



# Comparison of Ivor Lewis and Sweet esophagectomy for middle and lower esophageal squamous cell carcinoma: A systematic review and pooled analysis

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## ABSTRACT

**Background:** Lack of robust evidence highlights the important need to address the controversy on the clinical safety and effectiveness between Ivor Lewis versus Sweet procedure for middle and lower esophageal squamous cell carcinoma (ESCC).

**Methods:** Search results were filtered according to certain criteria and were analyzed in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

**Findings:** The inter-study heterogeneity was high. Ivor Lewis procedure might be associated with longer operation time ( $p < 0.01$ ) and higher lymph node yield ( $p < 0.01$ ) compared with Sweet procedure. There was no significant difference in the length of hospital stay and postoperative complications with similar reoperation rate between the two procedures ( $p > 0.05$ ). As the combined analysis of survival data revealed, there was no statistical difference in the oncologic efficacy of them ( $p = 0.97$ ).

**Interpretation:** The present study based on retrospective data with high heterogeneity indicated that Ivor Lewis esophagectomy might be associated with increased lymph node yield but longer operation time than Sweet. Prospective studies are warranted to compare the long-term survival of Ivor Lewis esophagectomy versus Sweet for middle and lower ESCC.

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## 1. Introduction

Esophageal carcinoma (EC) is the sixth most common malignant disease all over the world [1,2]. The prevalence of EC in China accounts for 50% of global EC-related morbidity and mortality [3–6]. In China, more than 90% of EC patients suffer from esophageal squamous cell carcinoma (ESCC). Esophagectomy, as the mainstay of treatment, should be considered for all patients who are physiologically suitable as long as there is no metastatic disease [7–9]. Ivor Lewis esophagectomy [10] and Sweet [11] are two main approaches for the treatment of middle and lower ESCC. However, there is still some controversy on the safety and oncologic outcomes of two procedures.

Sweet procedure confers a superiority of single incision and adequate exposure of the hiatus, but harvests few lymph nodes [12]. In

contrast, the right-sided Ivor Lewis procedure allows better visualization of the thoracic esophagus for lymph node retrieval, whereas it may bring more complications [12–15].

So far, only a few studies to date have compared the two procedures with conflicting outcomes [12,15,22,24] regarding short-term complications and long-term survival. To address the debate, we included seven studies to compare Ivor Lewis and Sweet procedure for middle and lower ESCC concerning perioperative morbidity and oncologic efficacy, which to our best knowledge is the largest on this subject.

## 2. Methods

### 2.1. Search strategy

This meta-analysis was conducted in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [16]. The studies were identified by searching databases including PubMed, EMBASE, Web of Science, and the Cochrane Library. Search date was from the inception to November 2019. The

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## Research in Context

### Evidence Before This Study

Ivor Lewis esophagectomy and Sweet are two main approaches for the treatment of middle and lower ESCC. However, there is still some controversy on the safety and oncologic outcomes of two procedures.

### Added Value of This Study

A comprehensive online search was performed to identify studies from the databases including PubMed, EMBASE, Web of Science and Cochrane libraries, which is the largest and latest pooled analysis so far comparing the two procedures. Subgroup analyses of postoperative complications and long-term survival were also performed.

### Implications of all the Available Evidence

The meta-analysis revealed no significant difference in postoperative complications and survival data between the two procedures. Ivor Lewis esophagectomy can harvest more lymph nodes than Sweet whereas requires longer operation time. Further large-scale multi-institutional prospective trials should be launched to address the controversy.

main search terms included 'esophageal', 'esophagus', 'carcinoma', 'left', 'right', 'Sweet' and 'Ivor Lewis'. The complete search strategy is listed in *Supplementary Table 1*.

