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SYSTEMATIC REVIEW

Linear- versus circular-stapled esophagogastric anastomosis during esophagectomy: systematic review and meta-analysis

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Abstract

Background Different techniques have been described for esophagogastric anastomosis. Over the past decades, surgeons have been improving anastomotic techniques with a gradual shift from hand-sewn to stapled anastomosis. Nowadays, circular-stapled (CS) and linear-stapled (LS) anastomosis are commonly used during esophagectomy.

Methods PubMed, MEDLINE, Scopus, and Web of Science were searched up to June 2022. The included studies evaluated short-term outcomes for LS vs. CS anastomosis in patients undergoing esophagectomy for cancer. Primary outcomes were anastomotic leak (AL) and stricture (AS). Risk ratio (RR) and standardized mean difference (SMD) were used as pooled effect size measures whereas 95% confidence intervals (95%CI) were used to assess relative inference.

Results Eighteen studies (2861 patients) were included. Overall, 1371 (47.9%) underwent CS while 1490 (52.1%) LS. Compared to CS, LS was associated with a significantly reduced RR for AL (RR = 0.70; 95% CI 0.54–0.91; $p < 0.01$) and AS (RR = 0.32; 95% CI 0.20–0.51; $p < 0.0001$). Stratified subgroup analysis according to the level of anastomosis (cervical and thoracic) still shows a tendency toward reduced risk for LS. No differences were found for pneumonia (RR 0.78; $p =$ 0.12), reflux esophagitis (RR 0.74; $p = 0.36$), operative time (SMD −0.25; $p = 0.16$), hospital length of stay (SMD 0.13; $p = 0.51$), and 30-day mortality (RR 1.26; $p = 0.42$).

Conclusions LS anastomosis seems associated with a tendency toward a reduced risk for AL and AS. Although surgeon's own training and experience might direct the choice of esophagogastric anastomosis, our meta-analysis encourages the use of LS anastomosis.

Keywords Esophagogastric anastomosis · Linear-stapled · Circular-stapled · Leak · Stenosis

Introduction

Esophageal cancer is the sixth most common cancer and the eighth most common cause of cancer-related death worldwide [1]. The prognosis is poor while related 5-year overall survival ranges from 15 to 20% [2]. Esophagectomy, lymphadenectomy, and restoration of the gastrointestinal continuity via gastric conduit reconstruction represent the gold standard treatment [3]. The esophagogastric anastomosis is the most delicate and trickiest part of the operation while related complications are feared problems [4]. Anastomotic leak (AL) may occur up to 10% of patients. It has been reported to be associated with a 3-fold increase in mortality, prolonged hospital stay, delayed oral feeding, risk of reintervention, increased risk of recurrence, and decrease of overall/disease-free survival [5, 6]. Anastomotic stricture (AS) may occur up to 30% of patients and may require endoscopic dilation with a negative effect of postoperative recovery, nutritional status, and quality of life [7].

Different techniques have been described for esophagogastric anastomosis such as hand-sewn and mechanical stapled anastomosis [8, 9]. Over the past few decades, surgeons have been improving anastomotic techniques with a gradual

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shift from hand-sewn to stapled anastomosis [10–13]. Nowadays, circular-stapled (CS) and linear-stapled (LS) anastomosis are largely adopted into clinical practice for both cervical and thoracic anastomoses [14]. CS and LS have their own advantages and weaknesses while the decision to use one technique over another mainly depends on surgeon expertise and personal preference [15]. Currently, a definitive indication on the best stapling technique for esophageal anastomosis is still to be defined since previous studies showed contrasting results.

Hence, aim of the present systematic review and meta-analysis was to perform an updated literature analysis to compare outcomes for LS vs. CS anastomosis in the setting of esophagectomy for the treatment of esophageal cancer.

Materials and methods

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and MOOSE guidelines [16, 17]. Institutional review board approval was not required. PubMed, MEDLINE, Scopus, Web of Science, Cochrane Central Library, and ClinicalTrials.gov were used [18]. The last date of search was the June 30th, 2022. A combination of the following MeSH terms (Medical Subject Headings) was used ("esophagectomy" (tiab), OR "esophagectomies" (tiab), OR, "esophagogastric" (tiab), OR "esoph*" (tiab)) AND ("anastomosis" (tiab), OR "suture" (tiab)) AND ("linear" (tiab), OR "circular" (tiab)) AND ("outcomes" (tiab), OR "complication" (tiab)) AND ("leak" (tiab), OR "leakage" (tiab)) AND ("stricture" (tiab), OR "stenosis" (tiab)). All titles were evaluated and suitable abstracts extracted. The search was completed by consulting the references of each article. The study protocol was registered at the PROSPERO (international prospective register of systematic reviews) (Registration Number: CRD42022328741).

Eligibility criteria

Inclusion criteria: (a) cohort studies and randomized controlled trials (RCTs) comparing outcomes for LS vs. CS among adult patients (>18 year old) undergoing elective esophagectomy for cancer; (b) English-written; (c) when two or more papers were published by the same institution, study group, or used the same dataset, articles with the longest follow-up or the largest sample size; (d) in case of duplicate studies with accumulating numbers of patients only the most complete reports were included for quantitative analysis. Exclusion criteria: (a) not English-written; (b) poor methodology; (c) no clear outcome distinction between LS vs. CS; (d) articles with less than 7 patients per study arm.

Data extraction

The following data were collected: authors, year of publication, country, study design, number of patients, sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, comorbidities, surgical indication, tumor characteristics, histological type, tumor location, cancer stage, neoadjuvant chemoradiotherapy, and postoperative outcomes. All data were computed independently by three investigators (AA, AS, FL) and compared at the end of the reviewing process. A fourth author (DB) reviewed the database and determined discrepancies.

