Interventions to prevent anastomotic leak after esophageal surgery: A systematic review and meta-analysis

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Abstract

Background: Anastomotic leakage (AL) is a common and serious complication following esophagectomy. We aimed to provide an up-to-date review and critical appraisal of interventions designed to reduce AL risk.

Methods: We searched MEDLINE and Embase from 1946 to January 2019 for randomized controlled trials (RCTs) evaluating interventions to minimize esophagogastric AL. Pooled risk ratios (RR) for AL was performed using random effects.

Results: Two reviewers screened 441 abstracts and identified 17 RCTs eligible for inclusion; 11 studies were meta-analyzed. Omentoplasty reduced the risk of AL significantly by 78% [RR: 0.22; 95% CI: 0.10, 0.50] compared to no omentoplasty (3 studies, n = 611 patients). Early removal of NG tube reduced AL risk significantly by 62% [RR: 0.38; 95% CI: 0.02, 0.65] compared to prolonged NG tube (2 studies, n = 293 patients); Stapled (vs. hand-sewn) anastomosis did not significantly reduce AL risk [RR: 0.92; 95% CI: 0.45, 1.87] compared to hand-sewn (6 studies, n = 1,454 patients). The quality of evidence was high for omentoplasty (vs. no omentoplasty), moderate for early removal of NG tube (vs. conventional removal), and very low for stapled anastomosis (vs. hand-sewn).

Conclusions: This is the first meta-analysis to summarize the graded quality of evidence for all RCT interventions designed to reduce AL following esophagectomy. Our findings demonstrated that omentoplasty reduced the risk of AL with a high quality of evidence. Although early nasogastric tube removal reduced AL risk, there is a need for further research to strengthen the quality of evidence. Evidence profiles presented in our review may help inform the development of clinical practice recommendations.

Systematic review registration: CRD42019127181

Background

Esophagectomy is a critical component of curative treatment for esophageal cancer. This procedure carries a significant risk for certain adverse events among patients undergoing esophagectomy. One of the most serious adverse events associated with esophagectomy is an anastomotic leak, which involves the leak of gastric fluid outside of the anastomosis postoperatively [1]. The presence of anastomotic leakage, with the rates being shown to occur up to 50% in some studies, is a potentially serious adverse event for patients and it has previously been significantly associated with prolonged length of stay, the formation of strictures, and increased morbidity and mortality [2,3].

There have been several interventions conducted previously that aimed to prevent AL, ranging from surgical interventions to more conservative measures. Omentoplasty is a standardized surgical technique that harnesses a pedicle flap from the omentum (a layer of abdominal fat that is attached to the greater curvature of the stomach) to cover or wrap around the anastomosis site. The omental flap, secured in place with hand-sewn sutures, is well perfused by vascularity from the preserved left gastro-epiploic artery [4, 5, 6]. Thus, the good vascularity the omental flap provides to the surgical site, including oxygen and nutrient-rich blood, is thought to enhance wound healing [7]. Omentoplasty after an esophagectomy has demonstrated promising findings in previous RCTs to prevent AL postoperatively, which has been summarized in a meta-analysis conducted six years ago by Chen et al. in 2014 and Yuan et al 2019 [8, 9]. Another intervention investigated previously in the literature includes the early removal of the nasogastric (NG) tube after surgery. The strain on the wall of the esophagus when the anastomotic site is dilated is thought to lead to poor vascular perfusion of the surgical site, which may increase the risk for anastomotic leakage; NG decompression, which reduces dilation of the tissue, may reduce the risk for an anastomotic leak [11]. Weijs et al. in 2017 meta-analyzed previous controlled trials and reported that the early removal of NG tubes did not significantly alter the rates of AL compared to standard NG tube use after esophagectomy [12]. Other studies have explored the potential for administering different anastomotic surgical techniques to prevent of AL [11]. A meta-analysis by Beitler et al. compared the rates of AL according to the use of hand-sewn vs. stapled anastomoses but found no difference among groups that used hand-sewn vs. stapled anastomoses [10]. An up-to-date summary of the literature is warranted to consider more recently published literature.