#### 2.1.1. Study selection and inclusion criteria

First, the titles and abstracts were screened to assess research eligibility, and then the full text is reviewed. Any differences can be resolved through discussion or by hiring a third reviewer (W.W.) to reach consensus. Inclusion criteria: (1) Purpose of the literature is to compare advantages or disadvantages of Ivor Lewis and Sweet; (2) The literature should provide at least one of the surgical-related indicators and complication or survival data, such as surgical time, number of lymph node dissections, postoperative hospital stay, the occurrence of complications and hazard ratio (HR) of the postoperative survival, including 95% confidence interval (CI); (3) The primary location of the tumor should be at the middle and lower esophagus; (4) Full text is available. Exclusion criteria: (1) The literature involving case reports, experience summaries, reviews, abstracts, and experimental studies; (2) The literature contained the effects of minimally invasive or endoscopic surgery; (3) Literatures with repeated publications; (4) Endpoints including none of the aforementioned indicators; (5) Insufficient data for estimating a HR and 95% CI.

#### 2.1.2. Data extraction and quality assessment

Two reviewers (X.Y. and C.D.) independently conducted data extraction and cross-checked the extraction results. Any difference can be resolved through discussion or mediated by a third reviewer (W.W.). The extracted information includes author name, publication time, research type, number of patients who underwent Ivor Lewis or Sweet procedure, total number of cases, time range of case collection. The meta-analyzed indicators include operation time, number of lymph node dissections, postoperative hospital stay, postoperative complications (anastomotic leakage, laryngeal recurrent nerve injury, pulmonary infection, etc.) and the occurrence rate of reoperations. The HRs estimates (with the corresponding 95% CIs) for different endpoints were extracted from the studies which were uniformly adjusted as Ivor Lewis vs Sweet procedure.

Quality assessment of the included studies was performed based on seven aspects (*Supplementary Table 2*). Scores of 7 or higher were certified as high-quality scores, and the other were defined low-quality scores. Any differences were resolved through full discussion.

#### 2.1.3. Statistical analysis

Meta-analysis was performed using RevMan 5.3 software shared by the Cochrane Collaboration Network. Mean difference (MD) was used to evaluate continuous data (the difference between the mean and standard deviation of each study is less than 10 times) and odds ratio (OR) was used to evaluate binary data. Each effect was 95% CI. A  $p$  value  $< 0.05$  is considered to be statistically significant. Because the mean and variance are not given in some continuous data which may not conform to the normal distribution, we used statistical methods to estimate the mean and variance [17,18], and used R Studio 3.6.1 for normalized transformation and analysis. We also performed statistical processing to obtain the standard error of  $\ln(\text{HR})$  for survival data [19]. After that, we selected a calculation model based on the heterogeneity results. If the heterogeneity of data was not significant ( $p > 0.1$ ,  $I^2 < 50\%$ ), a fixed-effects model was used for meta-analysis; If there is significant heterogeneity among the data ( $p < 0.1$ ,  $I^2 > 50\%$ ), the cause of the heterogeneity should be analyzed, containing subtype analysis and sensitivity analysis. Then a random effects model was used for data without significant clinical heterogeneity or significant difference. Given that the number of included studies in this meta-analysis was limited, we employed the Egger's test to analyze potential publication bias since a funnel plot was inappropriate for assessing publication bias.

#### 2.2. Role of the funding source

The funders had no role in the execution of this study or the interpretation of the results.

## 3. Results

### 3.1. Identification of studies and study characteristics

The flowchart of our literature searching is shown in *Fig. 1*. In summary, our literature retrieval strategy initially identified 200 articles. Finally, 7 studies were eligible for inclusion in our meta-analysis.

The main characteristics of the included studies were shown in *Supplementary Table 3*. A total of 2451 patients were included in this meta-analysis. Among them, 948 cases underwent Ivor Lewis procedure and 1503 cases underwent Sweet. Detailed characteristics of these included articles were provided in *Table 1*. It is worth being noticed that one of the included studies [12] is the post hoc analysis of a randomized trial [15], which mainly focused on the survival analysis and lacked other major information. Therefore, while including the post hoc analysis [12], we also needed most of the data from the previous article [15]. Among the seven studies, four studies [21,22,24,25] processed their raw data by propensity-score matching, which ensured the comparability of Ivor Lewis and Sweet procedures.

