Hand-sewn versus stapled anastomoses for esophagectomy: We will probably never know which is better

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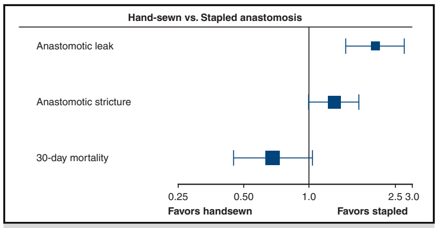
ABSTRACT

Objective: Esophagectomy remains the mainstay of treatment for nonmetastatic esophageal cancer. The optimal technique for anastomosis after esophagectomy remains unknown. The purpose of this systematic meta-analysis is to combine the available high-quality evidence to provide esophageal surgeons with an evidence base for their decision making.

Methods: A systematic search of multiple databases was conducted to find randomized controlled trials of esophageal anastomotic techniques. A meta-analysis of the pooled data was conducted.

Results: A total of 19 studies with 2123 patients were included in the meta-analysis. The pooled analysis revealed a 102% higher incidence of anastomotic leak after hand-sewn anastomosis compared with stapled anastomosis (odds ratio [OR], 2.02; 95% confidence interval [CI], 1.48-2.75). Anastomotic stricture rate was also 31% higher with hand-sewn anastomosis (OR, 1.31; 95% CI, 1.00-1.7). Thirty-day mortality did not show statistical difference favoring one anastomosis technique to another (OR, 0.68; 95% CI, 0.45-1.04). None of anastomotic leak rate, anastomotic stricture rate, or 30-day overall survival differed between anastomotic techniques in studies with only thoracic anastomoses. In cervical position hand-sewn anastomosis was associated with higher rate of anastomotic leak (OR, 2.02; 95% CI, 1.33-3.05) and stricture (OR, 1.77; 95% CI, 1.15-2.72), but no difference in 30-day mortality.

Conclusions: This meta-analysis showed a signal of higher rate of leak and stricture in hand-sewn anastomoses, but sensitivity analyses did not show a consistent outcome, so these results should be interpreted with caution. (JTCVS Open 2021;7:338-52)



Forest plot for rate of anastomotic leakage between hand-sewn and stapled anastomosis.

CENTRAL MESSAGE

A higher rate of leakage and stricture with hand-sewn anastomotic technique was found in this meta-analysis. The studies were heterogeneous, and with variance in results of the sensitivity analyses.

PERSPECTIVE

The rate of anastomotic leakage after esophagectomy remains significant, and there is no consensus on the optimal anastomotic technique. This meta-analysis provides a summary of the current evidence, highlighting the need for more quality studies, especially in minimally invasive settings.

See Commentaries on pages 353 and 355.

Video clip is available online.

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Esophagectomy—Ivor Lewis, McKeown, or transhiatal—is the established treatment for locoregional esophageal cancer. After esophageal resection, the reconstruction is generally performed by gastric pull-up and either intrathoracic or cervical esophagogastric anastomosis.[1] The standard approach has historically been open esophagectomy, but during the past few decades minimally invasive esophagectomy has gained popularity, with benefits over open esophagectomy in regard to overall and disease-specific survival,

Abbreviations and Acronyms
AL = anastomotic leak
OS = overall survival
RCT = randomized controlled trial

pulmonary complications, quality of life, and hospital stay.[2-4] Anastomotic leak (AL) is a devastating complication with a relatively high incidence; a recent meta-analysis of randomized trials reported an incidence of 11.2%.[5,6] The development and adoption of minimally invasive techniques raises the questions regarding optimal anastomotic technique because hand-sewn anastomosis is challenging by the thoracoscopic/laparoscopic approach. There is a paucity of high-quality evidence examining the effect of anastomotic technique on the development of AL, particularly in the minimally invasive setting.

The purpose of this meta-analysis was to determine whether contemporary evidence highlights superiority of 1 anastomotic technique (hand-sewn vs mechanical stapler) over another with respect to the development of AL, anastomotic stricture, and overall survival (OS).

METHODS

Design

This is a systematic literature review and meta-analysis that followed a predetermined study protocol according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses.[7]

Literature Search Strategy

Two independent investigators conducted a systematic literature search contemporary to June 2020 from multiple databases (Embase, Medline, and Cochrane library). The search was performed by combining medical subject headings and related free-text search terms with Boolean operators “AND” or “OR.” The MeSH terms used were *esophageal neoplasms* and *anastomosis, surgical*. A full description of the search strategy is available in Table E1.

Study Selection

The inclusion criteria were as follows: randomized controlled study, study patients underwent esophagectomy, study compared different anastomotic techniques, and study reported anastomotic leak and/or stricture outcomes. Exclusion criteria were English translation of the manuscript not available.

Data Extraction

Titles and abstracts were scrutinized by the first author (T.J.) and duplicates were identified simultaneously. Full texts of potential studies were analyzed by 2 authors (T.J. and I.I.). Summary data were extracted from included studies. Extracted data included publication year, sample size, tumor location and histology, operative technique, anastomosis technique, follow-up, 30-day mortality, hospital mortality, AL, and stricture rate.

Quality Assessment

Quality of studies was assessed by 1 author (T.J.) using Cochrane Collaborations Risk of Bias Tool for randomized clinical trials, which is presented in Table E2.

Informed Consent

Because this was a meta-analysis that does not process individual patient data, no informed consent, as per Helsinki University Institutional Review Board guidelines, was needed.

Outcome Measures and Statistical Analysis

The primary outcome measures evaluated were odds ratios (OR) for AL rate and stricture. The secondary outcome measure was hazard ratio for 30-day mortality. Subset analyses dichotomizing patients according to anastomotic location (cervical vs thoracic) was performed.

Meta-analysis of data was conducted using a random effects model due to high heterogeneity. Publication bias was assessed by funnel plots (plots of effect estimates against sample size) to detect outliers or asymmetry. Funnel plot asymmetry was analyzed visually and by Egger test for small-study effects and publication bias. The statistical significance for Egger test was set at $P < .10$, as originally described by Egger and colleagues.[8] To maximize the number of patients included in the meta-analysis, studies that investigated subgroups within either only hand-sewn or only stapled anastomoses were included in the summary quantitative synthesis representing only a single group, either hand-sewn or stapled anastomosis, with the opposing group size being 0. Forest plots; that is, graphical display of estimated ORs and 95% confidence intervals (CIs) and summary statistics were used to elucidate the results of the studies. Post hoc sensitivity analyses were performed without the inclusion of these single-group studies to investigate the robustness of this analysis. Sensitivity analyses were also performed with studies containing only thoracic anastomoses or only cervical anastomoses and also without the inclusion of studies predating 2000 to elucidate the possible differences of outcomes within these subgroups.

