk of publication bias using Egger's test. For primary outcomes, this review found moderate confidence in estimates of the true effect for overall complication risk, anastomosis-related complications, and a high degree of confidence for mortality rates, which has critical implications for patient outcomes and clinician decision-making. Operative time, LOS, volume of intraoperative bleeding, time to flatus and soft diet, and SSI rates were reported with a high level of confidence; other outcomes were reported with either low or very low confidence.

There are several methodological weaknesses and limitations to note. First, this meta-analysis included observational studies of variable qualities which affect the heterogeneity and sensitivity of outcomes reported. Additionally, important characteristics such as cancer stage, area of lymph node dissection, and long-term prognosis were not included in baseline demographics due to limited data availability. However, this was partly accounted for by sensitivity analysis and robustness using GRADE.

Second, the majority of the available literature failed to define certain outcomes clearly, such as wound infection, pulmonary infection, or anastomotic leak. This is of particular importance

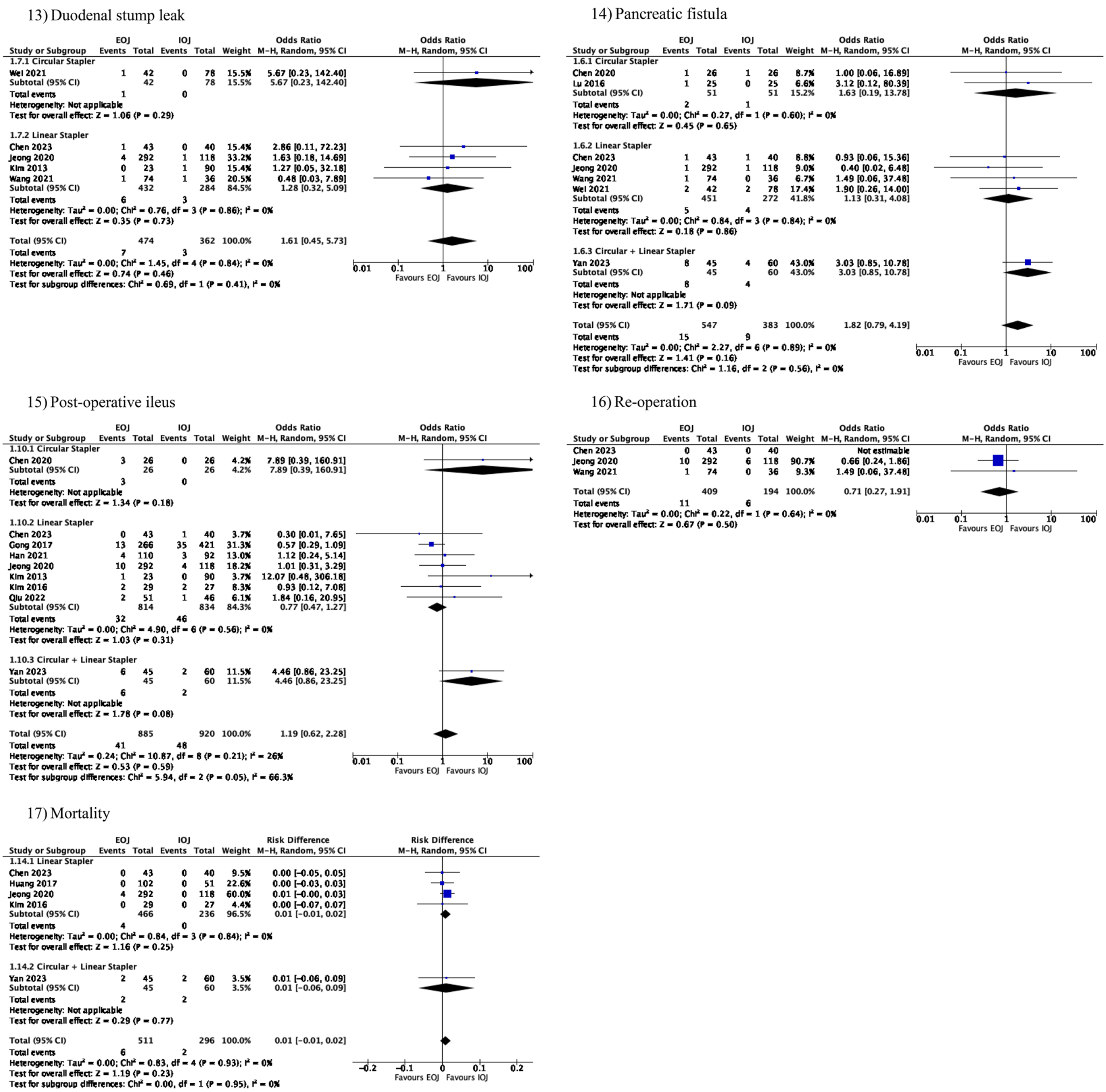

Figure 2. Continued.

as definitions may not be standardized internationally, and all of the included studies were from the Far East. This review emphasises the need for interpretation and analysis of results in accordance with international measures: wound infection as defined by the Centre for Disease Control and Prevention (CDC)[39]; anastomotic leak as defined by the Internal Study Group of Rectal Cancer (ISRC)[40].

Third, as demonstrated in Table 1, all of the included studies consistently used a circular stapled anastomosis in the EOJ group compared with different reconstruction techniques employed in the IOJ group. This may have introduced bias in the pooling of results and generalizability of our effect estimates. A meta-analysis[2] of 32 studies reported linear stapling devices to be safer and more efficient during laparoscopic anastomosis formation following gastrectomy across all postoperative outcomes. Although we performed a subgroup analysis of different stapling techniques and found concordant results, the heterogenous stapling methods within the IOJ group may have influenced our pooled outcomes, including that of anastomotic stricture occurrence. Moreover, various patient-related and technical factors can influence anastomotic outcomes including surgical technique: use of handsewn vs. stapling (linear vs. circular) devices, single-layer vs. double-layer anastomosis, and interrupted vs. continuous suturing. Additionally, nutritional

Table 6

Summary of evidence using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework

Summary of Findings

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects: Risk with intracorporeal oesophagojejunostomy in laparoscopic total gastrectomy for proximal gastric or gastro-oesophageal cancer	Anticipated absolute effects: Risk difference with extracorporeal oesophagojejunostomy
Anastomotic leak	2,778 (16 non-randomized studies)	⊕ ⊕ ⊕○ Moderate	OR 0.86 (0.55 to 1.36)	42 per 1,000	6 fewer per 1,000 (18 fewer to 14 more)
Anastomotic bleeding	1,235 (9 non-randomized studies)	⊕ ⊕ ⊕○ Moderate	OR 1.91 (0.49 to 7.37)	8 per 1,000	7 more per 1,000 (4 fewer to 50 more)
Anastomotic stricture	2,823 (16 non-randomized studies)	⊕ ⊕ ⊕○ Moderate	OR 2.00 (1.16 to 3.44)	18 per 1,000	17 more per 1,000 (3 more to 41 more)
Operative time	2,875 (17 non-randomized studies)	⊕ ⊕ ⊕ ⊕ High	-	The mean operative time was 0	MD 1.79 higher (5.6 lower to 9.19 higher)
LOS	2,607 (15 non-randomized studies)	⊕ ⊕ ⊕ ⊕ High	-	The mean LOS was 0	MD 0.43 higher (0.39 lower to 1.26 higher)
Intraoperative hemorrhage	1,655 (13 non-randomized studies)	⊕ ⊕ ⊕ ⊕ High	-	The mean intraoperative blood loss was 0	MD 37.22 higher (19.52 higher to 54.92 higher)
Harvested lymph nodes	2,022 (12 non-randomized studies)	⊕ ⊕ ⊕○ Moderate[c]	-	The mean harvested lymph nodes was 0	MD 1.56 lower (3.77 lower to 0.66 higher)
Time to first flatus	2,231 (13 non-randomized studies)	⊕ ⊕ ⊕ ⊕ High	-	The mean time to first flatus was 0	MD 0.02 lower (0.17 lower to 0.12 higher)
Time to first soft diet	1,529 (7 non-randomized studies)	⊕ ⊕ ⊕ ⊕ High	-	The mean time to first soft diet was 0	MD 0.14 higher (0.14 lower to 0.42 higher)
Intra-abdominal infection	1,916 (10 non-randomized studies)	⊕○○○ Very low[a]	OR 0.74 (0.45 to 1.20)	50 per 1,000	12 fewer per 1,000 (27 fewer to 9 more)
Pulmonary infection	988 (10 non-randomized studies)	⊕○○○ Very low[a]	OR 1.20 (0.74 to 1.95)	85 per 1,000	15 more per 1,000 (21 fewer to 68 more)
SSI	1,729 (8 non-randomized studies)	⊕ ⊕ ⊕ ⊕ High	OR 2.10 (1.03 to 4.27)	22 per 1,000	23 more per 1,000 (1 more to 65 more)
Duodenal stump leak	836 (5 non-randomized studies)	⊕ ⊕○○ Low	OR 1.61 (0.45 to 5.73)	8 per 1,000	5 more per 1,000 (5 fewer to 37 more)
Pancreatic fistula	930 (7 non-randomized studies)	⊕ ⊕○○ Low	OR 1.82 (0.79 to 4.19)	23 per 1,000	18 more per 1,000 (5 fewer to 68 more)
Postoperative Ileus	1,805 (9 non-randomized studies)	⊕ ⊕○○ Low[a]	OR 1.19 (0.62 to 2.28)	52 per 1,000	9 more per 1,000 (19 fewer to 59 more)
Reoperation	603 (3 non-randomized studies)	⊕○○○ Very low[b]	OR 0.71 (0.27 to 1.91)	31 per 1,000	9 fewer per 1,000 (22 fewer to 27 more)
Mortality	807 (5 non-randomized studies)	⊕ ⊕ ⊕ ⊕ High	not estimable	6 per 1,000	6 fewer per 1,000 (6 fewer to 6 fewer)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; OR: odds ratio.
GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Explanations
[a]The risk has been found to be inconsistent across the studies.
[b]Reported by only three studies.
[c]Type of intervention does not affect the outcome.

status, intra-operative contamination, prolonged operative time, and need for multiple blood transfusions can all affect anastomosis-related outcomes. Consequently, rigorous studies are needed to evaluate the effects of various factors on immediate and long-term anastomosis-related complications.

Fourth, bias may have been introduced in the present review through the exclusion of non-English language articles potentially impacting effect estimates and limiting generalisability of our findings.

Finally, our included studies almost exclusively originated from the Far East (namely China, South Korea, and Japan) again potentially affecting the generalizability of our results to a broader population. This phenomenon is likely attributed to the relatively high incidence and disease burden of gastric malignancies within those populations. The population-based study by Morgan *et al.*[2] highlighted an incidence rate of gastric cancer in Japanese males of approximately 48.1 per 100,000. Therefore, our review strongly highlights the need to define outcomes in future, high-level, RCTs to ascertain long-term prognosis.

Conclusion

Meta-analysis of the best available evidence (level 2a) demonstrated that LTG for gastric malignancy with IOJ may be associated with lower risk of anastomotic stricture and SSI compared to the extracorporeal approach. However, future adequately-powered randomised studies are needed to compare the two techniques and draw more robust conclusions.

Ethical approval

This study was a meta-analysis of published data so no prior ethical approval was required. This work has not been published previously, and the manuscript (including related data) is not under consideration elsewhere.

Consent

Not required.

Sources of funding

No funding was required for this study.

Author contributions

Study concept and design: S.Z., M.I.H., C.S. Acquisition of data: M.K., O.E.S.M., A.Y.M. Analysis and interpretation of data: M.K., O.E.S.M., S.H., S.H.. Drafting of manuscript: S.Z., S.H., S.H., R.C.. Critical revision of manuscript: S.H., R.C., C.S. Final approval: all authors.

Conflicts of interest disclosure

The authors declare no conflict of interest.

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Data availability statement

All data relevant to this study are included in the article. Additional data are available on request from the corresponding author.

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