There is a need for an up-to-date review comparing the efficacy of all previous interventions designed to prevent AL after esophagectomy. A systematic approach to grading the quality, which can be accomplished using frameworks such as GRADE (Grading of Recommendations, Assessment, Development, and Evaluations), is essential to guide clinical practice recommendations.
Therefore, the present meta-analysis aims to provide a comprehensive and up-to-date summary of all previous interventional randomized controlled trials that aimed to reduce esophagogastric anastomotic leakage rates after esophagectomy and conduct a systematic grading of quality among interventions meta-analyzed.

**Methods**

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA checklist) [37]. The protocol is available in the International Prospective Register of Systematic Reviews (CRD42019127181).

**Search strategy**

MEDLINE (OVID interface, including In-process and Epub Ahead of Print) and Embase (OVID interface) databases were searched from 1946 to February 2019 (Supplemental 1). The literature search results were uploaded and reviewed using Covidence Software (Covidence, Melbourne, Australia).

**Selection criteria**

Search results and full-text articles meeting full eligibility criteria were reviewed independently and in duplicate. Potentially relevant studies were screened by title and abstract (stage 1) followed by full-text article screening to assess full eligibility (stage 2). Two review authors assessed the eligibility of full reports. Any disagreement was resolved through discussion with a third reviewer. The reasons for excluding studies were recorded. RCTs that evaluated any intervention to minimize AL following esophagectomy were included with no restriction on language. Only studies that reported our primary outcome, AL, were included. Properly conducted RCTs are the gold standard for evaluating the effectiveness of an intervention [13]. Thus, only RCT articles were included and other articles, including review articles, editorials, preclinical studies, observational studies, and abstracts, were excluded.

**Outcome justification and prioritization**

Our primary outcome of interest was an anastomotic leak, required to be recorded for both interventional and control groups. AL was defined as the presence of extraluminal collections of air or contrast, excess bile-stained fluid on drainage, or a combination of these [13]. Secondary outcomes of interest were anastomotic stricture, mortality, and length of stay in hospital postoperatively.

**Data extraction**

Patient characteristics and demographic information, methodology, intervention details, outcomes of interest, and risk of bias were recorded. Two reviewers performed all data extraction. The study and patient characteristics for included studies were recorded. This included the first author name, year of publication, study country of origin, number of patients investigated (intervention and control groups), and the indication for esophagectomy (e.g. esophageal cancer). The methods used for interventions to prevent AL were recorded (e.g. omentoplasty, stapled vs. hand-sewn anastomosis, early NG tube removal). Details recorded included the use of neoadjuvant therapy (e.g. radiation and chemotherapy), medical management (e.g. antibiotics), endoscopic management (e.g. nasogastric tube use), or surgical management (e.g. re-operation), the modality used to diagnosis AL, and the surgical approach for esophagogastric anastomosis (e.g. cervical or thoracic anastomosis). Disagreements were resolved through discussion with a third-party member.

**Summary measures and synthesis of results**

DerSimonian and Laird's random-effects method was used to pool relative risk effect estimates with corresponding 95% CIs for dichotomous variables. Continuous measures were reported for individual studies as a mean with standard deviation (± SD) or a median with interquartile range (IQR) or the overall range from minimum to maximum. The pooled mean difference between the length of stay in the intervention and control groups was determined using a DerSimonian and Laird's random-continuous effects method [15]. Studies that reported median with IQR were excluded from the pooled mean difference estimation for the length of stay. The heterogeneity of effect sizes for pooled estimates was assessed using the Cochrane $I^2$ statistic. The following thresholds were used to describe the $I^2$ threshold: 0 – 40% (low heterogeneity), 30 – 60% (moderate heterogeneity), 50 – 90% (substantial heterogeneity).
heterogeneity) and 75 – 100% (considerable heterogeneity) [15]. Open Meta-Analyst was used to generate forest plots, heterogeneity, and effect estimates for risk ratios and mean differences (Open-source, USA).

Pooled effect estimates are stratified according to intervention type. A risk ratio of greater than one demonstrated a higher risk of AL, stricture, or mortality. A risk ratio of less than one demonstrated a lower risk of AL, stricture, or mortality. A mean difference in length of stay less than zero represented a shorter length of stay in the intervention group compared to the control group. A mean difference in length of stay greater than zero represented a longer length of stay in the intervention group compared to the control group. Subgroup analysis of AL was performed according to the type of disease (e.g. esophageal cancer), age (≤ or > 18 years old), type of surgery (cervical vs. thoracic anastomosis), and use of induction or neoadjuvant therapy.