### 3.2. Key outcomes: intraoperative condition

*Fig. 2A* shows that seven studies [15,20–25] mentioned the operation time. Due to significant heterogeneity obtained by combined analysis ( $I^2 = 99\%$ ,  $p < 0.01$ ), a random effects model was applied. The operation time of Ivor Lewis esophagectomy was significantly longer than that of Sweet (MD = 104.30, 95% CI: 64.01–144.59,  $p < 0.01$ ). Six studies [15,20–24] were involved to assess the number of lymph node removed during the operation (*Fig. 2B*). Significant heterogeneity found after combined analysis ( $I^2 = 88\%$ ,  $p < 0.01$ ), a random effects model was employed as well, which showed that more lymph

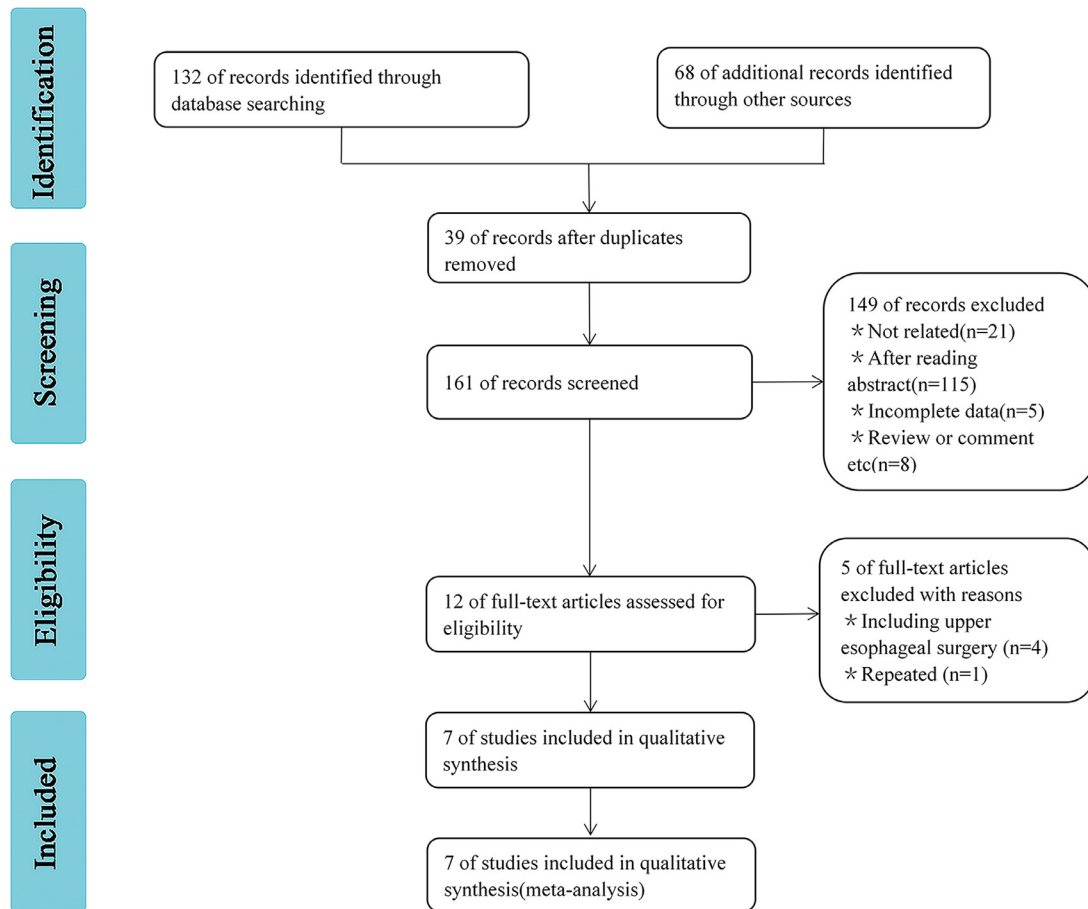


Fig. 1. PRISMA flowchart of literature search strategy.

nodes could be harvested in patients undergoing Ivor Lewis procedure (MD = 4.04, 95% CI: 1.44–6.59,  $p < 0.01$ ).