The I^2 test was used to evaluate statistical heterogeneity, also known as the outcome variability in excess of what would be expected due to measurement error alone of the included studies, with levels of heterogeneity defined as not important (I^2, 0%-25%), moderate (I^2, 25%-50%), substantial (I^2, 50%-75%), or considerable (I^2, 75%-100%). Statistical analysis was done with R version 2020 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The database search generated 3153 study titles, of which 19 studies met the inclusion criteria (Figure 1). The anastomotic approaches used were evenly distributed: 1160 (50.3%) hand-sewn anastomoses and 1148 (49.7%) mechanical stapler anastomoses. Eight of the 19 studies (42.1%) included only cervical anastomoses,[9-16] 6 studies (31.6%) included only thoracic anastomoses,[17-22] and 5 studies (26.3%) had both cervical and thoracic anastomoses.[23-27] Two of the studies were randomized trials of antireflux anastomotic techniques, of which 1 did not report any of the prespecified outcomes between hand-sewn and stapled groups and the other had no adequate text in English available, so both were excluded from the summary statistics.[20,21] Remaining studies included 2230 patients across 17 studies. Characteristics of the studies are presented in Table 1.

The studies had somewhat differing definitions for AL, although all of the studies used routine radiographic imaging on postoperative day 3 through 10. Stricture definitions differed somewhat between studies, the most common definitions being the inability to pass a small diameter (9-10 mm) enteroscope past the anastomosis, a small diameter

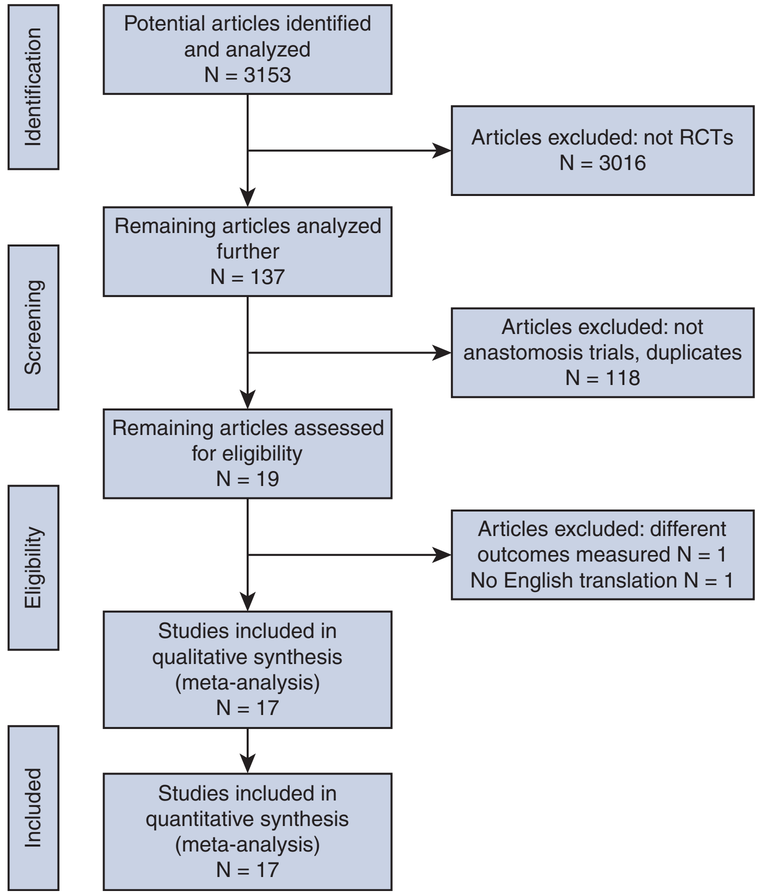


FIGURE 1. Flow chart of the literature search according to preferred reporting items for systematic reviews and meta-analyses statement. *RCTs*, Randomized controlled trials.

of the anastomosis (<8-10 mm) in imaging or the need for dilatation based on symptoms. The definitions of AL and anastomotic stricture and related methods of diagnosis of each study are presented in Table 2.

All 17 studies reported AL rates. The pooled analysis revealed a 102% higher incidence of AL after hand-sewn anastomosis compared with stapled anastomosis (OR, 2.02; 95% CI, 1.48-2.75). Figure 2 shows the associated forest plot. Statistical heterogeneity of the studies was moderate (*I*2, 42%; $P = .08$). Funnel plot showed symmetry visually and statistically (Egger test, 0.87). The funnel plot is displayed in Figure 3, *A*.

Anastomotic stricture rates were reported by all but 1 study. Hand-sewn anastomosis group had a 31% increased incidence of anastomotic stricture; however, the statistical significance was borderline significant (OR, 1.31; 95% CI, 1.00-1.7). The forest plot is presented in Figure 4. Statistical heterogeneity was substantial (*I*2, 58%; $P = .006$). Visual and statistical symmetry was confirmed by funnel plot (Egger test, 0.20). The funnel plot is presented in Figure 3, *B*.

Thirty-day mortality was reported only by 9 (52.9%) studies. Thirty-day mortality did not show statistical difference favoring 1 anastomosis technique over another (OR, 0.68; 95% CI, 0.45-1.04). Figure 5 displays the related forest plot. Statistical heterogeneity of these studies was not important (*I*2, 22%; $P = .35$). Funnel plot was symmetrical visually and by statistical analysis (Egger test, 0.39). Figure 3, *C*, presents the funnel plot.

Sensitivity Analyses

Figure 6 shows the summary statistics of the sensitivity analyses. Without single-group studies, the leak rate and stricture rate were not statistically different, but the 30-day mortality rate favored the hand-sewn anastomosis (OR, 0.52; 95% CI, 0.33-0.84). When studies predating 2000 were excluded, the results did not change from the original analysis: leak rate favored stapled anastomosis

TABLE 1. Characteristics of included randomized controlled trials

	Characteristic						N		
Study	Country	Location of the anastomosis	Surgical approaches	Group A	Group B	Group C	Group A	Group B	Group C
Ribet et al, 1992[23]	France	Both	IL* and McK†	Hand sewn, Cervical	Hand sewn, Thoracic		30	30	
Zieren et al, 1993[9]	Germany	Cervical	IL*, McK† and TH‡	1-layer hand sewn	2-layer hand sewn		54	52	
Bardini et al, 1994[10]	Italy	Cervical	TH‡	Hand sewn, continuous	Hand sewn, interrupted		21	21	
Valverde et al, 1996[24]	France	Both	IL*, McK† TH‡	Hand sewn	Stapled		74	78	
Law et al, 1997[17]	China	Thoracic	IL*	Hand sewn	Circular stapled		61	61	
Laterza et al, 1999[11]	Italy	Cervical	McK†	Hand sewn	Stapled		21	20	
Walther et al, 2003[25]	Sweden	Both	IL* and McK†	Hand sewn, Cervical	Circular stapled, Thoracic		41	42	
Hsu et al, 2004[15]	Taiwan	Cervical	McK† and TH‡	Hand sewn	Circular stapled		32	31	
Okuyama et al, 2007[26]	Japan	Both	IL* and McK†	Hand sewn, Cervical	Circular stapled, Thoracic		18	14	
Luechakiettisak et al, 2008[18]	Thailand	Thoracic	IL*	Hand sewn	Circular stapled		59	58	
Zhang et al, 2010[19]	China	Thoracic	L Thoracotomy	Hand sewn	Circular stapled		244	272	
Aly et al, 2010[20]	Australia	Thoracic	IL*	Stapled with fundoplication	Stapled without fundoplication		29	27	
Ma et al, 2010[27]	China	Both	N/A	Hand sewn	Stapled, side-to-side	Stapled, circular	52	45	47
Nederlof et al, 2011[12]	The Netherlands	Cervical	IL* & TH‡	Hand sewn, end to side	Hand sewn, end-to-end		64	64	
Liu et al, 2011[21]	China	Thoracic	N/A	Stapled with fundoplication	Stapled without fundoplication		35	35	
Saluja et al, 2012[13]	India	Cervical	McK†	Hand sewn	Side to side stapled		87	87	
Cayi et al, 2012[14]	China	Cervical	N/A	Hand sewn	Stapled		125	125	
Wang et al, 2013[22]	China	Thoracic	L Thoracotomy	Hand sewn	Circular stapled	Semi-mechanical	52	47	45
Hayata et al, 2017[16]	Japan	Cervical	Hybrid & McK†	Ciruclar stapled	Triangular linear stapled		49	51	