Risk of Bias

The Cochrane revised risk of bias tool for randomized trials was used to evaluate the individual risk of bias for studies reviewed [17]. Within each risk of bias domain, a series of questions ('signaling questions') were chosen to elicit information about features of the trial that were felt to be relevant to the risk of bias. Publication bias was included in the assessment. Judgement is classified as 'low', 'high', or as having 'some concerns' [17]. Meta-bias (risk of bias across studies) was summarized by pooling the individual study risk of bias for each risk of bias domain.

Grading of Recommendations, Assessment, Development, and Evaluations

The quality of the treatment effects was graded by using a systematic and comprehensive approach known as GRADE [17]. GRADE provides a reproducible and transparent framework for grading the quality of evidence or certainty in the evidence. The quality of evidence reflects the extent to which we are confident that an estimate of the effect is correct. High grade of evidence means the true estimate lies close to the estimate of effect; moderate grade means that the true effect is likely to be close to the estimate of the effect; low grade means that the effect estimate may substantially differ from the true estimate of the effect; very low grade means we have little confidence in the effect estimate [17].

Results

The systematic searches returned a total of 731 citations. Following deduplication, 441 citations were identified. Of the 441 citations, 73 full manuscripts were identified as potentially eligible with a total of 17 RCTs meeting our eligibility criteria (n = 3,157 patients). Eleven studies were included in our meta-analysis as shown in our PRISMA flow diagram (Figure 1).

Studies were published between 1996 and 2019, with sample sizes ranging from 32 to 516 participants. The mean age of participants was similar across studies ranging from 50.8 to 67.5 years old. Follow-up periods were highly variable ranging from 3 months to 3 years. Most studies were performed in China (5 studies, 19%), India (4 studies, 24%), Japan (3 studies, 18%), or other (5 studies [Iran, Hong Kong, Thailand, Netherlands, France], 29%). The number of male participants was higher than female participants in all studies except one. The incidence of AL ranged from 1.4 to 17%. The patient characteristics of the included studies are provided in Table 1.

Table 1. Characteristics of the Included Studies and Participants Studies
| Last author (year) | Country | Total participants (N) | Total participants in intervention groups (n) | Prevalence AL (%) | Male-to-female ratio evaluated (T, I, C) | Age, years (y) Mean ± SD | Neoadjuvant therapy | Follow-up, months (mo, wk, or y) Mean ± SD |
|-------------------|---------|------------------------|-----------------------------------------------|-------------------|------------------------------------------|-------------------------|-------------------|-------------------------------------------|
| at 20066          | India   | 194                    | 97                                            | 8.8               | T: 3:1.8                                 | T: 52.5                 | Excluded patients with previous neoadjuvant Tx | F/U every 3-mo for 3 y post-op every 4- to 6-mo post-op |
| i 20115           | China   | 253                    | 127                                           | 3.1               | T: 4:01                                  | T: 63.5                 | Excluded patients with previous neoadjuvant Tx | *22 mo (3- 52 mo) |
| ryaei 200819      | Iran    | 40                     | 18                                            | 15                | NR                                       | T: 58.4 ± 10.3          | NP                | NP |