Given that 4 studies used propensity-score matching, we performed a subgroup analysis to assess whether heterogeneity in operation time and lymph node yields could be altered based on well-matched data. The subgroup analysis on operation time (Matched,  $I^2 = 96\%$ ; Not matched,  $I^2 = 94\%$ ; subtype difference,  $Q = 17.05$ ,  $p < 0.01$ ) revealed that the heterogeneity was not significantly changed and operation time of Ivor Lewis was significantly longer than Sweet (Fig. 3A). The subgroup analysis regarding number of harvested lymph nodes (Matched,  $I^2 = 93\%$ ; Not matched,  $I^2 = 78\%$ ; subtype difference,  $Q = 0.04$ ,  $p = 0.87$ ) indicated the heterogeneity had a certain increase which exerted no effect on the results (Fig. 3B). After that, we considered whether the heterogeneity came from studies, in which some patients had received neoadjuvant therapy. The results (Fig. 3C) showed that the subgroups stratified by treatment modality decreased the heterogeneity in operation time (Neoadjuvant therapy,  $I^2 = 77\%$ ; Surgery alone,  $I^2 = 99\%$ ; subtype difference,  $Q = 0.47$ ,  $p = 0.03$ ) which confirmed longer operation time of Ivor Lewis than Sweet (MD = 152.58, 95% CI: 107.36–197.80,  $p < 0.01$ ). In contrast, there was an increase in heterogeneity in lymph node yields (Neoadjuvant therapy,  $I^2 = 96\%$ ; Surgery alone,  $I^2 = 80\%$ ; subtype difference,  $Q = 0.12$ ,  $p = 0.73$ ) in subgroups analysis stratified by different treatment modalities. However, the MD between the two procedures became narrowed in terms of lymph node dissection (Fig. 3D), which seemed to be statistically non-significant (MD = 1.92, 95% CI: –11.38–15.22,  $p = 0.78$ ). Subsequently, we found that the heterogeneity in operation time or lymph node yields was not caused by any study (all  $p < 0.05$ ) after performing a sensitivity analysis (Supplemental Fig. 1).

### 3.3. Secondary outcomes: postoperative events

Six articles [15,20,21,23–25] reported postoperative hospital duration (Supplemental Fig. 2A), one of which [20] had too much data missing. With the study [20] excluded, a random effects model ( $I^2 = 86\%$ ,  $p < 0.01$ ) was applied. As shown in Supplemental Fig. 2A, the difference had no statistical significance (MD = –0.04, 95% CI: –3.88–3.81,  $p = 0.98$ ). Besides, a random effects model was used to assess the difference in reoperations rates mentioned in three studies [15,20,22] ( $I^2 = 62\%$ ,  $p = 0.01$ ), and no statistically significant difference (OR = 0.66, 95% CI: 0.11–3.10,  $p = 0.65$ ) were found between the two approaches (Supplemental Fig. 2B).