Outcomes

Primary outcomes were postoperative AL and AS. The quantitative analysis was performed for the global population and after stratification according to the level of anastomosis (cervical and thoracic). Secondary outcomes were reflux esophagitis, pulmonary complications, operative time (OT) (minutes), hospital length of stay (HLOS) (days), and 30-day mortality. AL was defined as evidence of contrast extravasation at postoperative swallow study and/or CT scan, or endoscopic visualization of anastomotic dehiscence/fistula, or visible loss of saliva through surgical drains combined with clinical signs. AS was diagnosed in case of postoperative dysphagia, evidence of anastomotic lumen stricture, and need for endoscopic dilatation up to 6 months after the operation. Reflux esophagitis was defined as higher than grade A according to the Los Angeles Classification of severity.

Quality assessment

Three authors (AA, AS, MC) independently assessed the methodological quality of included studies. The ROBINS-I tool was used for observational studies [19]. The following domains were considered: confounding bias, selection bias, classification bias, intervention bias, missing data bias, outcomes measurement bias, and reporting bias. Each domain is evaluated with one of the following: "yes," "probably yes," "probably no," or "no." The categories of judgment for each study are low, moderate, serious, and critical risk of bias. The methodological quality of randomized controlled trials (RCTs) was appraised with the Cochrane risk of bias tool [20]. This tool evaluates the following criteria: [1] method of randomization; [2] allocation concealment; [3] baseline comparability of study groups; and [4] blinding and completeness of follow-up. Trials were graded as follows: A = adequate, B = unclear, and C = inadequate on each criterion. Thus, each RCT was graded as having low, moderate, or high risk of bias. Disagreements were solved by discussion. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool to assess the quality of the body of evidence across studies [21].

Statistical analysis

The results of the systematic review were summarized quantitatively into frequentist random effect meta-analysis of pooled risk ratio (RR) and standardized mean difference (SMD). An inverse-variance method and DerSimonian–Laird estimator for the variance of the true effect size (τ^2) were performed [22, 23]. Heterogeneity among studies was evaluated by the I^2 index and Cochran's Q test [24]. Statistical heterogeneity was considered low, moderate, and high for I^2 values of 25, 50, and 75%, respectively, and significant when $p < 0.10$ [25, 26]. The Wald-type 95% confidence interval (CI) was computed for pooled measurements; otherwise, the 95% CI for the I^2 index was calculated according to Higgins and Thompson [27]. The prediction interval for the treatment effect of a new study was calculated according to Borenstein et al. [24]. As the sample size was not the same in all studies, we performed a sensitivity analysis by excluding one study each time and rerunning the analysis to verify the robustness of the overall results. The publication bias was also investigated with the trim and fill funnel plot and Egger test. A two-sided p value was considered statistically significant when $p < 0.05$. All analyses and figures were carried out using the R software program, version 3.2.2 [28].

Results

Systematic review

The PRISMA flow chart is reported in Fig. 1. Four-hundred fifty-eight publications were identified. After duplicates removal, 402 titles were screened. Sixteen articles were excluded after title assessment. Overall, 386 abstracts were reviewed while 21 articles were found possibly relevant for full-text assessment. After full-text evaluation, 18 studies meet the inclusion/exclusion criteria and were included in the quantitative synthesis. Fifteen studies were of retrospective design while three were RCTs. The quality of

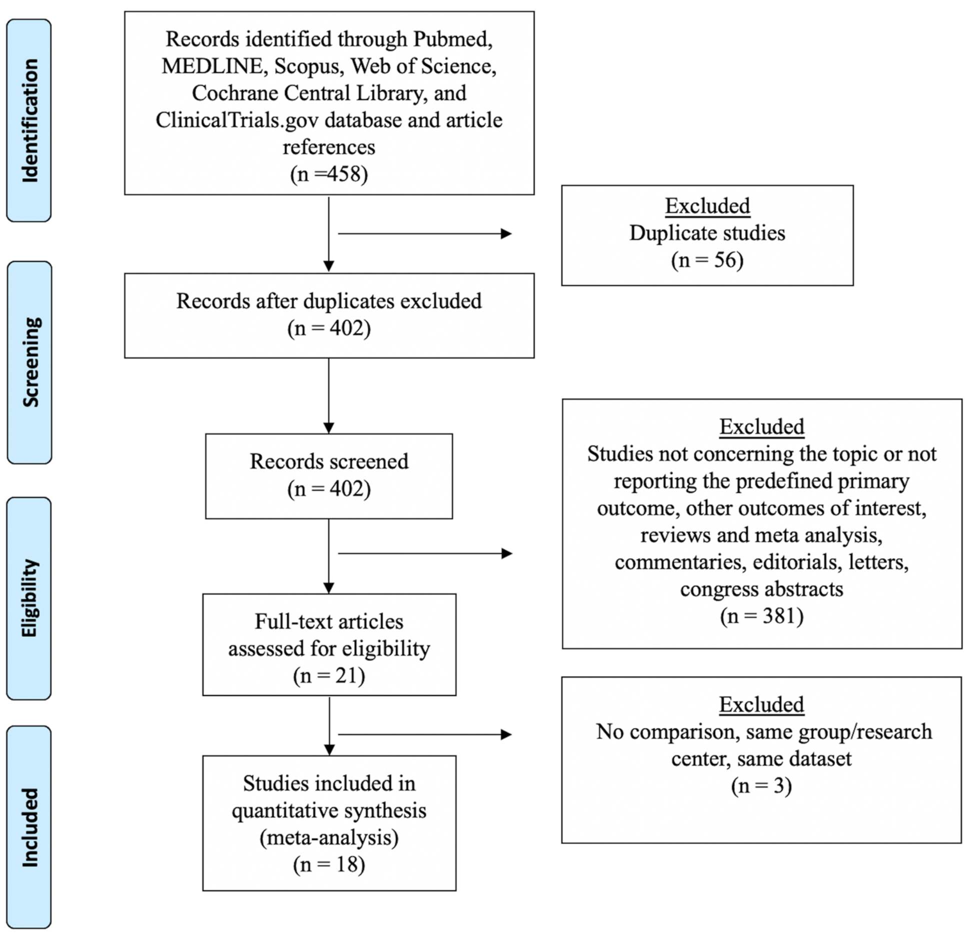

Fig. 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram

observational studies and RCTs is reported in Supplementary Table 1 and Supplementary Figure 1.