IL, Ivor Lewis; *McK*, McKeown; *TH*, transhiatal; *N/A*, not available. *Ivor Lewis esophagectomy. †McKeown esophagectomy. ‡Transhiatal esophagectomy

(OR, 2.37; 95% CI, 1.63-3.43), no difference in stricture rate or mortality.

When analyzing thoracic anastomoses only, including 4 studies, neither AL rate (OR, 1.74; 95% CI, 0.95-3.17), anastomotic stricture rate (OR, 0.73; 95% CI, 0.42-1.28) nor 30-day OS rate (OR, 0.48; 95% CI, 0.15-1.57) differed between anastomotic techniques.[17-19,22] Figure E1 shows the associated forest plot.

In cervical position, analysis of 8 studies showed that hand-sewn anastomosis was associated with higher rate of AL (OR, 2.02; 95% CI, 1.33-3.05) and stricture (OR, 1.77; 95% CI, 1.15-2.72), but no difference in 30-day OS

TABLE 2. Identification and definition of anastomotic leak and anastomotic stricture in the included studies

Study	Anastomotic leak diagnosis	Routine postoperative anastomotic assessment	Stricture diagnosis	Last follow-up
Ribet et al, 1992[23]	Any radiographic evidence	7th day postoperative swallow study*	N/A	N/A
Zieren et al, 1993[9]	Any radiographic evidence	7th day postoperative swallow study	• Any form of anastomotic narrowing requiring endoscopic dilatation or operative revision • Inability to proceed into the gastric tube with a 9 mm endoscope	N/A (mean follow-up of 44 wk)
Bardini et al, 1994[10]	Any radiographic evidence	10th day postoperative swallow study	• Radiographic anastomotic diameter <1 cm • Any dysphagia	3 mo
Valverde et al, 1996[24]	• Drain output of intestinal fluids or orally ingested methylene blue • Any radiographic evidence • Repeat operation or autopsy	3-8 postoperative swallow study and methylene blue	• Any form of anastomotic narrowing requiring endoscopic dilatation or operative revision	3 mo
Law et al, 1997[17]	• Any radiographic evidence • Any endoscopic evidence	7th day postoperative swallow study and endoscopy	• Inability to proceed into the gastric tube with a 10 mm endoscope	1 y
Laterza et al, 1999[11]	• Drain output of intestinal fluids or orally ingested methylene blue • Any radiographic evidence	postoperative day 9-10 swallow study and methylene blue	• Any form of anastomotic narrowing requiring endoscopic dilatation or operative revision	At least 6 mo
Walther et al, 2003[25]	• Drain output of intestinal fluids • Any radiographic evidence	5th day postoperative swallow study	• Inability to proceed into the gastric tube with a 9 mm endoscope	1 y
Hsu et al, 2004[15]	• Drain output of intestinal fluids • Any radiographic evidence	7-10 d postoperative swallow study	• Inability to proceed into the gastric tube with a 10 mm endoscope	N/A (24 mo follow-up mean)
Okuyama et al, 2007[26]	Any radiographic evidence	9-10 d postoperative swallow study	• Any form of anastomotic narrowing requiring endoscopic dilatation or operative revision	6 mo
Luechakiettisak et al, 2008[18]	Any radiographic evidence	7th day postoperative swallow study	• Inability to proceed into the gastric tube with an endoscope	3 mo
Zhang et al, 2010[19]	• Drain output of intestinal fluids • Any radiographic evidence	5-10 d postoperative swallow study	• Inability to proceed into the gastric tube with a 10 mm endoscope	1 y
Aly et al, 2010[20]	Not described	N/A	• Dysphagia was assessed using a previously validated scoring system based on a 9-item graded food scale with no dysphagia scoring 0 and a maximum score of 457 as well as a 0-10 analog scale. • Any form of anastomotic narrowing requiring endoscopic dilatation or operative revision	1 y
Ma et al, 2010[27]	N/A	N/A	• Radiographic anastomotic diameter <0.8 cm	3 mo
Nederlof et al, 2011[12]	• Drain output of intestinal fluids • Any radiographic • Any endoscopic evidence	6th postoperative day swallow study and 7th postoperative day endoscopy	• Inability to proceed into the gastric tube with a 9 mm endoscope	12 mo

(Continued)

TABLE 2. Continued

Study	Anastomotic leak diagnosis	Routine postoperative anastomotic assessment	Stricture diagnosis	Last follow-up
Liu et al, 2011[21]	N/A	N/A	N/A	N/A
Saluja et al, 2012[13]	• Drain output of intestinal fluids • Any radiographic evidence	7th postoperative day swallow study	Not described	3 y
Cayi et al, 2012[14]	N/A	N/A	N/A	N/A
Wang et al, 2013[22]	N/A	N/A	• Radiographic anastomotic diameter <0.8 cm	3 mo after surgery
Hayata et al, 2017[16]	• Drain output of intestinal fluids • Any radiographic evidence • Any endoscopic evidence	7th postoperative day swallow study, endoscopy and CT	• Inability to proceed into the gastric tube with a 9 mm endoscope	12 mo

N/A, Not available; *CT*, computed tomography. *Swallow esophagogram with either water-soluble or barium contrast.

(OR, 0.95; 95% CI, 0.51-177).[9-16] The full forest plot of these studies can be appreciated in Figure E2.

DISCUSSION

This systematic review and meta-analysis of 17 randomized controlled trials (RCTs) with 2230 patients shows that hand-sewn anastomosis is associated with a higher rate of AL and anastomotic stricture, but no difference in 30-day mortality as illustrated in Figure 7 and summarized in Figure 8 and Video 1.