As shown in Supplemental Fig. 2C, the occurrence of anastomotic leakage was analyzed in a random effects model ( $I^2 = 51\%$ ,  $p = 0.07$ ) and no statistically significant difference (OR = 1.30, 95% CI: 0.54–3.10,  $p = 0.56$ ) was observed [15,20–25]. The other postoperative complications are integrated in Supplemental Fig. 3: (1) The occurrence of laryngeal recurrent nerve injury showed the difference was not statistically significant (OR = 1.77, 95% CI: 0.78–4.02,  $p = 0.17$ ) between the two procedures without heterogeneity ( $I^2 = 0\%$ ,  $p = 0.46$ ) [15,21,23,25]; (2) The occurrence of cardiac complications revealed no statistically significant difference (OR = 0.91, 95% CI: 0.59–1.41,  $p = 0.68$ ) without heterogeneity ( $I^2 = 0\%$ ,  $p = 0.62$ ) [15,20,22–25]; (3) The occurrence of pulmonary infection indicated insignificant difference (OR = 1.25, 95% CI: 0.72–2.16,  $p = 0.43$ ) calculated by a random effects model ( $I^2 = 63\%$ ,  $p = 0.01$ ) [15,20–25]; (4) No statistically significant difference (OR = 1.30, 95% CI: 0.54–3.10,  $p = 0.56$ ) in gastroparesis between the two procedures was shown based on the random effects model data ( $I^2 = 63\%$ ,  $p = 0.01$ ) [15,20–24].

**Table 1**  
Baseline characteristics of all 8 included studies.

No.	Reference	Country	Inclusion Period	Study Design	Cases (I/S)	Median Age (years)		Location		Operative time (min)		lymph nodes		Hospital stay (I/S)	Anastomotic leakage (I/S)	Pulmonary infection (I/S)	Laryngeal recurrent nerve injury (I/S)	Cardiac complication (I/S)	Gastro-paresis (I/S)	Reoperations (I/S)	Neoadjuvant therapy	Pre-operative radiotherapy
						I	S	Middle (I/S)	Lower (I/S)	I	S	I	S									
1	Wang 2019 [20]	China	2010–2015	Retro-spective	624 (325/299)	62 (59–68)	62 (58–68)	182/181	143/118	165 (150–180)	160 (145–180)	20 (4–42)	16 (3–31)	12 (10–17)	18/11	26/32	8/4	6/10	24/5	11/6	No	Yes
2	Li 2018 [12,15]	China	2010–2012	Retro-spective	300 (150/150)	61 (54–66)	60 (55–64)	95/82	55/68	202 (38)	174 (35)	22 (17–33)	18 (13–26)	18 (10–90)	2/8	13/16	3/4	17/21	7/4	1/8	No	Yes
3	Feng 2019 [21]	China	2003–2009	Retro-spective	150 (75/75)	60.49±8.46	58.27±8.32	NA	NA	425.22±74.05	293.58±74.73	24.65±7.97	16.08±8.32	18.20±10.02	1/2	9/5	NA	NA	1/1	NA	Yes	NA
4	Liu 2017 [22]	China	1990–2010	Retro-spective	114 (57/57)	73.0 (71–79)	72.4 (71–79)	51/53	6/4	372±120	92±48	23.7 ± 13.7	14.8 ± 9.0	NA	4/1	13/5	3/0	9/8	2/1	1/1	No	No
5	Ma 2014 [23]	China	2007–2010	Retro-spective	915 (167/748)	NA	NA	111/501	56/247	208 ± 63	181 ± 71	18.89±10.085	17.45±8.591	17.3 ± 15.6	7/16	5/23	1/1	2/9	8/13	NA	No	No
6	Mu 2016 [24]	China	2009–2015	Retro-spective	90 (45/45)	58.9 ± 7.6	59.9 ± 8.5	35/55	10/10	390±117	212±48	19±12	24±10	19±8	3/7	1/4	NA	3/0	4/9	NA	Yes	NA
7	Wang 2016 [25]	China	2007–2013	Retro-spective	258 (129/129)	59.43±7.29	61.04±8.109	98/107	31/22	316.67±89.054	211.51±52.222	NA	NA	15.29±12.435	7/3	41/20	NA	4/3	NA	NA	No	No

Abbreviations: NA, not available. I/S, Ivor Lewis/Sweet.