Overall, 2861 patients were included (Table 1). Of those 1371 (47.9%) underwent CS while 1490 (52.1%) underwent LS. The age of the patient population ranged from 47 to 87 years, the BMI ranged from 15.3 to 30.2 kg/m^2, and the majority (74.9%) were males. The tumor was located in the upper (12.4%), middle (51.6%), and lower (36%) esophagus. Tumor histology was specified in 9 studies; squamous cell carcinoma and adenocarcinoma were diagnosed in 83% and 15.5% of patients, respectively. Pathological tumor staging according to the 7th and 8th edition of the American Joint Committee on Cancer (AJCC) and Japanese gastric cancer classification (JGCC) was detailed in 7 studies (stage 0–I: 25.1%, stage II: 37.1%, stage III: 34.5%, and stage IV: 3.3%). Open, hybrid, or totally minimally invasive esophagectomy were performed depending on operating surgeon preference and expertise. Both cervical and intrathoracic anastomoses were described according to tumor location, operating surgeon preferences, and oncological principles. The use of neoadjuvant chemoradiation therapy was heterogeneously reported in nine studies (i.e., protocols, regimens, etc.). The extent of lymphadenectomy (2-field and 3-field) was specified in 5 studies and varied depending on surgeon expertise and tumor clinical stage/location.

Meta-analysis—primary outcomes

AL was reported in eighteen studies (2861 patients). The cumulative incidence of AL was reduced for LS vs. CS (7.9% vs. 12.2%). Compared to CS, LS was associated with a significantly reduced AL risk (RR = 0.70; 95% CI 0.54–0.91; $p < 0.01$) (Fig. 2A). The prediction lower and upper limits were 0.47 and 1.06, respectively. The heterogeneity was zero ($I^2 = 0.0\%$, 95% CI 0.0–50%; $p < 0.01$) and $\tau^2 = 0.01$. The funnel plot (Fig. 2B) and the Egger test ($p = 0.49$) did not show evidence of publication bias. The sensitivity analysis showed the robustness of these findings in terms of point estimation, relative confidence intervals, and heterogeneity. After stratification, LS showed a significant AL risk reduction for cervical anastomosis (7 studies; 952 patients) (RR = 0.61; 95% CI 0.38–0.96; $I^2 = 11\%$; $p = 0.039$) while no significant differences were found for thoracic anastomosis (9 studies, 1581 patients) (RR = 0.78; 95% CI 0.57–1.05; $I^2 = 0.0\%$; $p = 0.10$) (Supplementary Figure 2 A-B).

AS was reported in 15 studies (1922 patients). The cumulative incidence of AS was reduced for LS vs. CS (7.7% vs. 18.9%). Compared to CS, LS was associated with a significantly reduced AS risk (RR = 0.32; 95% CI 0.20–0.51; $p < 0.0001$) (Fig. 3A). The prediction lower and upper limits were 0.11 and 1.05, respectively. The heterogeneity was moderate ($I^2 = 33.3\%$, 95% CI 0.0–50%; $p < 0.01$) and $\tau^2 = 0.24$. The funnel plot (Fig. 3B) and the Egger test ($p = 0.04$) showed that publication bias could not be excluded. The sensitivity analysis showed that omitting the study by Xu et al., the heterogeneity decreased to low ($I^2 = 12\%$). After stratification, LS showed a significant AL risk reduction for both cervical (7 studies; 1162 patients) (RR = 0.42; 95% CI 0.30–0.58; $p < 0.001$; $I^2 = 43\%$) and thoracic anastomosis (7 studies, 749 patients) (RR = 0.32; 95% CI 0.14–0.77; $p < 0.01$; $I^2 = 33\%$) (Supplementary Figure 3 A-B).

Subgroup analysis by including only RCTs (3 studies; 285 patients) showed a trend toward reduced AL (RR = 0.56; 95% CI 0.19–1.09; $p = 0.32$; $I^2 = 0.0\%$) and AS risk (RR = 0.17; 95% CI 0.02–1.88; $p = 0.15$; $I^2 = 29\%$) for LS vs. CS.

Meta-analysis—secondary outcomes

Reflux esophagitis (RR = 0.74; 95% CI 0.30–1.41; $p = 0.36$; $I^2 = 62\%$), pneumonia (RR = 0.78; 95% CI 0.57–1.06; $p = 0.12$; $I^2 = 0.0\%$), OT (SMD −0.25; 95% CI −0.25, 0.09; $p = 0.16$; $I^2 = 77\%$), HLOS (SMD 0.13; 95% CI −0.25, 0.51; $p = 0.51$; $I^2 = 91\%$), and 30-day mortality (RR = 1.26; 95% CI 0.72–2.21; $p = 0.42$; $I^2 = 0.0\%$) were similar for LS vs. CS (Fig. 4A-C). Using the GRADE tool, we rated the quality of evidence supporting each outcome as low-moderate mainly because of limitations in study design (Supplementary Table 2).