The strengths of this study are inclusion of only RCTs and the associated extensive literature search, resulting in

Study	Leakage (handsewn)	Leakage (stapled)	OR	95% CI
Ribet et al. 1992	11 / 60	NA / 0		
Zieren et al.	20 / 107	NA / 0		
Bardini et al. 1994	1 / 42	NA / 0		
Valverde et al. 1996	12 / 74	12 / 78	1.06	0.45 - 2.55
Law et al. 1997	1 / 61	3 / 61	0.32	0.03 - 3.19
Laterza et al. 1999	1 / 21	4 / 20	0.2	0.02 - 1.97
Walther et al. 2003	1 / 41	0 / 42		
Hsu et al. 2004	7 / 32	8 / 31	0.8	0.25 - 2.57
Okuyama et al. 2007	3 / 18	1 / 14	2.6	0.24 - 28.15
Luechakiettisak et al. 2008	4 / 59	2 / 58	2.04	0.36 - 11.57
Zhang et al. 2010	1 / 244	6 / 272	0.18	0.02 - 1.53
Ma et al. 2010	3 / 52	1 / 92	5.57	0.56 - 55
Nederlof et al. 2011	40 / 128	NA / 0		
Saluja et al. 2012	14 / 87	16 / 87	0.85	0.39 - 1.87
Cayi et al. 2012	18 / 125	3 / 125	6.84	1.96 - 23.87
Wang et al. 2013	3 / 52	1 / 47	2.82	0.28 - 28.05
Hayata et al. 2017	NA / 0	6 / 100		
Summary			**2.02**	**1.48 - 2.75**

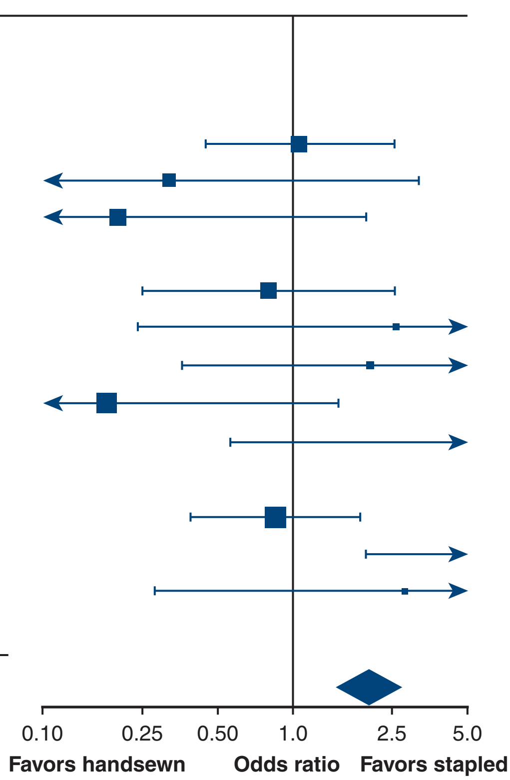


FIGURE 2. Forest plot for anastomotic leak comparing hand-sewn anastomosis to stapled anastomosis. *OR*, Odds ratio; *CI*, confidence interval; *NA*, not available.

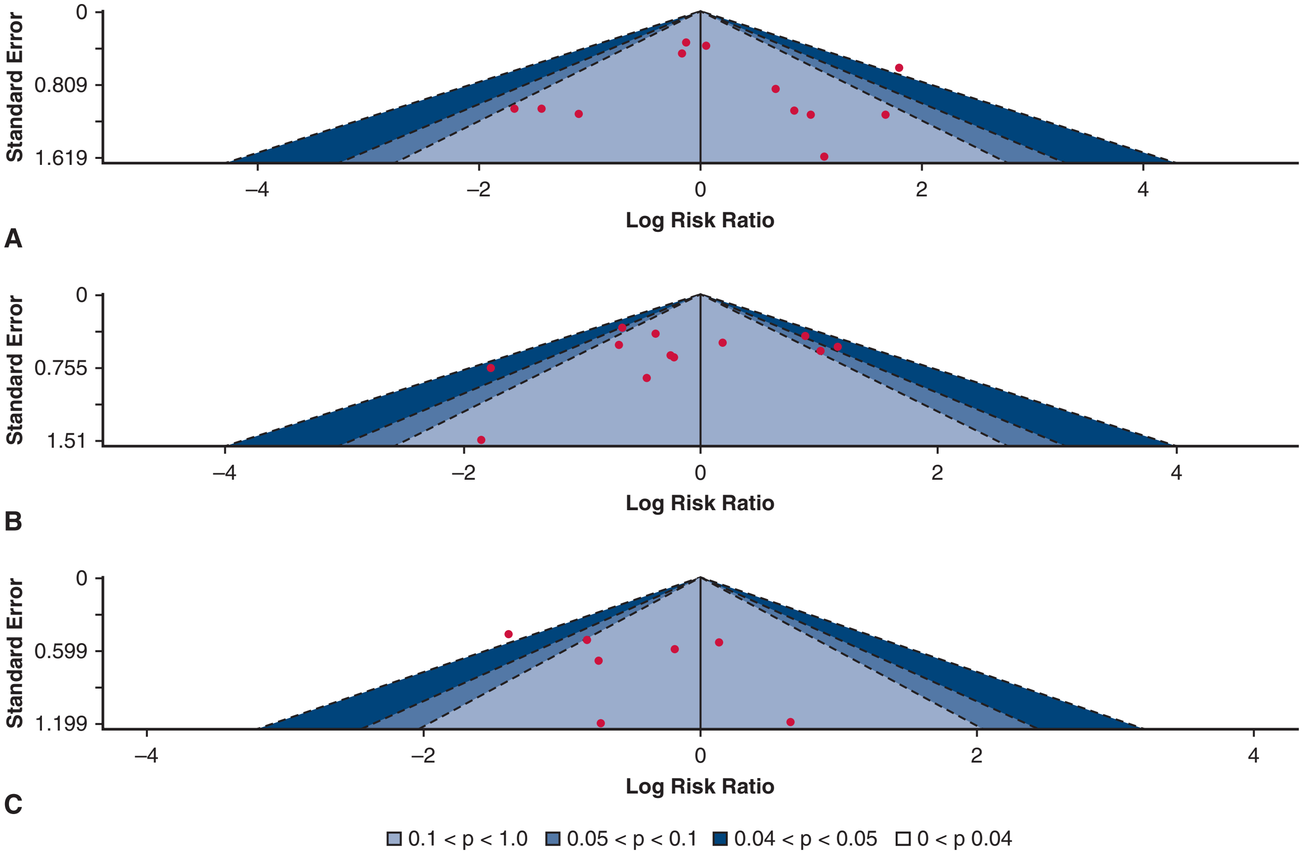


FIGURE 3. Funnel plots for (A) anastomotic leak, (B) anastomotic stricture, and (C) 30-day mortality.

a large number of applicants and minimal confounding by patient-related prognostic factors. Limitations include the heterogeneity of reported outcomes in the RCTs, especially in regard to mortality, which was either not reported, reported as in-hospital mortality, or 30-day mortality. To facilitate comparisons among groups, 30-day all-cause mortality was used. The studies included were performed over a 25-year time span, which introduces more heterogeneity in the form of different neoadjuvant, perioperative oncologic therapies and overall postoperative treatment protocols. The difference of patient populations and disease characteristics between Asian and Western studies is a probable source of bias. Studies that used either only hand-sewn or stapled anastomoses were included in the meta-analysis, which might exaggerate different reporting criteria between the studies. Different surgical methods were employed (eg, single-layer or 2-layer anastomosis, circular [end-to-end anastomosis] or side-stapled anastomosis), and the effects of these variations in methods are hard to quantify. Moreover, the superiority between these specific techniques cannot be established from this study and should be further investigated in future studies/reports.