| pta 200120        | India   | 100                    | 48                                            | 12                | I: 0.8:1 C: 0.7:1                        | I: 51.3 ± 13.0 C: 50.8 ± 13.2 | Rad ± Chemo: 22/100 and Chemo alone: 56/100 | 3 mo or more |
| yashi 201921      | Japan   | 71                     | 34                                            | 5.6               | T: 6:8                                   | T: 63.04                | NP                | NP |
| w 199722          | Hong Kong | 122                  | 61                                            | 3.3               | I: 7.7:1 C: 6.6:1                        | I: 64 ± 1.2 C: 63 ± 1.0 | NP                | 20 (SD 2.2) mo hand-sewn and 19 (2.2) mo stapled group (p= NS) |
| i 20147           | China   | 378                    | 188                                           | 4.2               | T: 3:01                                  | T: 64                   | Excluded patients with previous neoadjuvant Tx | NP |
| i 201523          | China   | 432                    | 219                                           | 5                 | I: 3:1 C: 3:1                            | I: 62 ± 8 C: 61 ± 9     | Rad + chemo: 64/478 | 17.8 (3.2) mo hand-sewn and 18.3 (3.4) mo stapled |
| echakiettisak 0824| Thailand | 104                    | 52                                            | 4.8               | I: 4.8:1 C: 5.6:1                        | I: 63.6 ± 62.0          | NP                | NP |
| stry 201225       | India   | 253                    | 127                                           | 3.1               | T: 2.1:1                                 | I: 53.4 ± 56.7          | NP                | NP |
| derlof 1126       | Netherlands | 128              | 64                                            | 31                | I: 2.1:1 C: 7:1                         | I: 60 ± 1.2 C: 63 ± 1.4 | Rad + Chemo: 27/64 and Chemo alone: 17/64 | 3- or 6-wk outpatient visit. 3 mo first y post-op. Every 4 mo second y post-op. |
| uyama 0727        | Japan   | 32                     | 14                                            | 12                | I: 13:1 C: 16:2                          | I: 63.6 ± 64.3          | Excluded patients with previous neoadjuvant Tx | 5 y |
| luja 201228       | India   | 174                    | 87                                            | 17                | I: 2.3:1 C: 1.6:1                        | I: 51.4 ± 50.9 ± 14     | Rad + Chemo: 107/174 | NP |
| ang 201029        | China   | 516                    | 272                                           | 1.4               | I: 1.4:1 C: 1.4:1                        | I: 59 ± 1.2 C: 60 ± 1.3 | Excluded patients with previous neoadjuvant Tx | 12 mo |
| First author | Country | Total participants (N) | Total participants in intervention groups (n) | Prevalence AL (%) | Male-to-female ratio evaluated (T, I, C) | Age, years (y) Mean ± SD | Neoadjuvant therapy | Follow-up, months (mo, wk, or y) Mean ± SD |
|--------------|---------|------------------------|---------------------------------------------|-------------------|----------------------------------------|--------------------------|------------------|-----------------------------------|
| eng 2013⁴    | China   | 164                    | 82                                          | 8.5               | I: 1.6:1 C: 1.4:1                       | I: 67.5 ± 11.2 C: 65.7 ± 9.4 | None of the patients received chemotherapy or radiotherapy pre-op | 3 y                 |
| bira 2004³⁰  | Japan   | 44                     | 22                                          | 14                | I: 6.3:1 C: 10:1                        | I: 64 ± 8 C: 60 ± 8        | NP               | NP                                |
| Iverde 96³¹  | France  | 152                    | 78                                          | 16                | I: 9.6:1 C: 10.1:1                      | I: 59 ± 9 C: 59 ± 10        | NP               | NP                                |

**Abbreviations:** C, control; Chemo, chemotherapy; I, intervention; mo, months; NP, not provided; pre-op, pre-operatively; post-op, post-operatively; Rad, radiation; SD, standard deviation; Tx, therapy; wk, weeks; Y, years

*Median (range)*

Seven studies (41%) investigated stapled (vs. hand sewn) anastomosis, three studies (18%) investigated omentoplasty (vs. hand-sewn or stapled) anastomosis, three studies (18%) investigated early removal (postop day 1 or 2 days) or no nasogastric tube (vs. conventional 7 to 10 days to nasogastric tube removal), two studies (12%) that investigated subtotal gastric resection (vs. slender gastric tube) reconstruction, one study (6%) investigated valvuloplasty (vs. stapled) anastomosis, and one study (6%) that compared end-to-end (vs. end-to-side) anastomosis. Sixteen studies (94%) used contrast to diagnose AL and six studies (35%) used additional endoscopy and/or chest tube or drain output. Seven studies (41%) administered medical management, three studies (18%) administered surgical management, and two studies (12%) administered endoscopic management for the treatment of AL. The length of stay in hospital postoperatively varied from 10.7 to 29.4 days. The study intervention characteristics are outlined in Table 2.

**Table 2.** Intervention Characteristics of the Included Studies
| First author (year) | Intervention and control groups | Surgical approach to intervention | Length of Stay, days | Diagnostic modality for anastomosis | Medical management | Endoscopic management | Surgical management |
|---------------------|---------------------------------|----------------------------------|---------------------|-------------------------------------|-------------------|----------------------|---------------------|
| at 20066            | Omentoplasty (I) vs hand-sewn anastomosis alone (C) | Cervical: 102 Thoracic: 92 | NP | Water-soluble contrast | Abx, bronchodilators, chest physiotherapy | Re-insertion NG tube | Re-exploration, refashioning anastomosis |
| i 20115             | Omentoplasty (I) vs stapled anastomosis alone (C) | Cervical: 75 Thoracic: 180 | I: 20.4 (11.5)** C: 23.1 (15.2)** | Contrast | NP | NP | NP |
| ryaei 200819        | NG tube (I) vs Metoclopramide (C) | Cervical: 20 Thoracic: 20 | I: 10.9 (3.5)** C: 13.9 (8.2)** | Gastrografin contrast | Metoclopramide (C) | NP | NP |
| pta 2001V20         | Subtotal (I) vs slender anastomosis (C) | Cervical only | I: 10.7 (3.6)** C: 11.9 (5.6)** | Water-soluble contrast | Not reported | NP | NP |
| yashi 19V21         | No or early NG tube removal (I) vs prolonged NG tube (C) | Thoracic only | I: 25.7 (12.76)** C: 29.4 (18.06)** | Contrast agent | All patients received PPI, ICU admission post-op | Re-insertion of NG tube | Tracheostomy, mini-tracheostomy |
| w 199722            | Stapler (I) vs hand sewn anastomosis (C) | Thoracic only | NP | Gastrografin contrast, endoscopy | NP | NP | NP |
| t 20147             | Valvuloplasty (I) vs stapled anastomosis alone (C) | Cervical: 126 Thoracic: 259 | I: 20.4 (11.5)** C: 22.1 (15.2)** | Contrast, endoscopy | NP | NP | NP |
| t 201523            | Stapler (I) vs hand sewn anastomosis (C) | Cervical: 113 Thoracic: 354 | I: 20.1 (6.8)** C: 18.9 (7.3)** | Barium swallow, endoscopy | Nutrition, chest tube drain | NP | NP |
| eckakiettisak 0824  | Stapler (I) vs hand sewn anastomosis (C) | Thoracic only | NP | Gastrografin contrast | NP | NP | NP |
| stry 201225         | Short-term (I) vs prolonged NG tube (C) | Cervical: 33 Thoracic: 117 | I: 12 (9 - 17)* C: 12 (10 - 17)* | Contrast | NP | NP | NP |
| derlof 11V26        | End-to-end (I) vs side-to-end (C) anastomosis | Cervical: 88 Thoracic: 40 | I: 15 (9 - 125)* C: 22 (8 - 281)* | Contrast, endoscopy, neck wound saliva | NP | NP | Re-operation |
| uyama 0727          | Stapler (I) vs hand sewn anastomosis (C) | Cervical: 18 Thoracic: 14 | NP | Water-soluble contrast | Conservative | NP | NP |
| ujja 201228         | Stapler (I) vs hand sewn anastomosis (C) | Cervical only | I: 12.8 (8)** C: 11.9 (6)** | Gastrografin contrast | Abx, opening neck wound | NP | NP |
| ang 201029          | Stapler (I) vs hand sewn anastomosis (C) | Thoracic only | NP | Chest tube output, contrast barium, endoscopy | Nutrition, chest tube drain | NP | NP |
| eng 20134           | Omentoplasty (I) vs hand-sewn anastomosis (C) | Thoracic only | I: 21 (5)** C: 23 (6)** | Gastrografin contrast | NP | NP | NP |
| bira 200440         | Subtotal (I) vs slender gastric tube (C) | Thoracic only | NP | NP | Conservative | NP | NP |
| Iverde 96V31        | Stapler (I) vs hand sewn anastomosis (C) | Cervical: 45 Thoracic: 107 | NP | Swallow, methylene blue, interstitial fluid in drains | NP | NP | NP |
Abbreviations: Abx, antibiotics; C, control; I, intervention; mo, months; NP, not provided; POD, post-operative day; TE, transesophageal; TH, transhiatal; TT, transthoracic; wk, weeks; Y, years

*Median (IQR)
**Mean (SD)

Excluded from meta-analysis (Valverde 1996, Group results influenced by multiple additional interventions; Nederlof 2011, only study to report intervention type; Hayashi 2019, excluded from AL pooled results because of restriction to reporting grade 3+ AL only; Gupta 2001, only study to report intervention type)

Primary Outcome

Anastomotic leak

The pooled results for 11 meta-analyzed studies are summarized in Figure 2 and the descriptive results for single RCT interventions are summarized in Supplemental 2. Esophagectomy patients that received stapled esophagogastric anastomosis demonstrated a similar reduction in risk of AL (RR: 0.92; 95% CI: 0.45, 1.87; $I^2$ 40.1%) compared to hand-sewn (6 studies, n = 1,454 patients).

Esophagectomy patients that received omentoplasty had a significant 78% lower risk of leakage (RR: 0.22; 95% CI: 0.10, 0.50; $I^2$ 0%) compared to hand-sewn or stapled anastomosis alone (3 studies, n = 611 patients). Esophagectomy patients with early removal or no nasogastric tube demonstrated a significant 62% reduction in risk of leakage (RR: 0.38; 95% CI: 0.02, 0.65; $I^2$ 0%) compared to prolonged nasogastric tube removal (2 studies, n = 293 patients).

The pooled risk ratios (RR) for AL were sub-grouped according to the site of esophagogastric anastomosis among 2 studies (Table 3). The pooled risk ratio for esophagectomy patients grouped according to cervical esophagogastric anastomosis (2 studies, RR: 0.23; 95% CI: 0.069, 0.788; $I^2$ 0%) was similar to the pooled RR for thoracic esophagogastric anastomosis (2 studies, RR: 0.19; 95% CI: 0.034, 1.032; $I^2$ 0%). The pooled risk ratios (RR) for AL among omentoplasty patients were also sub-grouped according to whether comparison groups received a stapled or hand-sewn anastomosis (Supplemental 3). The risk ratio for patients in the stapled anastomosis study (1 study, n = 194 patients, RR: 0.214; 95% CI: 0.064, 0.722) was similar to the pooled risk of AL for patients in the hand-sewn anastomosis study (2 studies, n = 417 patients, RR: 0.264; 95% CI: 0.089, 0.789). Due to a lack of reporting of AL according to neoadjuvant therapy type (radiation and/or chemotherapy), it was not possible to conduct a stratified analysis.

Table 3. Risk ratios for anastomotic leak for omentoplasty intervention (sub-group by cervical or thoracic approach)

| Group     | Study (Author, year) | Risk ratio | 95% CI (lower, upper) | $I^2$ |
|-----------|----------------------|------------|-----------------------|-------|
| Cervical* | Bhat 2006<sup>6</sup> | 0.22       | 0.080, 0.88<sup>*</sup> | -     |
|           | Dai 2011<sup>5</sup> | 0.26       | 0.030, 2.08            | -     |
| Overall (n = 2 studies) |                | 0.23       | 0.080, 0.88<sup>*</sup> | 0     |
| Thoracic* | Bhat 2006<sup>6</sup> | 0.19       | 0.020, 1.52            | -     |
|           | Dai 2011<sup>5</sup> | 0.18       | 0.010, 3.68            | -     |
| Overall (n = 2 studies) |                | 0.19       | 0.030, 1.03            | 0     |

*omentoplasty vs. stapled or hand-sewn anastomosis

Secondary Outcomes

Anastomotic stricture

Esophagectomy patients that received stapled esophagogastric anastomosis had a 2-fold increased risk of stricture (RR: 2.11; 95% CI: 1.36, 3.26; $I^2$ 35.0%) compared to hand-sewn esophagogastric anastomosis (6 studies, n = 1,380 patients). Esophagectomy patients that received omentoplasty had an 8% lower and not significantly different risk of stricture (RR: 0.92; 95% CI: 0.33, 2.57; $I^2$ 65.1%) compared to no omentoplasty (3 studies, n = 613 patients). The pooled results are summarized in Figure 3.

Mortality rate

Esophagectomy patients that received stapled esophagogastric anastomosis had no statistically significant difference in risk of mortality (RR: 1.22; 95% CI: 0.75, 1.98; $I^2$ 0%) compared to hand-sewn esophagogastric anastomosis (6 studies, n = 1,363 patients).
Esophagectomy patients that received omentoplasty had a 20% lower risk of mortality (RR: 0.80; 95% CI: 0.32, 2.0; I² 0%) compared to no omentoplasty (3 studies, n = 736 patients). Esophagectomy patients with early removal or no nasogastric tube demonstrated no statistically significant difference in risk of mortality (RR: 0.90; 95% CI: 0.317, 2.55; I² 0%) compared to prolonged nasogastric tube removal (2 studies, n = 190 patients). The pooled results are summarized in Figure 4.