Discussion

This meta-analysis shows that compared to CS, LS seems associated with a reduced RR of AL and AS during esophagectomy. After stratification for both cervical and thoracic anastomosis, LS shows a trend toward reduced AL and AS risk. Reflux esophagitis, pneumonia, and 30-day mortality seem similar among treatments.

The esophagogastric anastomosis represents a central part of esophagectomy and may potentially contribute to the significant short- and long-term morbidity and mortality [4, 6, 47]. AL is a major complication with a reported incidence ranging from 10 and 20% [48]. It is associated with increased postoperative morbidity, high postoperative mortality rates, prolonged hospital stay, and increased costs [49–52]. In addition, it has been shown to decrease long-term quality of life and oncological survival [6, 53]. Factors that may contribute to anastomosis failure are lack of serosa layer, tension, inadequate blood supply of the gastric conduit, surgical technique, malnutrition, and patient comorbidities [54]. Furthermore, it has been suggested that gut microbiome may influence the suture line healing process thus possibly contributing to anastomosis breakdown [55]. Various techniques for esophagogastric anastomosis (hand-sewn vs. stapled) have been described [56–58]. Interestingly, there has been a gradual shift from hand-sewn to

Table 1 Demographic, clinical, and operative data for patients undergoing linear-stapled (LS) and circular-stapled (CS) esophagogastric anastomosis. *RCT*, randomized controlled trial; *Ret*, retrospective; *PS*, propensity score adjusted; *BMI*, body mass index; *U*, upper esophagus; *M*, middle esophagus; *L*, lower esophagus; *SCC*, squamous cell carcinoma; *AC*, adenocarcinoma; *Lymhp*, level of lymphadenectomy; *UICC-TNM*, Union for International Cancer Control; *AJCC-TNM*, American Joint Committee on Cancer; *JGCC*, Japanese gastric cancer classification; *Op*, open esophagectomy; *Hyb*, hybrid esophagectomy; *MIE*, minimally invasive esophagectomy; *2FL*, 2-field lymphadenectomy; *3FL*, 3-field lymphadenectomy; *, robotic; *NA*, not available. Data are reported as numbers, mean ± standard deviation, and median (range)

Author, year, country	Study design	Group	No.	M/F	Age (yrs)	BMI (kg/m^2)	Location U-M-L	SCC-AC-other	Classification	Stage 0–I	Stage II	Stage III	Stage IV	Neoadjuvant treatment	Surgical approach	Lymhp	Anastomosis level
Furukawa et al., 2005—Japan [29]	Ret	CS	8	NA	NA	NA	0-8-0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		LS	12	NA	NA	NA	0-12-0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Blackmon et al., 2007—USA [30]	Ret	CS	23	19/4	62 ± 12	26 ± 5	0-1-22	1-22-0	AICC-TNM	4	11	7	1	21	Op	2FL-3FL	Thorax
		LS	23	20/3	61 ± 9	26 ± 4	0-1-22	1-22-0	AICC-TNM	3	17	2	1	19	Op	2FL-3FL	Thorax
Xu et al., 2011—China [31]	Ret	CS	68	61/7	61.3 ± 7.6	NA	2-44-22	NA	AJCC-TNM7	8	23	27	0	0	Op	NA	Thorax
		LS	166	143/23	60.2 ± 8.4	NA	1-112-53	NA	AJCC-TNM7	17	56	93	0	0	Op	NA	Thorax
Wang et al., 2013—China [32]	RCT	CS	47	41/6	61.4 ± 7.7	NA	0-38-9	NA	NA	6	19	22	0	NA	Op	NA	Thorax
		LS	45	41/4	59.7 ± 7.4	NA	0-27-13	NA	NA	4	15	26	0	NA	Op	NA	Thorax
Price et al., 2013—USA [33]	Ret	CS	48	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Op/MIE	NA	Thorax/cervical
		LS	260	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Op/MIE	NA	Thorax/cervical
Li et al., 2014—China [34]	Ret	CS	51	27/6	61 (45–75)	NA	7-36-8	51-0-0	NA	20	15	10	6	NA	MIE	NA	Cervical
		LS	33	41/10	61 (46–79)	NA	2-21-10	33-0-0	NA	14	10	5	4	NA	MIE	NA	Cervical
Mungo et al., 2015—USA [35]	Ret	CS	38	NA	66 (63.5–72.5)	26.9 (24.3–26.9)	NA	NA	NA	NA	NA	NA	NA	NA	MIE	NA	Thorax
		LS	12	NA	67 (63.5–72.5)	26.9 (24.3–26.9)	NA	NA	NA	NA	NA	NA	NA	NA	MIE	NA	Thorax
Hayata et al., 2017—Japan [36]	RCT	CS	49	40/9	68 ± 8	22.7 ± 7.9	1-33-15	46-3	NA	4	19	24	2	26	Hyb/MIE	NA	Cervical
		LS	51	37/14	65 ± 9	21.4 ± 2.7	5-28-18	47-4	NA	13	13	23	2	29	Hyb/MIE	NA	Cervical
Huang et al., 2017—China [37]	Ret	CS	42	26/16	57.9 ± 8.2	21.5 ± 3.5	12-24-6	42-0-0	NA	12	16	14	0	7	MIE	NA	Cervical
		LS	39	30/9	61.0 ± 8.9	22.8 ± 3.3	6-27-6	39-0-0	NA	13	12	13	1	5	MIE	NA	Cervical

Table 1 (continued)

Author, year, country	Study design	Group	No.	M/F	Age (yrs)	BMI (kg/m^2)	Location U-M-L	SCC-AC-other	Classification	Stage 0–I	Stage II	Stage III	Stage IV	Neoadjuvant treatment	Surgical approach	Lymhp	Anastomosis level
Yanni et al., 2019—UK [38]	Ret	CS	85	NA	68	NA	NA	NA	AJCC-TNM8	NA	NA	NA	NA	NA	Op/Hyb	2FL	Thorax
		LS	74	NA	68.5	NA	NA	NA	AJCC-TNM8	NA	NA	NA	NA	NA	Op/Hyb	2FL	Thorax
Schroder et al., 2019—Germany [39]	Ret	CS	427	NA	64 (57–70)	26 (23–29)	NA	NA	NA	NA	NA	NA	NA	NA	MIE	NA	Thorax
		LS	364	NA	65 (57–70)	27 (23–29)	NA	NA	NA	NA	NA	NA	NA	NA	MIE	NA	Thorax/cervical
Wang et al., 2019—China [40]	Ret	CS	164	136/28	64 (43–74)	NA	36-90-38	NA	AJCC-TNM7	53	65	46	0	7	MIE	NA	Cervical
		LS	34	23/11	60 (41–73)	NA	1-24-9	NA	AJCC-TNM7	7	18	9	0	4	MIE	NA	Cervical
Zhang et al., 2019—China [41]	Ret	CS	42	35/7	61.9 ± 7.8	22.9 ± 2.2	0-0-42	34-5-3	NA	4	14	22	0	8	MIE*	2FL	Thorax
		LS	35	33/2	61.4 ± 9.2	22.6 ± 4.4	0-0-35	25-9-1	NA	4	19	12	0	8	MIE*	2FL	Thorax
Tian et al., 2020—China [42]	Ret	CS	87	47/97	NA	NA	27-41-19	87-0-0	AJCC-TNM7	37	38	12	0	NA	MIE	2FL and 3FL	Cervical
		LS	137	80/68	NA	NA	34-62-41	137-0-0	AJCC-TNM7	40	62	35	0	NA	MIE	2FL and 3FL	Cervical
Hirano et al., 2020—Japan [43]	Ret, PS	CS	86	68/18	66 ± 8	21.4 ± 2.6	NA	74-8-4	NA	34	12	27	13	51	Op/Hyb/MIE	3FL	Cervical
		LS	86	64/22	65 ± 8	21.4 ± 3.6	NA	74-8-4	NA	35	15	26	10	59	Op/Hyb/MIE	3FL	Cervical
Hosoi et al., 2022—Japan [44]	RCT	CS	42	31/11	70 (46–81)	21.8 (15.3–29.7)	3-23-16	39-3-0	NA	9	9	18	6	38	Hyb	NA	Cervical
		LS	53	45/8	66 (47–82)	21.1 (15.8–28.0)	2-26-25	47-6-0	NA	11	9	28	5	40	Hyb	NA	Cervical
Sugita et al., 2021—Japan [45]	Ret, PS	CS	30	25/5	72 (47–87)	24.7 (18.5–30.2)	NA	NA	JGCC 3rd	NA	NA	NA	NA	NA	Hyb	NA	Thorax
		LS	30	24/6	72 (51–87)	24.2 (21.6–30.7)	NA	NA	JGCC 3rd	NA	NA	NA	NA	NA	Hyb	NA	Thorax
Fabbi et al., 2022—Italy–Neth [46]	Ret, PS	CS	36	24/12	63 (59–70)	24 (22–29)	0-0-36	7-28-1	AJCC-TNM	7	12	16	1	25	MIE	NA	Thorax
		LS	36	25/11	65 (29–83)	23 (15.9–31.5)	0-0-36	6-29-1	AJCC-TNM	7	11	17	1	22	MIE	NA	Thorax

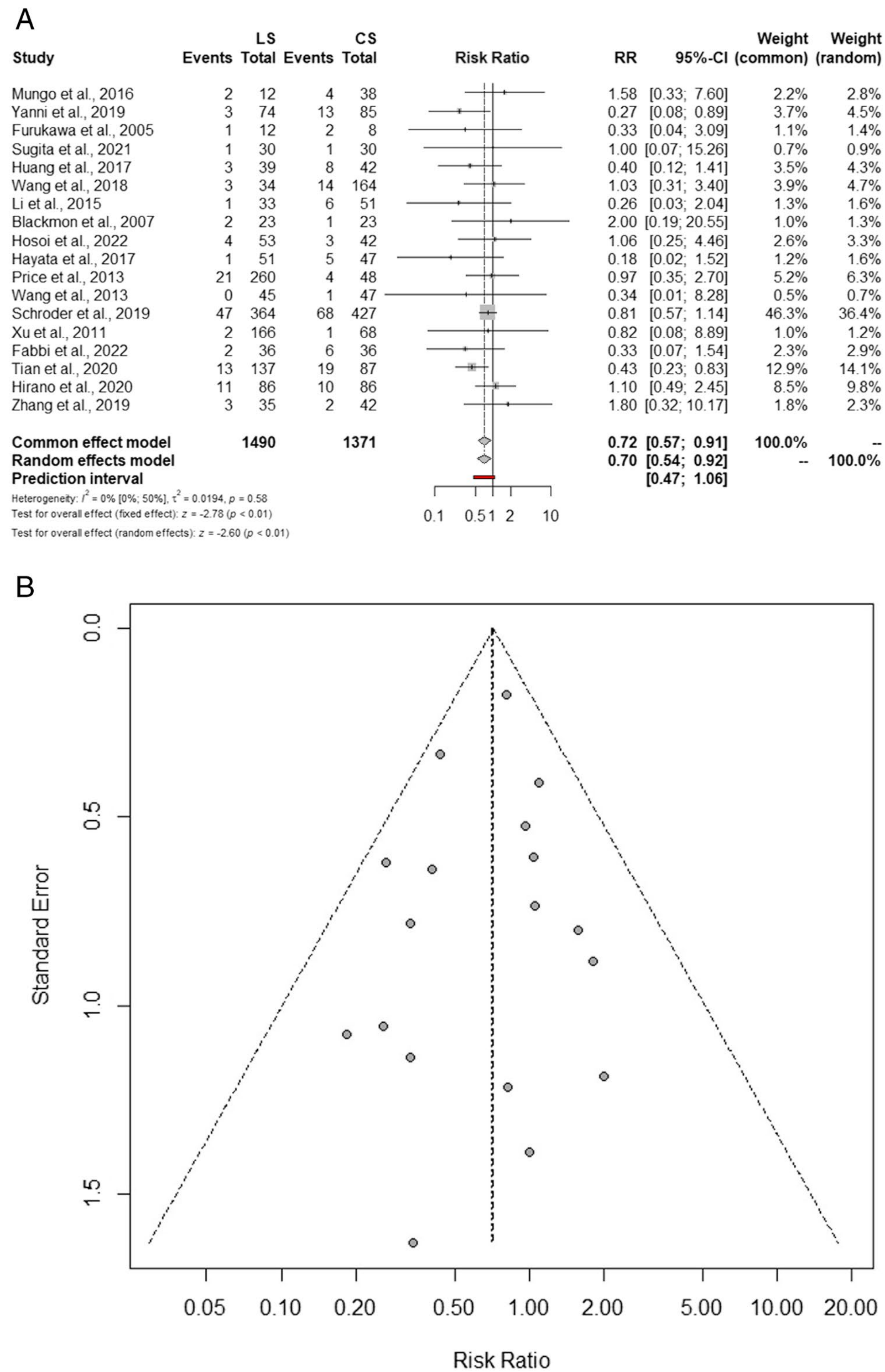

Fig. 2 Anastomotic leak. Forrest (**A**) and funnel (**B**) plot. RR, risk ratio; 95% CI, confidence interval

stapled anastomosis because technical simplicity, comparable safety, and time saving [59]. Currently, both LS and CS anastomosis are used for esophagogastric anastomosis. Their utilization is mainly dependent on surgeon preference while each technique has its pros and cons. Specifically, CS facilitates the anastomosis at the apex of the thorax (cupula pleuralis); however, the anastomotic lumen is dependent on the original esophageal diameter with problems related to possible size mismatch. Furthermore, CS creates an inverted anastomosis where esophageal and gastric mucosa margins are separated by muscular layers thus potentially resulting in a high stricture rates. Conversely, LS anastomosis makes

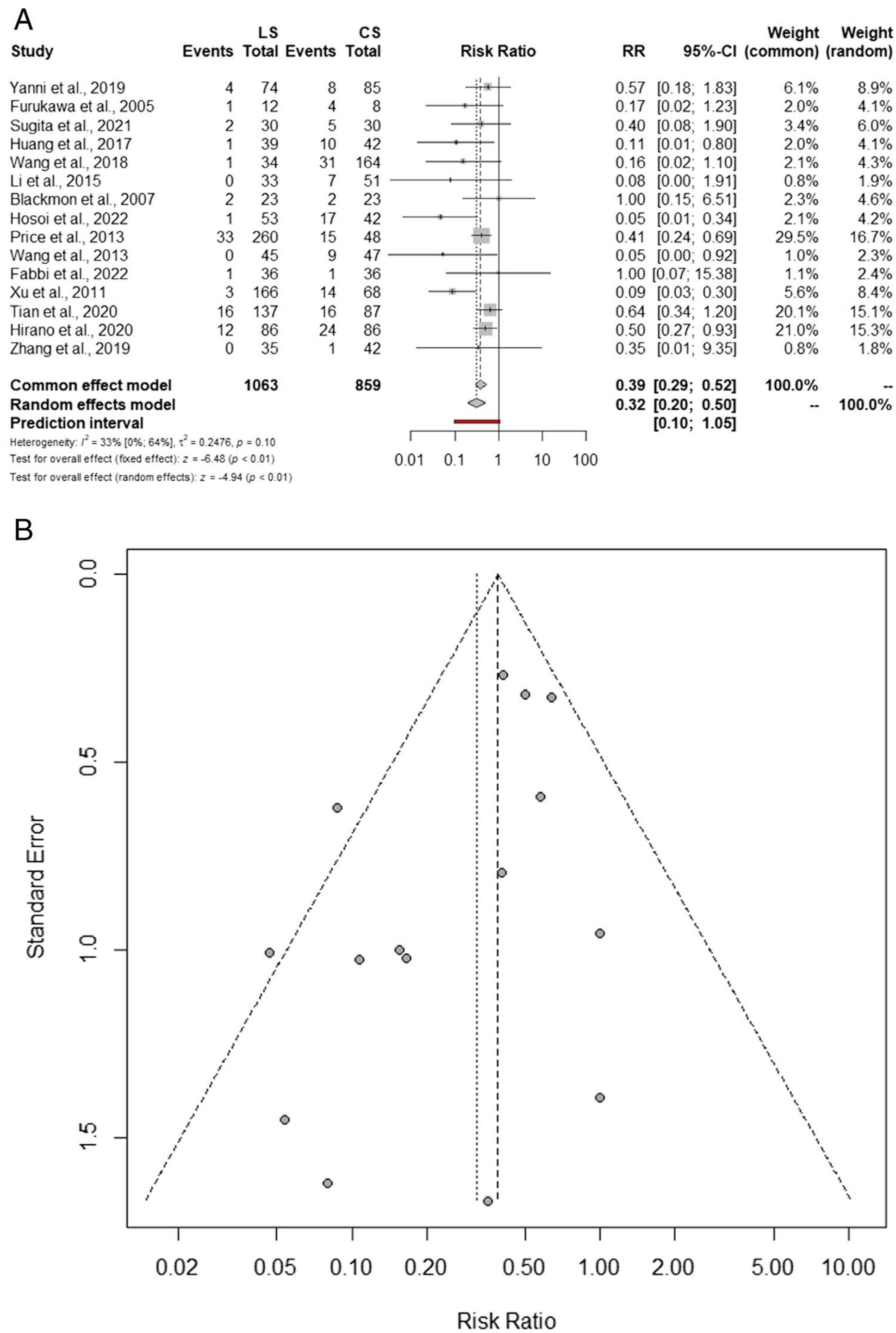

Fig. 3 Anastomotic stricture. Forrest (**A**) and funnel (**B**) plot. RR, risk ratio; 95% CI, confidence interval

a larger anastomotic diameter, minimizes problems related to visceral mismatch, and makes an extroverted anastomosis which leads to improved mucosa-to-mucosa apposition [29, 37]. Furthermore, it has been postulated that LS might be advantageous in terms of blood supply as the staple line results parallel to the axis of the gastric conduit thus leading to maximum preservation of the vasculature network at the anastomosis mainly perfused through intramural capillaries [44, 60, 61]. Recently Nickel et al. explored the principles of gastric conduit capillaries dynamics in live porcine models undergoing minimally invasive esophagectomy with LS anastomosis. Authors concluded that the dominant direction of flow through the conduit mainly arises through the right gastroepiploic artery and capillaries along the transverse conduit axis thus suggesting the use of short (30 mm) linear staplers to preserve optimal tissue oxygenation at the

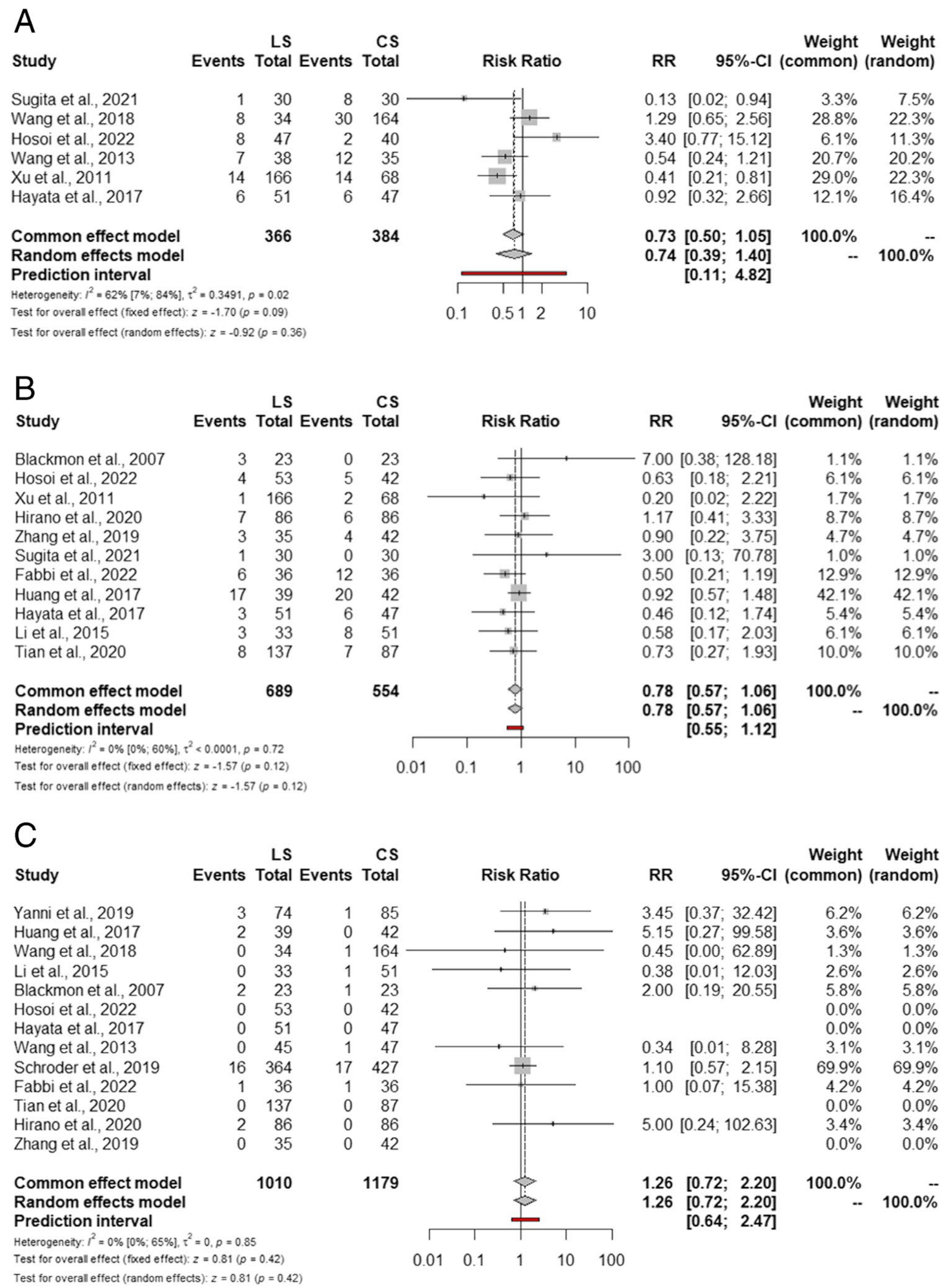

Fig. 4 Forrest plot for reflux esophagitis (**A**), pneumonia (**B**), and 30-day mortality (**C**). RR, risk ratio; 95% CI, confidence interval

anastomotic site [62]. Finally, LS anastomosis requires a longer esophageal remnant (at least 2 cm); thus, fashioning an aligned high intra-thoracic tension-free anastomosis is challenging because of limited space.