Studies included in this trial had mostly a moderate risk of bias, as shown with Cochrane Collaborations Risk of Bias Tool analysis because with surgical clinical studies, the masking of the intervention from the subjects and the care team is difficult or even impossible. No studies tried to analyze or to account for this bias. Very limited description of the randomization process was available and use of blinded investigators in the analysis of data was rare.

The sensitivity analyses show some variance in results compared with the original meta-analysis. The inclusion of the single group-studies into the quantitative analysis favored the stapled anastomosis groups because without these groups in the analysis, intergroup differences in AL rate become nonsignificant and 30-day mortality then favors hand-sewn anastomoses. When interpreting these results, one must note that some of the included RCTs compared intrathoracic stapled anastomoses to hand-sewn cervical anastomoses.[23,25,26] Intrathoracic anastomosis requires intrathoracic entry, and because many of these studies were done before the widespread use of minimally invasive techniques, this meant performing a thoracotomy, which has been shown to negatively influence outcomes

Study	Sticture (handsewn)	Stricture (stapled)	OR	95% CI
Ribet et al. 1992	NA / 60	NA / 0		
Zieren et al.	35 / 107	NA / 0		
Bardini et al. 1994	2 / 42	NA / 0		
Valverde et al. 1996	8 / 74	7 / 78	1.23	0.42 - 3.58
Law et al. 1997	4 / 61	5 / 61	0.79	0.2 - 3.08
Laterza et al. 1999	2 / 21	3 / 20	0.6	0.09 - 4.01
Walther et al. 2003	8 / 41	12 / 42	0.61	0.22 - 1.68
Hsu et al. 2004	4 / 32	5 / 31	0.74	0.18 - 3.07
Okuyama et al. 2007	0 / 18	2 / 14		
Luechakiettisak et al. 2008	10 / 59	19 / 58	0.42	0.17 - 1
Zhang et al. 2010	2 / 244	13 / 272	0.16	0.04 - 0.74
Ma et al. 2010	9 / 52	5 / 92	3.64	1.15 - 11.53
Nederlof et al. 2011	35 / 128	NA / 0		
Saluja et al. 2012	17 / 87	7 / 87	2.78	1.09 - 7.08
Cayi et al. 2012	11 / 125	4 / 125	2.92	0.9 - 9.43
Wang et al. 2013	5 / 52	9 / 47	0.45	0.14 - 1.45
Hayata et al. 2017	NA / 0	17 / 100		
Summary			**1.31**	**1 - 1.7**

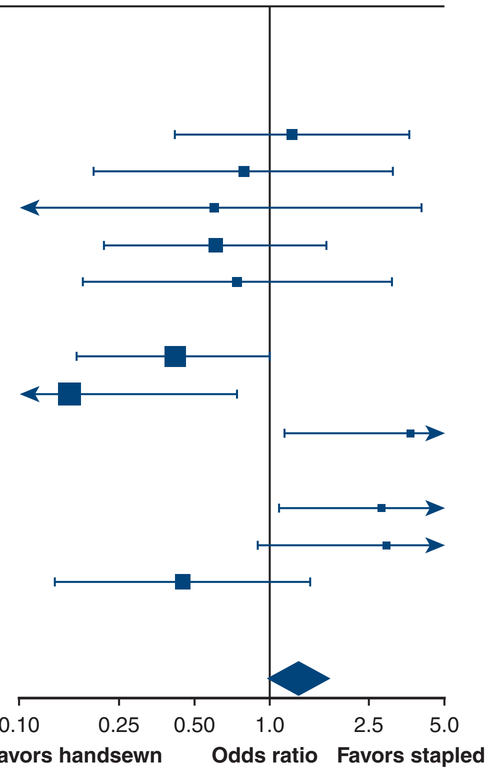


FIGURE 4. Forest plot for anastomotic stricture comparing hand-sewn anastomosis to stapled anastomosis. *OR*, Odds ratio; *CI*, confidence interval; *NA*, not available.

compared with minimally invasive techniques.[2] In fact, among the studies included, only 1 study applied minimally invasive techniques.[16] In contrast, the majority of cervical anastomosis were done via a transhiatal approach (390 transhiatal esophagectomies vs 287 McKeown esophagectomies), which spares the patient thoracotomy-related morbidity, but at the expense of thoracic lymph node yield, possibly sacrificing long-term survival.[28,29] This might bias the results of the 30-day mortality to favor the hand-sewn anastomosis group because the comparison is between operations and surgical risk with thoracotomy and transhiatal esophagectomies. When observing only thoracic anastomoses, no difference between the anastomotic techniques could be established in any of the outcomes. The results of the sensitivity analyses of thoracic-only anastomoses are subject to possible random error because only 4 studies used exclusively thoracic anastomoses. The same can be said of the OS results of cervical anastomoses because only 2 studies of this group reported 30-day mortality. Exclusion of studies conducted before the turn of the millennium did not change the summary statistics results, speaking against any significant confounding effect of studies published earlier.

The reported rates of AL between the studies varied between 1.2% and 31.3%. Definitions for AL were heterogeneous, or not elucidated in the article, which most likely explains the variability of the incidence and produces more heterogeneity to this analysis. Explanation for high degree of difference for the difference in stricture rates between the techniques when used in the thorax or in the cervical region is not known to the authors. It may be possible that circular stapling and side-to-side stapling provide different rates of stricture and/or AL, which may confound the findings of this meta-analysis. Unfortunately, due to the low amount of studies reporting the use of side-to-side stapling, such a separate analysis between the techniques is not feasible.[13,16,27]

Studies did not report whether their institutions, or the surgeons, had a preferred anastomotic technique. If there is a preferred technique that is in routine use at the institution, the alternative anastomotic technique used in the study might be subject to higher rate of complication and/or observation bias.

Although this meta-analysis includes a fair number of randomized controlled studies ($n = 19$) and patients ($n = 2308$) there is clearly need for better quality data, if

Study	Sticture (handsewn)	Stricture (stapled)	OR	95% CI
Ribet et al. 1992	9 / 60	NA / 0		
Zieren et al.	NA / 107	NA / 0		
Bardini et al. 1994	NA / 42	NA / 0		
Valverde et al. 1996	5 / 74	12 / 78	0.4	0.13 - 1.19
Law et al. 1997	5 / 61	20 / 61	0.18	0.06 - 0.53
Laterza et al. 1999	2 / 21	1 / 20	2	0.17 - 23.96
Walther et al. 2003	NA / 41	NA / 42		
Hsu et al. 2004	1 / 32	2 / 31	0.47	0.04 - 5.44
Okuyama et al. 2007	NA / 18	NA / 14		
Luechakiettisak et al. 2008	7 / 59	6 / 58	1.17	0.37 - 3.71
Zhang et al. 2010	3 / 244	7 / 272	0.47	0.12 - 1.84
Ma et al. 2010	NA / 52	NA / 92		
Nederlof et al. 2011	4 / 128	NA / 0		
Saluja et al. 2012	5 / 87	6 / 87	0.82	0.24 - 2.8
Cayi et al. 2012	NA / 125	NA / 125		
Wang et al. 2013	NA / 52	NA / 47		
Hayata et al. 2017	NA / 0	0 / 100		
Summary			**0.68**	**0.45 - 1.04**