**Length of Stay**

The weighted mean difference (WMD) in the postoperative length of stay in hospital was determined based on the mean (± SD) reported among the included studies. Esophagectomy patients that received stapled anastomosis did not have a significantly different mean length of stay in hospital with a stay of 1.1 days longer [95% CI: -0.01, 2.2; I² 0%] compared to hand-sewn (2 studies, n = 606 patients). Esophagectomy patients that received omentoplasty had a statistically significant 2.1 day shorter mean length of stay in hospital (WMD: -2.1; 95% CI: -3.6, -0.6; I² 0%) compared to hand-sewn or stapled anastomosis alone (2 studies, n = 417 patients). Esophagectomy patients with early removal or no nasogastric tube demonstrated a non-significant 3.2 day shorter mean length of stay in hospital (WMD: -3.2; 95% CI: -6.5, 0.2; I² 0%) compared to prolonged nasogastric tube removal (2 studies, n = 111 patients). Mistry et al. 2012 was excluded from the pooled WMD estimate as the investigators reported a median (IQR). Mistry et al. 2012 reported that the early removal or no nasogastric tube and prolonged nasogastric tube removal groups both had a length of stay of 12 days with no statistically significant difference (P=0.18) [26].

**Risk of Bias**

Seven (64%) meta-analyzed studies did not report whether the allocation of participants was concealed. Nine (82%) meta-analyzed studies lacked any details surrounding blinding of outcome assessment was blinded. Ten (91%) meta-analyzed studies lacked reporting of outcome assessment blinding. The risk of bias results are summarized in Figure 5 (Individual study risk of bias summarized in Supplemental 4).

**Grade**

There was a high quality of evidence for AL in the omentoplasty intervention. The unclear risk of bias in omentoplasty studies was due to the lack of allocation concealment in one study decreased the quality of evidence by one level. The large magnitude of effect in the omentoplasty studies increased the quality of evidence by one level. There was a moderate quality of evidence for AL in the early removal or no nasogastric tube intervention. The high risk of bias due to both the lack of randomization and allocation concealment in all studies decreased the quality of evidence by two levels. The large magnitude of effect increased the quality of evidence by one level. There was a very low quality of evidence for AL in the stapled anastomosis intervention. The high risk of bias due to both the lack of randomization and allocation concealment in nearly all studies decreased the quality of evidence by two levels. The imprecision of the measure of effect due to the lack of statistical significance reduced the quality of evidence by one level. The moderate level of heterogeneity in the pooled estimate decreased the quality of evidence by one level. The evidence profile is summarized according to intervention type in Table 4 (GRADE summarized in Supplemental 5).

**Table 4. Summary of Findings (11 meta-analyzed studies)**
| Intervention                                      | No. Participants (studies) | Quality of Evidence                                                                 | Measure of effect, RR (95% CI)                                                                                                                                 |
|-------------------------------------------------|---------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Omentoplasty vs conventional anastomosis†       | 611 (3 studies)           | + + + + (high quality)                                                              | RR = 0.22 (78% risk reduction)\n95% CI = 0.1, 0.5*                                                                                                    |
| Early or no NG tube decompression vs standard    | 374 (2 studies)           | + + + - (moderate quality)                                                           | RR = 0.38 (62% risk reduction)\n95% CI = 0.02, 0.65*                                                                                           |
| Stapled vs hand-sewn anastomosis                | 1532 (6 studies)          | - - - - (very low quality)                                                           | RR = 0.92 (8% risk reduction)\n95% CI = 0.45, 1.87                                                                                                       |

**RR**: Risk ratio; **CI**: Confidence Interval

**GRADE**: working group grades of evidence

- **High quality (+ + + +):** more research very unlikely to change the estimate of effect
- **Moderate quality (+ + + -):** means further research is likely to have an important impact on our confidence in the estimate of effect and may alter the estimate
- **Low quality (+ + - -):** means that the effect estimate is limited and may substantially differ from
- **Very low quality (+ - - - or - - - -):** grade means that we have little confidence in the effect estimate

*statistically significant confidence interval
†stapled or hand-sewn anastomosis
¹one study lacked allocation concealment
²lack of randomization and allocation concealment
³optimal information size not met (appendix 8) and the 95% CI for the effect estimate crosses the null (RR = 1.0)
⁴moderate heterogeneity (I² = 40.1%)

**Discussion**

This is the first systematic review and meta-analysis to provide graded quality of evidence for all previous RCTs investigating interventions to reduce anastomotic leakage (AL) following esophagectomy. Our review suggests there is a high quality of evidence that omentoplasty significantly reduces the risk of AL. The mechanism of benefit (improved perfusion to the surgical site) that omentoplasty has on wound healing may offer further justification to the high quality of evidence supporting this significant reduction in risk of AL [21, 34 – 35]. Our findings showed that omentoplasty not only reduced AL, but also lowered the risk of anastomotic stricture, mortality, and mean length of stay in hospital following esophageal cancer resection; However, this finding was not statistically significant in anastomotic stricture or mortality. The early removal or no nasogastric tube intervention showed a substantial reduction in the risk of AL when compared to prolonged nasogastric tube removal; however, the moderate quality of evidence for this intervention indicates the need for further research. There was a small difference in risk of AL for stapled vs hand-sewn anastomosis, but it was not significant. The quality of evidence for stapled (vs. hand-sewn) anastomosis was very low.

In the present meta-analyses, subgroup group analysis based on the location of anastomosis revealed that there was a less protective effect of omentoplasty to prevent AL in the cervical esophagogastric anastomosis groups; This finding should be interpreted with caution due to the low number of omentoplasty studies sub-grouped. The finding that esophagogastric anastomosis location has some association with the presence of anastomotic leak is consistent with previous literature. Many studies have shown that there are higher rates of AL in patients who undergo transhiatal surgery compared to transthoracic. However, the possible mechanism(s) explaining differences in AL rates based on location remains somewhat controversial [4,19]. Some studies have attempted to better elucidate the underlying mechanisms. In two previous meta-analyses, the rates of AL in patients that had transhiatal esophagectomy (use of cervical anastomosis) were significantly higher compared to patients that had transthoracic or Ivor Lewis esophagectomy (use of thoracic anastomosis) [33, 34]. Other literature has hypothesized that the differences in AL rates based on cervical and thoracic locations may be due to perfusion issues of the gastric conduit reaching the neck. The latter is supported by the well-established understanding that perfusion and oxygen delivery to the site of wound healing after surgical resection has a substantial influence on the integrity of the wound healing process [33 – 35].
There is a need for further research and improved reporting in future RCTs to allow for elucidation of possible group differences. The paucity of studies surrounding the investigation of early removal or no nasogastric tube removal, subtotal gastric reconstruction intervention vs. a slender tube, and other techniques such as valvuloplasty may reflect the need for further research to better understand the role of these interventions in the prevention of AL. Another limitation of our meta-analysis of omentoplasty studies is that the comparison group included both stapled and hand-sewn anastomosis. However, the risk of AL among omentoplasty studies was not significantly different when sub-grouped by stapled vs. hand-sewn anastomosis. Thus, we do not anticipate this limitation to influence our conclusions. Finally, we were unable to obtain data in the included studies to allow for subgroup analysis according to the presence or absence of adjuvant radiation and/or chemotherapy.

Our review identified some gaps in the literature that may be better understood with further research. The lack of reported measures of quality of life or psychometric outcomes was one area where further exploration may be beneficial. The patient-reported outcomes may allow us to better understand key aspects of patient experience to improve the quality of care around the delivery of interventions. Another barrier was the lack of RCTs performed in North America, which means that findings may not necessarily be representative of North American populations undergoing esophageal cancer treatments. It may be useful to confirm whether the findings are generalizable to North American populations.

**Conclusion**

Our systematic review and meta-analysis summarizes the efficacy and safety of interventions aiming to reduce anastomotic leakage following esophagectomy. Our findings demonstrated that omentoplasty reduced the risk of anastomotic leak (compared to conventional anastomosis) with a high quality of evidence. Since early nasogastric tube removal findings provided a moderate quality of evidence, further research is recommended. Future RCTs should aim to strengthen the quality of evidence for this intervention; it demonstrates promising results that are likely to be strengthened by further research. Quality of evidence profiles presented our review may help inform future guideline recommendations surrounding the role of omentoplasty in clinical practice.

**Abbreviations**

AL, anastomotic leak; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; IQR, interquartile range; NG, nasogastric; PRISMA, preferred reporting in systematic reviews and meta-analysis; RCT, randomized controlled trial; RR, risk ratio; TE, transesophageal; TH, transhiatal; TT, transthoracic; WMD, weighted mean difference.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The dataset generated and analysed in our review are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**
Ms. Grigor had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript.

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