3.4. Tertiary outcomes: long-term survival

Finally, we performed a combined analysis of survival based on five studies [20–23,25]. As shown in Fig. 4A, significant heterogeneity ( $Q = 9.83, p = 0.04, I^2 = 59.3\%$ ) observed, we used a random effects model to confirm similar oncologic efficacy between the two surgical procedures ( $HR = 1.00; 95\% CI = 0.85–1.18, p = 0.97$ ). To be noted, we attempted to carry out a subgroup analysis of different treatment modality. However, data on neoadjuvant therapy available in only one study [21], the subgroup analysis could be regarded as a merged analysis of the other four studies (Fig. 4B). It can be seen that the absence of neoadjuvant therapy did not increase heterogeneity and had no effect on HR ( $p = 0.59$ ).

3.5. Publication bias

We performed the Egger's test for all the previous analyses (Table 2). The results showed that there was no publication bias except the operation time ( $t = 7.28, p < 0.01$ ). All studies showed that the operation time of Ivor Lewis esophagectomy was longer than that of Sweet (Table 1) with opposite results unavailable, which was likely to cause the publication bias regarding operation time. In addition, the existing publication bias might be caused by different surgical manipulations by different surgeons, as well as the difference in statistical methods among these studies.

4. Discussion

This study exhibits the pooled data concerning both short-term and long-term events after Ivor Lewis esophagectomy and Sweet, which is the only and largest meta-analysis available for middle and lower ESCC surgery. In present study, we found that the operation time of Sweet esophagectomy was shorter and the lymph node yields in Ivor Lewis tended to be higher. There were no statistically significant differences in postoperative hospital stay, postoperative complications, occurrence of reoperations and 5-year survival rate between the two procedures. Potential publication bias for operation time might be caused by the lack of studies with opposite results.

The analysis of operation time and lymph node dissection revealed high inter-study heterogeneity, which indicated the necessity of further subgroup analysis and sensitivity analysis. Subgroup analysis suggested that neoadjuvant therapy might be one of the reasons for the high heterogeneity. Sensitivity analysis demonstrated that any single study didn't cause change in heterogeneity. In addition, there was no obvious difference in the results of the sensitivity analysis. In other word, the results of our original analysis were stable.

Significant statistical heterogeneity revealed a large variability in the benefits of surgery. Several clinical factors including the individual characteristics, the surgical team, and the equipment might contribute to the high heterogeneity. In terms of the individual characteristics, patients' own physiological conditions might determine the surgical procedures, such as complicated cardiovascular or pulmonary diseases that couldn't allow long-time surgery and extensive lymph node dissection. Meanwhile, the operation habits of the surgeons might further aggravate the heterogeneity among the studies. Equipment-related factors (including the quality of esophagogastric stapler and differences in usage) might also expand heterogeneity. Moreover, although sensitivity analysis showed stable results, statistical processing also possibly accounted for the inter-study heterogeneity.

As shown in the results section, the Sweet procedure can shorten the operation time ( $MD = 104.30, 95\% CI: 64.01–144.59, p < 0.01$ ) compared with Ivor Lewis. Six of the included literatures indicated that the length of time in Ivor Lewis esophagectomy was prolonged, which may be explained by the sophistication of thoracoabdominal