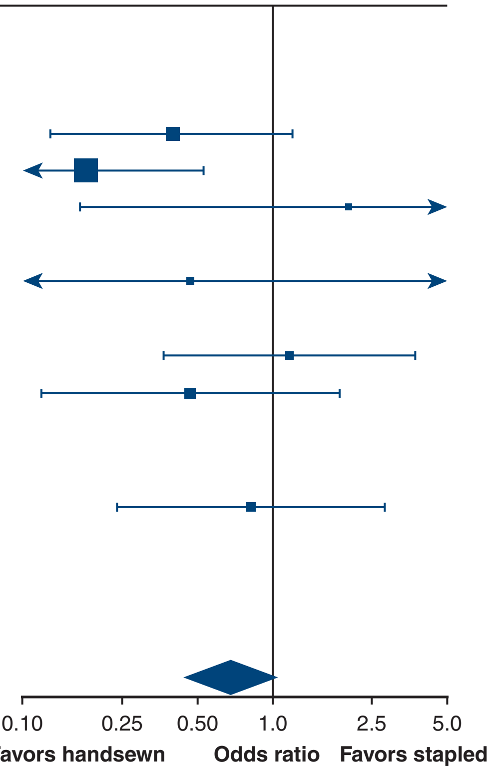


FIGURE 5. Forest plot for 30-day mortality comparing hand-sewn anastomosis to stapled anastomosis. *OR*, Odds ratio; *CI*, confidence interval; *NA*, not available.

		OR	95% CI
All studies	Leakage	2.02	1.48 - 2.75
Without single-group studies		1.89	1.33 - 2.68
Only thoracic anastomoses		1.74	0.95 - 3.17
Only cervical anastomoses		2.02	1.35 - 3.02
Studies after 2000		2.37	1.63 - 3.43
All studies	Stricture	1.31	1 - 1.7
Without single-group studies		1.1	0.81 - 1.49
Only thoracic anastomoses		0.73	0.42 - 1.28
Only cervical anastomoses		2.21	1.47 - 3.31
Studies after 2000		1.14	0.85 - 1.54
All studies	Mortality	0.68	0.45 - 1.04
Without single-group studies		0.58	0.37 - 0.91
Only thoracic anastomoses		0.48	0.15 - 1.58
Only cervical anastomoses		1.19	0.49 - 2.88
Studies after 2000		0.95	0.51 - 1.77

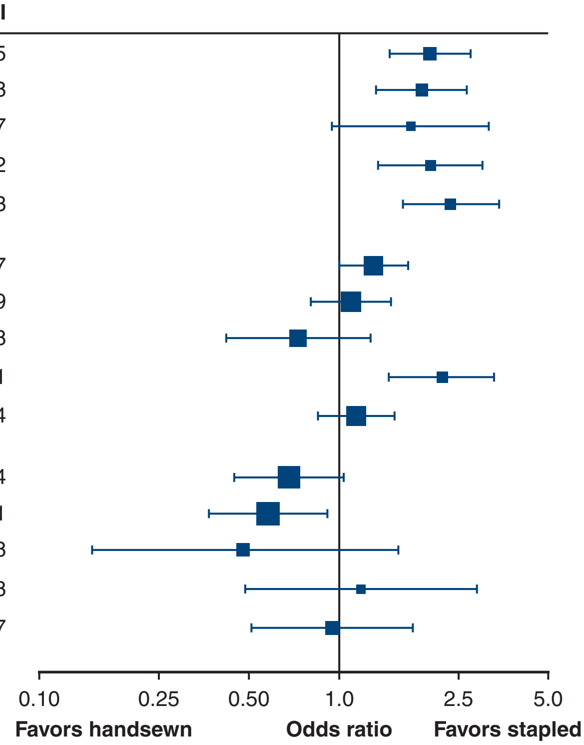


FIGURE 6. Sensitivity analyses of the anastomotic leak, anastomotic stricture, and 30-day mortality analyses. Sensitivity analyses included were analyses without single-group studies, thoracic anastomoses only, and cervical anastomoses only. *OR*, Odds ratio; *CI*, confidence interval.

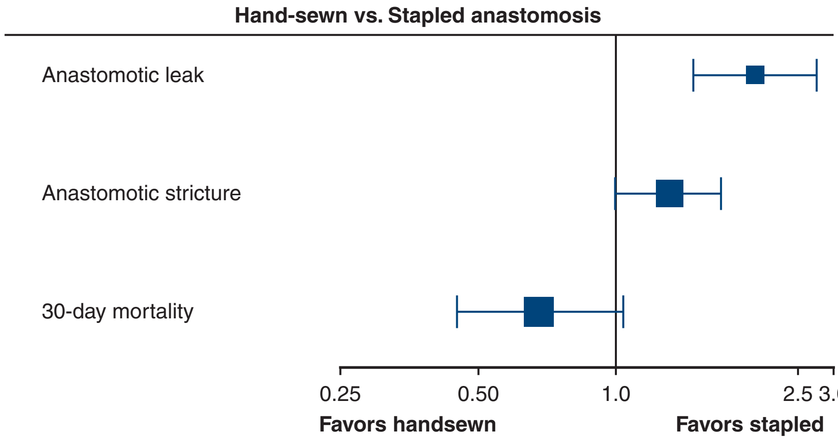


FIGURE 7. Forest plot showing the summary results for anastomotic leak, anastomotic stricture, and 30-day mortality.

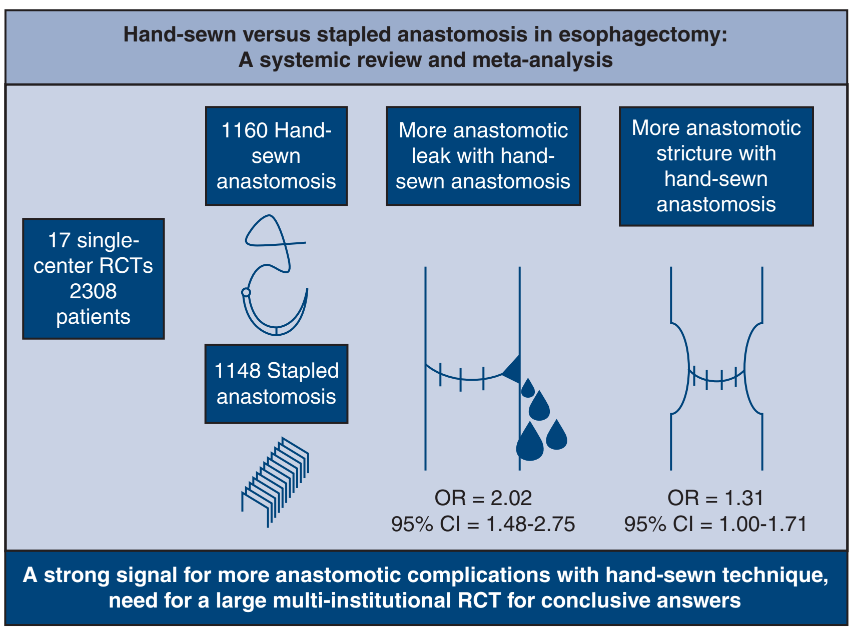
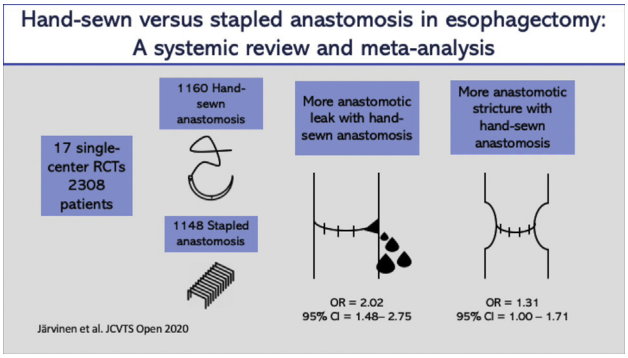