While both techniques are currently used, robust evidence describing the best technique for stapled-esophageal anastomosis is to be defined. A previous study by Yanni et al. reported significantly reduced thoracic AL for LS vs. CS (4.1% vs. 15.3%; $p = 0.019$) [38]. Equally, Huang et al. in their 2017 retrospective study described a significantly reduced incidence of cervical AL for LS vs. CS (7.7% vs. 19%) [37]. Despite the lack of statistical significance, Fabbi et al. [46] and Hosoi and colleagues [44] reported a tendency toward reduced AL for LS. In contrast, Zhou et al. in a 2015 meta-analysis affirmed no differences for postoperative AL comparing LS vs. CS (RR = 0.80; $p = 0.52$) [63]. In our study, we found that LS seems associated with a significantly reduced RR for AL (RR = 0.67; $p < 0.01$). The related heterogeneity was 0.0% thus adding robustness to the result. Possible explanations include a better vascular/oxygen supply to the anastomotic site, superior anastomosis orientation with concomitantly reduced traction-related tension, and minimization of visceral twisting. The stratification analysis still evidences a significant difference for cervical anastomosis (RR = 0.61; $p = 0.04$) while no significant differences were found for thoracic anastomosis. Notably, the point estimation was below 1.00 (RR = 0.61) thus suggesting a clinical tendency toward reduced RR. However, this initial indication mandates future analysis and possible confirmation by large trials. Despite the low heterogeneity, our result should be interpreted with caution because the presence of possible confounders related to technical variations (Collard vs. Orringer procedure), closure of the anterior wall (i.e., single layer vs. double layer vs. stapling), suture material (absorbable vs. non-absorbable vs. antibacterial suture), blood flow assessment with indocyanine green, gastric ischemic preconditioning, esophageal diameter (dilated or not), omental wrapping, route of reconstruction (retrosternal vs. posterior mediastinal), patient selection, baseline comorbidities (i.e., diabetes), smoking status, neoadjuvant treatment, tumor characteristics (i.e., grading, size, location, etc.), tumor-free resection margins (R0), and surgical approach.

In our meta-analysis, LS seems associated with a significantly reduced RR for AS (RR = 0.31; $p < 0.0001$) irrespective from the level of the anastomosis. This is similar to what previously reported by Zhou et al. that acknowledged a significant tendency toward reduced stricture risk for LS (RR = 0.26; $p = 0.002$) [63]. Similar results are reported by several retrospective analyses [32, 37, 44]. Possible explanations include a wider anastomotic diameter and reduced risk of staple line scarring/fibrosis for LS. Again, these results should be interpreted prudently because lacking of standardized techniques, different sizes (25 mm vs. 28 mm) and techniques for CS (i.e., purse-string suture vs. EEA™ vs. Orvil™), patient selection, postoperative leak occurrence, patient age, comorbidities (i.e., diabetes), smoking status, neoadjuvant treatment, tumor-free resection margins (R0), surgical approach (open vs. minimally invasive), and surgeon proficiency. Interestingly, no significant differences were found for reflux esophagitis (RR = 0.74; $p = 0.36$). This may be attributable to the increased utilization of proton pump inhibitors to reduce acid production and esophageal exposure. This is different from Hosoi et al. that affirmed a tendency toward higher rates of esophagitis for LS anastomosis [44]. Finally, no significant differences were found for postoperative pneumonia, 30-day mortality, OT, and HLOS.

Notably, both AL and AS may not directly reflect the quality of a specific technique but are also influenced by surgeon proficiency, learning curves, structured training/mentorship programs, and hospital volumes [64–66]. Surgical volume and operating surgeon proficiency are critical to obtain optimal surgical outcomes after esophagectomy. It has been shown that case-load centralization in high-volume centers significantly reduces mortality and may improve outcomes [67]. Specifically, during the learning curve, AL has been shown to decrease from 18% in the early phase to 4.5% after 119 cases [68]. Based on these considerations, it should be pondered that AL and AS may not entirely reflect the anastomotic technique but are also influenced by learning curve effect and surgeon experience. Finally, the introduction of new technologies such as fluorescence imaging with indocyanine green to assess the gastric conduit perfusion/anastomosis and the advent of robot-assisted esophagectomy may potentially improve outcomes [69–71].

Our study presents the typical limitations of a meta-analysis including observational studies. The lack of inclusion criteria defined a priori, lack of homogenous surgical approach, and lack of globally defined postoperative management protocols. Second, AL and AS were not uniformly defined and classified among included studies. Third, the majority of included studies (12/18) were performed in Asian countries; therefore, results may not be generalizable. Fourth, surgeon experience and volume were not measured with a conceivable effect on outcomes. Lastly, the creation of a single type of anastomosis might have diverse technical variations among different esophageal surgeons and should therefore be considered as possible source of heterogeneity.

Conclusions

There is a variety of different techniques for esophagogastric anastomosis. Compared to CS, LS anastomosis seems associated with a tendency toward a reduced risk for AL and AS even after stratification according to the level of anastomosis (cervical and thoracic). Although surgeon's own training, learning curve, and experience might direct the choice toward a definite technique for esophagogastric anastomosis, our meta-analysis encourages the implementation of LS anastomosis.

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Authors' contributions AA, AS, FL, and MC did the literature search. AA, GB, and DB formed the study design. Data collection done by AA, AS, FL, and MC. AA, GB, AS, and DB analyzed the data. AA, SC, PD, GC, and DB interpreted the data. AA wrote the manuscript. All authors critically reviewed the manuscript.

Data availability Data generated at a central, large-scale facility, available upon request.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval For this type of article, ethical approval is not required because does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate For this type of study, formal consent was not necessary.

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