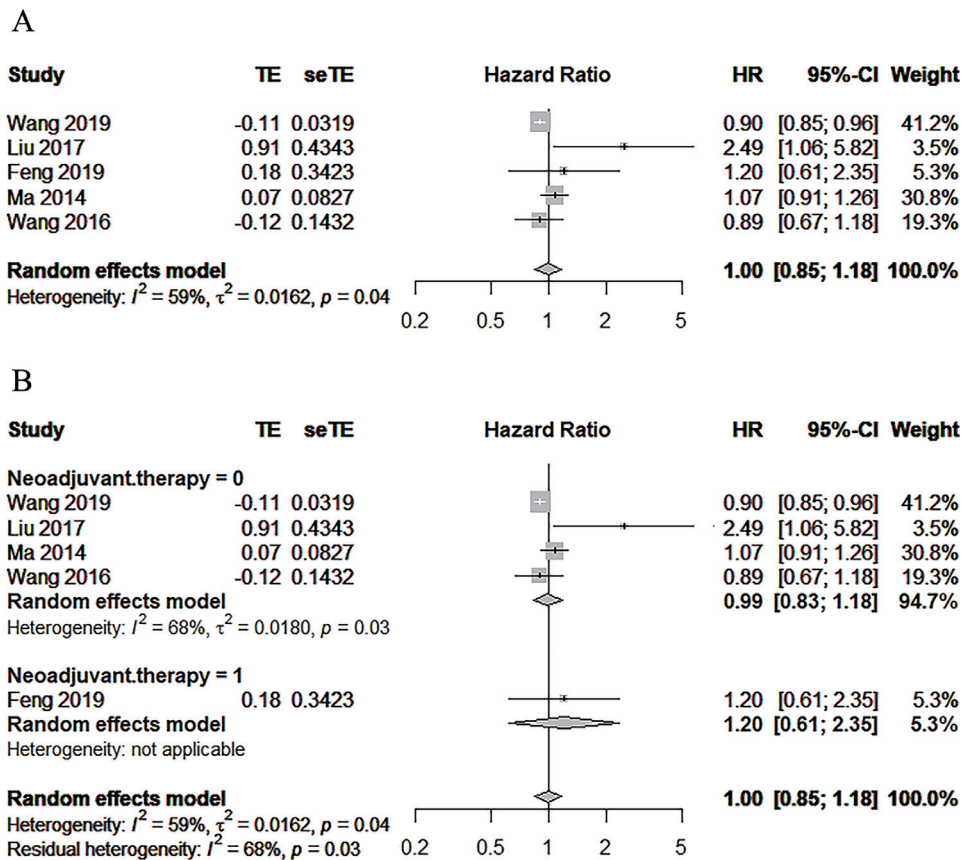


Fig. 4. A. Forest plot of 5-year survival; B. Subgroup analysis of 5-year survival stratified by different treatment modalities.

Table 2

Egger's test for publication bias.

	<i>t</i>	df	<i>p</i>
Operative time	7.2834	5	0.0007633
Lymph node dissection	0.072972	5	0.9447
Hospital stay	-1.7207	3	0.1838
Pulmonary infection	-0.2459	5	0.8155
Laryngeal recurrent nerve injury	1.2096	2	0.35
Anastomotic leakage	-0.0087008	5	0.9934
Gastroparesis	-0.83149	4	0.4525
Cardiac complication	2.2106	4	0.09157
Reoperations	-0.31127	1	0.8079
5-year survival rate	2.0224	3	0.1363

esophagectomy can hardly outperform Sweet concerning patient survival (HR = 1.00; 95% CI = 0.85–1.18,  $p = 0.97$ ), which might be explained by the limited number of included studies and the essentially unfavorable 5-year survival rate of ESCC patients.

There may be a problem of insufficient statistical power since only seven studies were included in this systematic review. It was easy to produce bias in the process of normalized transformation and analysis of continuous data (operation time, lymph node dissection and postoperative hospitalization). However, even in a well-matched situation, the results concerning operation time and lymph node yield did not alter (the difference was statistically significant and publication bias did not appear). There are other shortcomings in this study. As shown in Table 1, some data are unavailable, which could result in potential bias in our analysis. Regarding the long-term survival, with the exception of one study [15], the rest provided limited values in which substantial data on disease-free survival and proportional hazards model were unavailable.

In summary, Ivor Lewis procedure can possibly provide higher lymph node yield than Sweet, whereas Sweet esophagectomy may take shorter operation time compared with Ivor Lewis. The present study could only demonstrate non-inferiority results of Sweet and Ivor Lewis procedures from multiple aspects based on existing retrospective studies, which might provide preliminary evidence for surgeons to determine the optimal surgical approach.

#### Declaration of Interests

None declared.

#### Data sharing statement

The data used during the current study are available from the corresponding author upon reasonable request.

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#### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100497.

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