FIGURE 8. Graphical abstract summarizing the results of the study. From the left to right, Amount of randomized controlled trials (RCTs) and patients involved, number of patients in hand-sewn and stapled anastomosis groups, comparison of groups in anastomotic leak rates, and comparison of groups in anastomotic stricture rates. *OR*, Odds ratio; *CI*, confidence interval.

a definitive answer to the superiority of an anastomotic technique is to be proven. A large-scale multi-institutional RCT with clearly characterized and clinically meaningful outcomes could provide us with an answer, but for now the data can be interpreted in a multitude of ways. It could also be the case that the difference between the techniques is so subtle that a massive number of patients would be needed to ferret out a statistical difference between the anastomotic technique, in which case the difference would probably not be clinically significant.

CONCLUSIONS

This meta-analysis shows that RCTs of esophageal anastomotic techniques are heterogeneous with a risk of bias, and paucity of data in the minimally invasive setting. Our main finding is that there seems to be a signal favoring stapled anastomoses; however, these results show some discrepancy when subjected to sensitivity analyses and thus, no real recommendation of a preferred anastomotic technique can be made. We hope that this meta-analysis underscores the need for modern, well-performed RCTs. In



VIDEO 1. The corresponding author, Tommi Järvinen, summarizes the results of the meta-analysis. Video available at: https://www.jtcvs.org/article/S2666-2736(21)00207-2/fulltext.

the end, the authors all agree that the most important factor in anastomotic technique is a well-vascularized anastomosis constructed without tension rather than a specific anastomotic technique.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: esophagectomy, anastomosis, meta-analysis, systematic review, esophageal surgery

Study	Leakage (handsewn)	Leakage (stapled)	OR	95% CI
Hsu et al. 2004	7 / 32	8 / 31	0.8	0.25 - 2.57
Zhang et al. 2010	1 / 244	6 / 272	0.18	0.02 - 1.53
Cayi et al. 2012	18 / 125	3 / 125	6.84	1.96 - 23.87
Wang et al. 2013	3 / 52	1 / 47	2.82	0.28 - 28.05
Summary			**1.74**	**0.95 - 3.17**

Study	Stricture (handsewn)	Stricture (stapled)	OR	95% CI
Hsu et al. 2004	4 / 32	5 / 31	0.74	0.18 - 3.07
Zhang et al. 2010	2 / 244	13 / 272	0.16	0.04 - 0.74
Cayi et al. 2012	11 / 125	4 / 125	2.92	0.9 - 9.43
Wang et al. 2013	5 / 52	9 / 47	0.45	0.14 - 1.45
Summary			**0.73**	**0.42 - 1.28**

Study	30-d mortality (handsewn)	30-d mortality (stapled)	OR	95% CI
Hsu et al. 2004	1 / 32	2 / 31	0.47	0.04 - 5.44
Zhang et al. 2010	3 / 244	7 / 272	0.47	0.12 - 1.84
Cayi et al. 2012	NA / 125	NA / 125		NA - NA
Wang et al. 2013	NA / 52	NA / 47		NA - NA
Summary			**0.48**	**0.15 - 1.58**

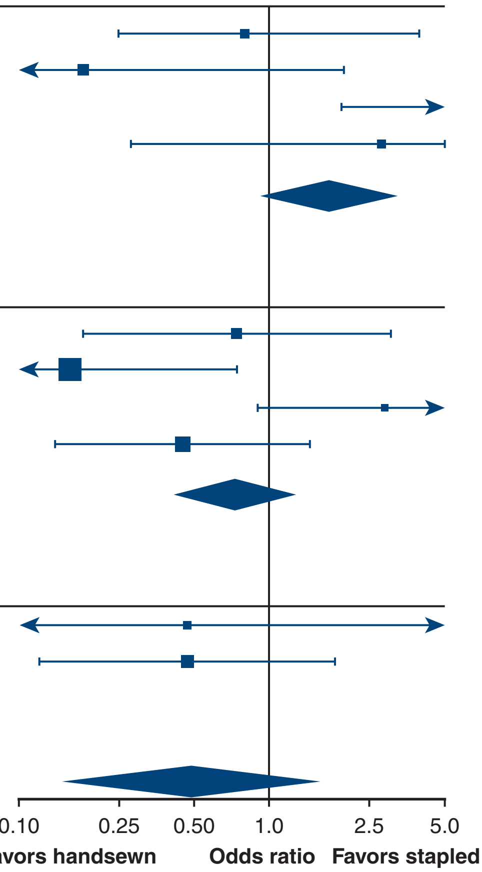

FIGURE E1. Forest plots of thoracic anastomosis-only studies. *OR*, Odds ratio; *CI*, confidence interval; *NA*, not available.

Study	Leakage (handsewn)	Leakage (stapled)	OR	95% CI
Zieren et al.	20 / 107	NA / 0		NA - NA
Bardini et al. 1994	1 / 42	NA / 0		NA - NA
Laterza et al. 1999	1 / 21	4 / 20	0.2	0.02 - 1.97
Hsu et al. 2004	7 / 32	8 / 31	0.8	0.25 - 2.57
Nederlof et al. 2011	40 / 128	NA / 0		NA - NA
Saluja et al. 2012	14 / 87	16 / 87	0.85	0.39 - 1.87
Cayi et al. 2012	18 / 125	3 / 125	6.84	1.96 - 23.87
Hayata et al. 2017	NA / 0	6 / 100		NA - NA
Summary			**2.02**	**1.35 - 3.02**

Study	Stricture (handsewn)	Stricture (stapled)	OR	95% CI
Zieren et al.	35 / 107	NA / 0		NA - NA
Bardini et al. 1994	2 / 42	NA / 0		NA - NA
Laterza et al. 1999	2 / 21	3 / 20	0.6	0.09 - 4.01
Hsu et al. 2004	4 / 32	5 / 31	0.74	0.18 - 3.07
Nederlof et al. 2011	35 / 128	NA / 0		NA - NA
Saluja et al. 2012	17 / 87	7 / 87	2.78	1.09 - 7.08
Cayi et al. 2012	11 / 125	4 / 125	2.92	0.9 - 9.43
Hayata et al. 2017	NA / 0	17 / 100		NA - NA
Summary			**2.21**	**1.47 - 3.31**

Study	30-d mortality (handsewn)	30-d mortality (stapled)	OR	95% CI
Zieren et al.	NA / 107	NA / 0		NA - NA
Bardini et al. 1994	NA / 42	NA / 0		NA - NA
Laterza et al. 1999	2 / 21	1 / 20	2	0.17 - 23.96
Hsu et al. 2004	1 / 32	2 / 31	0.47	0.04 - 5.44
Nederlof et al. 2011	4 / 128	NA / 0		NA - NA
Saluja et al. 2012	5 / 87	6 / 87	0.82	0.24 - 2.8
Cayi et al. 2012	NA / 125	NA / 125		NA - NA
Hayata et al. 2017	NA / 0	0 / 100		NA - NA
Summary			**1.19**	**0.49 - 2.88**

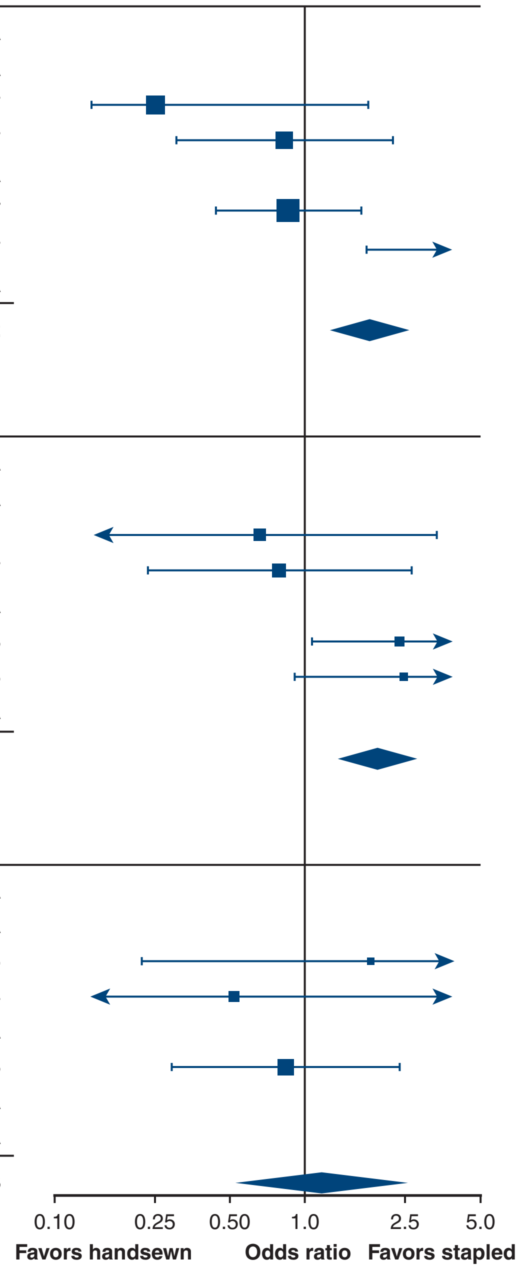

FIGURE E2. Forest plots of cervical anastomosis-only studies. *OR*, Odds ratio; *CI*, confidence interval; *NA*, not available.

TABLE E1. Electronic search strategies

Medline	Scopus
1. exp Esophageal neoplasms/	1. TITLE-ABS-KEY (esoph*)
2. ((esophag* or oesophag*) adj3 (cancer* or neoplas* or carcin* or adenocarcin* or tumour* or tumor* or malig*)).ti,ab,kf.	2. TITLE-ABS-KEY(cancer OR carc* OR malig* OR neoplas*)
3. or/1-2	3. 1 and 2
4. exp Anastomosis, surgical/	4. TITLE-ABS-KEY (anastomo*)
5. (anastomo*).ti,ab,kf	5. 3 and 4
6. or/4-5	6. TITLE-ABS-KEY ((clinic* W/1 trial*) OR (randomi* W/1 control*) OR (randomi* W/2 trial*) OR (random* W/1 assign*) OR (random* W/1 allocat*) OR (control* W/1 clinic*) OR (control* W/1 trial) OR placebo* OR (quantitat* W/1 stud*) OR (control* W/1 stud*) OR (randomi* W/1 stud*) OR (singl* W/1 blind*) OR (singl* W/1 mask*) OR (doubl* W/1 blind*) OR (doubl* W/1 mask*) OR (tripl* W/1 blind*) OR (tripl* W/1 mask*) OR (trebl* W/1 blind*) OR (trebl* W/1 mask*)) AND NOT (SRCTYPE (b) OR SRCTYPE (k) OR SRCTYPE (p) OR SRCTYPE (r) OR SRCTYPE (d) OR DOCTYPE (ab) OR DOCTYPE (bk) OR DOCTYPE (ch) OR DOCTYPE (bz) OR DOCTYPE (cr) OR DOCTYPE (ed) OR DOCTYPE (er) OR DOCTYPE (le) OR DOCTYPE (no) OR DOCTYPE (pr) OR DOCTYPE (rp) OR DOCTYPE (re) OR DOCTYPE (sh))
7. 3 and 6	7. 5 and 6
OvidSp	**CENTRAL**
1. exp Esophageal neoplasms/	1. ((esophag* or oesophag* or gastroesophag* or gastrooesophag*) near/3 (cancer* or neoplas* or carcin* or adenocarcin* or tumour* or tumor* or malig*)):ab,ti,kw
2. ((esophag* or oesophag*) adj3 (cancer* or neoplas* or carcin* or adenocarcin* or tumour* or tumor* or malig*)).ti,ab,kf.	2. (anastom*):ab,ti,kw
3. or/1-2	3. #1 and #2
4. exp Anastomosis, surgical/	
5. (anastomo*).ti,ab,kf	
6. or/4-5	
7. 3 and 6	

TABLE E2. Risk of bias using Cochrane Collaborations Risk of Bias Tool

Study ID	Author and year	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
1	Hsu et al, 2004[15]	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
2	Law et al, 1997[17]	Some concerns	Some concerns	Low	Low	Low	Some concerns
3	Okuyama et al, 2007[26]	Some concerns	High	Low	Low	Low	High
4	Luechakiettisak et al, 2008[18]	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
5	Wang et al, 2013[22]	High	Some concerns	Low	Low	Low	High
6	Zhang et al, 2010[19]	Some concerns	Some concerns	Low	Low	Low	Some concerns
7	Zieren et al, 1993[9]	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
9	Saluja et al, 2012[13]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
10	Walther et al, 2003[25]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
11	Nederlof et al, 2011[12]	Low	Some concerns	Low	Low	Low	Low
12	Ma et al, 2010[27]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
13	Ribet et al, 1992[23]	High	High	Low	Some concerns	Some concerns	High
14	Valverde et al, 1996[24]	Low	Some concerns	Low	Low	Some concerns	Some concerns
17	Bardini et al, 1994[10]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
18	Laterza et al, 1999[11]	Low	Some concerns	Low	Low	Some concerns	Some concerns
20	Hayata et al, 2017[16]	Low	Some concerns	Low	Low	Low	Low
21	Cayi et al, 2012[14]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns