REVIEW

Comparison of short-term outcomes between minimally invasive McKeown and Ivor Lewis esophagectomy for esophageal or junctional cancer: a systematic review and meta-analysis

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Purpose: Minimally invasive esophagectomy is increasingly performed for esophageal or gastroesophageal junctional cancer, with advantages of improved perioperative outcomes in comparison with open esophagectomy. McKeown and Ivor Lewis are widely used procedures of minimally invasive esophagectomy, and there have been controversies on which one is preferred for patients with resectable esophageal or junctional cancer.

Patients and methods: This review was registered at the International Prospective Register of Systematic Reviews (number CRD42017075989). Studies in PubMed, Embase, Web of Science, the Cochrane Library, and ClinicalTrials.gov were thoroughly investigated. Eligible studies included prospective and retrospective studies evaluating short-term outcomes of minimally invasive McKeown esophagectomy (MIME) vs minimally invasive Ivor Lewis esophagectomy (MILE) in patients with resectable esophageal or junctional tumors. Main parameters included anastomotic leak and 30-day/in-hospital mortality. Overall incidence rates (ORs)/weighted mean difference (WMD) with 95% confidence intervals (CIs) were calculated by employing random-effects models.

Results: Fourteen studies containing 3,468 cases were included in this meta-analysis. Age, male sex, and American Joint Committee on Cancer (AJCC) stage between the 2 groups were not statistically different. MIME led to more blood loss, longer operating time, and longer hospital stay than MILE. MIME was associated with higher incidence of pulmonary complications (OR =1.96, 95% CI =1.28–3.00) as well as total anastomotic leak (OR =2.55, 95% CI =1.40–4.63), stricture (OR =2.07, 95% CI =1.05–4.07), and vocal cord injury/palsy (OR =5.62, 95% CI =3.46–9.14). In addition, the differences of R0 resection rate, number of lymph modes retrieved, blood transfusion rate, length of intensive care unit stay, incidence of cardiac arrhythmia, and Chyle leak between MIME and MILE were not statistically significant. Notably, incidence of severe anastomotic leak (OR =1.28, 95% CI =0.73–2.24) and 30-day/in-hospital mortality (OR =1.76, 95% CI =0.92–3.36) as well as 90-day mortality (OR =2.22, 95% CI =0.71–6.98) between the 2 procedures were also not significantly different.

Conclusion: This study suggests that MIME and MILE are comparable with respect to clinical safety. MILE may be a better option when oncologically and clinically suitable. MIME is still a safe alternative procedure when clinically indicated. However, this evidence is at risk for bias; randomized controlled trials are needed to validate or correct our results.

Keywords: Ivor Lewis esophagectomy, McKeown esophagectomy, minimally invasive esophagectomy (MIE), cervical anastomosis, intrathoracic anastomosis

Introduction

Esophageal cancer has rapidly become a global concern. Its incidence increased by 44% in the past 2 decades, from 316,000 patients diagnosed in 1990 to 455,800 new cases estimated in 2012.[1,2] Despite the advancement of medical techniques, esophageal cancer still has a poor 5-year survival rate that varies between 15% and 25% in most countries.[3] Radical esophagectomy with adequate lymphadenectomy, sometimes after neoadjuvant therapy, is the main option for treating esophageal cancer.[4]

Minimally invasive esophagectomy (MIE) is being increasingly implemented because it has been proved to be superior for perioperative outcomes and possesses equal survival benefit compared with open esophagectomy.[5,6] MIE consists of McKeown, Ivor Lewis, and transhiatal procedures.[7] Surgeons prefer the transthoracic MIE procedures (McKeown and Ivor Lewis), because they can make adequate thoracic lymph node dissection.[8] However, the superiority of one procedure over the other continues to be controversial.[9,10]

A previous meta-analysis compared short-term outcomes between minimally invasive McKeown esophagectomy (MIME) and minimally invasive Ivor Lewis esophagectomy (MILE) for esophageal cancer,[8] however, it ignored preoperative clinical data and other relevant literature in People's Republic of China where new esophageal cancer cases account for about 50% of the cases worldwide annually.[11] In addition, it might not be proper to make a pooled analysis by combining the severe anastomotic leak in the biggest studies (1,011 cases) with total anastomotic leak in the other 4 studies (648 cases totally) to get the overall anastomotic leak rate in a meta-analysis. We, therefore, performed a more comprehensive meta-analysis involving the Chinese patients and other latest relevant publications.

Materials and methods

All procedures of this review were guided by *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*, and this meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was registered at the International Prospective Register of Systematic Reviews (number CRD42017075989).[12,13]

Searching strategy

PubMed, Embase, Science Citation Index, The Cochrane Library, and ClinicalTrials.gov were thoroughly searched with the following terms or combinations of these terms

(as either key words or MeSH terms): "Minimally Invasive esophagectomy/oesophagectomy" or "laparothoracoscop esophagectomy," "thoracolaparoscop esophagectomy," "video assisted thoracic surgery (VATS) Esophagectomy," "video-assisted esophagectomy" or "Minimally Invasive McKeown esophagectomy" or "Minimally Invasive Ivor Lewis esophagectomy" (date to March 2018). Following the initial screening based on abstracts, we obtained full texts of candidate publications and examined the reference lists of each retrieved article carefully in order to identify additional potentially relevant articles.

Selections of studies

All searching records were screened on title and abstract by the 2 authors (Deng and Su) independently. All studies that were not excluded in the screening stage were further assessed in full text for eligibility. If discrepancies occurred, discussion with a third author (Chu) would be held to reach a consensus. This process will be described in a flowchart according to the PRISMA statement.[13]

Inclusion criteria

The major inclusion criteria were the following: 1) prospective and retrospective studies and 2) studies that compare short-term outcomes of MIME and MILE in patients with resectable esophageal or junctional tumors.

Exclusion criteria

The exclusion criteria were as follows: 1) studies that were not compared, 2) overlapped studies, and 3) studies that did not report main results such as mortality and anastomotic leak.

Data extraction

All data were extracted from article texts, tables, and figures by 2 investigators (Deng and Su) independently. The following data were extracted: names of first authors, durations of studies, study design, countries, numbers of patients included, age, gender, tumor stage, location of cancer, as well as intraoperative and postoperative data and main complications including 30-day/in-hospital or 90-day mortality and anastomotic leak. If the 2 investigators had different ideas on any data, the third senior investigator (Chu) would be asked to check to reach consensus on the data.

Quality assessment

The quality of the included studies was evaluated by the Newcastle–Ottawa Quality Assessment Scale (NOS) for

cohort studies.[14] Each study was accessed separately by 2 independent reviewers (Ren and Wen). The NOS contains 3 sections: the selection of the involved groups, the comparability between the groups, and the assessment of follow-up and outcomes. The number of total stars was recorded to reflect the quality of the included studies, which ranged from 1 (lowest quality) to 9 (highest quality).

Statistical analysis

Meta-analysis was performed using the software Stata 12.0 (Stata Corp LP, College Station, TX, USA; 2011). Overall incidence rates (odds ratios; ORs)/weighted mean difference (WMD) with 95% confidence intervals (CIs) were calculated for binary and continuous parameters, respectively, by employing random-effects models regardless of the heterogeneity, thereby obtaining conservative results.[15] According to *Cochrane Reviewer Handbook 5.1.0*, if a study with a reasonably large sample size reports a parameter as a median and interquartile range where the central 50% of participants' outcomes lie for continuous data, the width of interquartile range will be approximately 1.35 standard deviations.[12] So, the value of standard deviation can be obtained by dividing the interquartile range by 1.35. Heterogeneity between studies was assessed using the Cochran Q and the I^2 statistic. An I^2 value >50% was considered substantial heterogeneity, and subgroup analysis or meta-regression analysis (when the number of studies included ≥10) was performed to find out the potential origin of heterogeneity, if necessary. A 2-sided P-value <0.05 was considered statistically significant. If the number of studies we had included was <20, Egger's test would be selected to reveal potential publication bias, because it is thought that if the number of included studies is <20, the Egger's test is more sensitive to find out potential publication bias than the Begg's test.[15] If there were more than 20 studies, both tests would be performed. If this test indicated apparent publication bias (P<0.1), the trim-and-fill computation was carried out to estimate the effect of publication bias on the interpretation of the results. Sensitivity analysis was performed using the leave-one-out approach.

Results
Study characteristics

A flowchart of the literature searching process according to PRISMA is shown in Figure 1. With our searching strategy, we identified 2,610 publications after removing duplicates. After carefully reviewing their titles and abstracts, 20 records were potentially eligible for our review. Then, we assessed full-text articles and found that among them 2 studies were meta-analyses,[8,16] 2 studies were duplicates of previous studies, and 2 studies did not report main results. Finally, 3,468 patients from 14 cohort studies underwent totally minimally invasive McKeown or Ivor Lewis esophagectomy were subjected to this meta-analysis.[9,10,17–28] No randomized controlled studies or studies adopting hybrid MIE were found. Major characteristics and NOS quality star of the included studies are summarized in Tables 1 and 2 (surgical details and other outcomes can be found in Supplementary materials). The results of our meta-analysis are shown in Table 3.

Preoperative clinical data

Ten studies reported age as mean (SD) or median (interquartile range) in the 2 groups; there was no statistical significance between the 2 groups after pooled analysis (WMD =0.77, 95% CI =–0.21 to 1.75, P=0.12). Ten studies containing 2,598 cases reported the number of male cases in 2 groups; no apparent difference was detected (OR =1.13, 95% CI =0.93–1.37, P=0.21). AJCC staging (stages 0, I, and II) of patients' esophageal cancer was reported in 7 studies with 1,132 cases; no statistical significance was found between the 2 groups (OR =0.87, 95% CI =0.63–1.22, P=0.42). Few studies reported the preoperative comorbidity and neoadjuvant therapy to provide meaningful pooled results.

Intraoperative data

Operating time was reported in 10 studies (1,666 cases). MIME was associated with significantly longer operating time (WMD =36.49, 95% CI =7.12–65.86, P=0.01). MIME was found to cause more intraoperative blood loss than MILE (WMD =16.9, 95% CI =3.22–30.58, P=0.02), but the difference of transfusion rate was of no statistical significance (OR =1.25, 95% CI =0.29–5.38, P=0.76). Seven studies with 2,419 cases reported the number of lymph nodes retrieved; there was no statistical significance between the 2 groups after pooled analysis (WMD =3.22, 95% CI =–0.95 to 7.40, P=0.13). The difference of R0 resection rate between the 2 groups was not statistically significant after pooled analysis of the data reported by 4 studies containing 1,687 cases (OR =1.34, 95% CI =0.36–5.02, P=0.67). Significant between-study heterogeneity was detected for operating time (I^2=98.5%), blood loss (I^2=73.2%), transfusion (I^2=71.4%), and lymph nodes retrieved (I^2=96.7%). Subgroup analysis according to a country (China/non-China) could not be performed for blood loss and transfusion because there was only 1 study in subgroup non-China. Such a subgroup
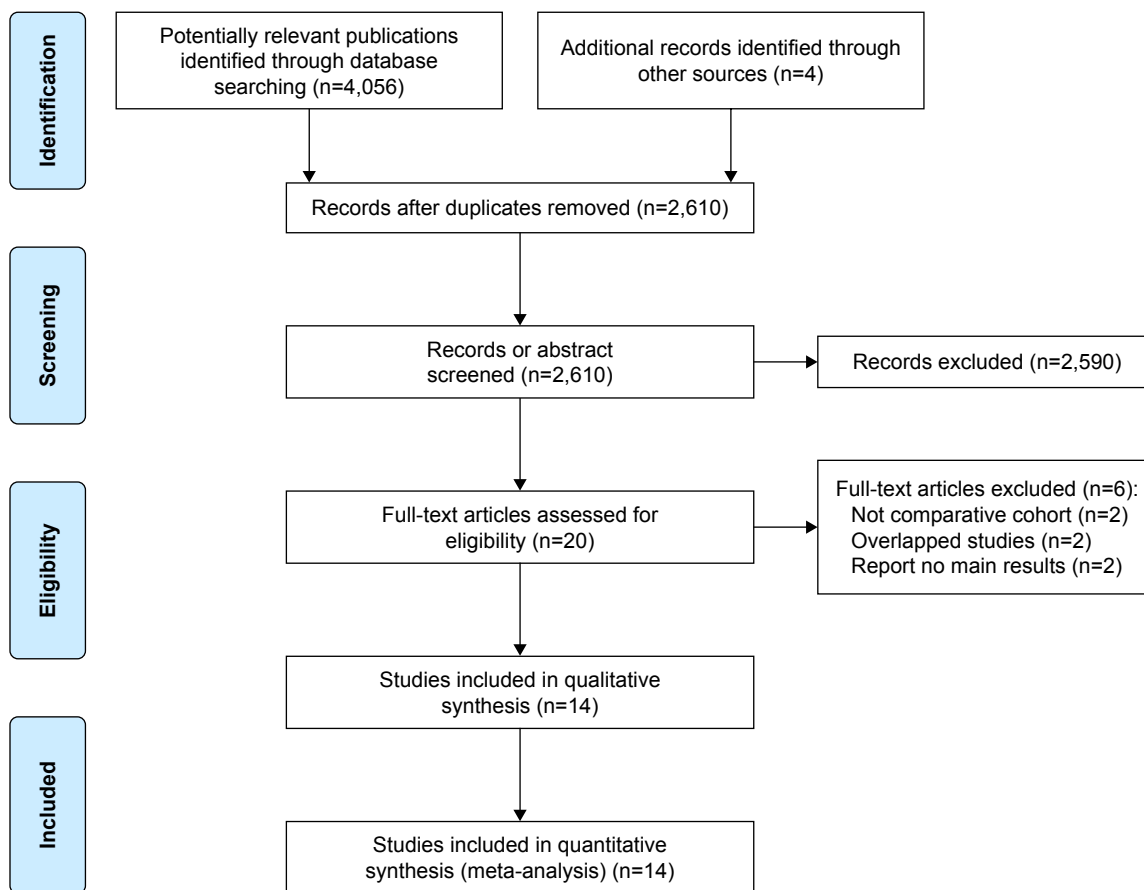
Figure 1 PRISMA 2009 flow diagram.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

analysis performed for lymph nodes retrieved showed that heterogeneity still existed in 2 groups. A RemL univariate meta-regression according to a country or publication year was performed to detect the potential origin of the heterogeneity of operating time, but neither of them was related to the heterogeneity statistically.

Postoperative data

Nine studies containing 2,439 patients reported the length of hospital stay. After pooled analysis, we found that MIME led to longer hospital stay (WMD =1.29, 95% CI =0.27–2.31, P=0.01). Four studies (1,496 cases) reported the length of intensive care unit (ICU) stay, and no significant difference between the 2 groups was found (WMD =–0.3, 95% CI =–1.28 to 0.67, P=0.54). We detected considerable heterogeneity for both postoperative outcome parameters (I^2>50%). We could only perform subgroup analysis according to a country (China/non-China) for length of hospital stay, and heterogeneity only existed in the China subgroup (I^2=88.0%).

Complications
Pulmonary and cardiac complications

Ten studies including 1,866 cases reported pulmonary complications, where 17.3% (177/1,026) were in the MIME group and 12.0% (101/840) were in the MILE group. There was evidence of reduced risk of pulmonary complications in the MILE group (OR =1.96, 95% CI =1.28–3.00, P=0.002). Five studies (824 cases) reported cardiac arrhythmia, and there was no significant difference between the MIME and MILE groups (OR =1.2, 95% CI =0.65–2.21, P=0.56). Moreover, no significant heterogeneity was found for pulmonary and cardiac complications.

Anastomotic leak

Thirteen studies including 2,457 cases reported the rates of anastomotic leak, where 12.9% (131/1,292) were in the MIME group and 5.7% (63/1,165) were in the MILE group; we found that MIME was associated with higher incidence of anastomotic leak than MILE (OR =2.55, 95% CI =1.40–4.63, P=0.002) after pooled analysis, as shown in Figure 2.

Table 1 Characteristics of included studies in this meta-analysis

Reference	Study interval	Cohort type	Country	Total cases	Number (MIME/MILE)	Gender (male) (MIME/MILE)	Location of cancer	Age (MIME/MILE)	AJCC staging 0, I, and II (MIME/MILE)	III and IV (MIME/MILE)	Anastomotic leak MIME	MILE	Mortality MIME	MIE
Luketich et al,[9] 2012	1996–2011	Retrospective	USA	1,011	481/530	392/415	All segments	65 (56–72)/64 (56–72)[a]	NA	NA	26/481	23/530	12	5
Brown et al,[10] 2017	2011–2016	Prospective	USA	110	61/49	51/40	All segments	63.0±8.7/60.9±9.0	41/26	20/23	5/61	2/49	1	3
Hao et al,[17] 2014	2008–2012	Retrospective	People's Republic of China	136	81/55	NA	All segments	NA	NA	NA	4/81	0	NA	NA
Nguyen et al,[18] 2008	1998–2007	Prospective	USA	98	47/51	39/33	All segments	65±10/64±12	NA	NA	3/47	5/51	2	1
Chen et al,[19] 2017	2014–2016	Prospective	People's Republic of China	251	51/200	38/169	All segments	61.4±9.1/59.9±8.4	29/110	22/99	4/51	1/200	1	0
Hou et al,[20] 2017	2014–2016	Retrospective	People's Republic of China	185	65/120	41/82	All segments	56.7±11.6/57.2±13.0	46/88	19/32	8/65	3/120	1	1
Zhai 2015[21]	2013–2015	Retrospective	People's Republic of China	72	40/32	37/28	Middle and low segments	60.0±6.9/60.0±9.1	31/27	9/5	12/40	3/32	NA	NA
Wu et al,[22] 2014	2011–2014	Retrospective	People's Republic of China	357	138/219	106/169	Middle and low segments	63.5±17.6/61.8±18.5	NA	NA	20/138	13/219	3	4
Lin et al,[23] 2014	2010–2014	Retrospective	People's Republic of China	288	185/103	142/80	Middle and low segments	58.3±8.7/59.1±8.4	89/65	96/38	24/185	2/103	1	0
Mei et al,[24] 2016	2012–2015	Retrospective	People's Republic of China	106	65/41	49/32	Middle and low segments	62.7±5.0/63.56±5.1	46/32	19/9	12/65	2/41	NA	NA
Wei 2016[25]	2013–2015	Retrospective	People's Republic of China	120	50/70	47/23	Middle and low segments	59.7±8.3/55.7±6.2	43/59	7/11	6/50	0/70	NA	NA
Rajan et al,[26] 2010	1997–2009	Retrospective	India	336	319/17	NA	All segments	NA	NA	NA	5/319	1/17	4	0
Schmidt et al,[27] 2017	2011–2016	Retrospective	Switzerland	334	146/188	NA	All segments	NA	NA	NA	25/146	26/188	2	1
Chang et al,[28] 2018	2015	Retrospective	People's Republic of China	53	33/20	NA	All segments	NA	NA	NA	4/33	4/20	1	0

Notes: Age (years) was reported mostly as the mean ± SD. [a]The study reported age as median (interquartile range). Mortality here means 30-day/in-hospital mortality.
Abbreviations: AJCC, American Joint Committee on Cancer; MILE, minimally invasive Ivor Lewis esophagectomy; MIME, minimally invasive McKeown esophagectomy; NA, not available.

Table 2 NOS for risk of bias assessment of studies included in the meta-analysis

Reference	Selection				Comparibility	Outcome			Overall
	Representative	Selection	Ascertainment of exposure	Demonstration		Outcome	Follow-up	Adequacy follow-up	
Luketich et al,[9] 2012	★	★	★	★	☆	★	★	★	7
Brown et al,[10] 2017	★	★	★	★	★	★	★	★	8
Hao et al,[17] 2014	★	☆	★	★	☆	★	★	★	6
Nguyen et al,[18] 2008	★	★	★	★	☆	★	★	★	7
Chen et al,[19] 2017	★	★	★	★	☆	★	★	★	7
Hou et al,[20] 2017	★	★	★	★	☆	★	★	★	7
Zhai 2015[21]	★	★	★	★	★	★	★	★	8
Wu et al,[22] 2014	★	★	★	★	☆	★	★	★	7
Lin et al,[23] 2014	★	★	★	★	☆	★	★	★	7
Mei et al,[24] 2016	★	★	★	★	☆	★	★	★	7
Wei 2016[25]	★	★	★	★	★	★	★	★	8
Rajan et al,[26] 2010	★	☆	★	★	☆	★	★	★	6
Schmidt et al,[27] 2017	★	★	★	★	★	★	★	★	8
Chang et al,[28] 2018	★	★	★	★	☆	★	★	★	7

Note: "★" means score one point, "☆" means score zero point.
Abbreviation: NOS, Newcastle–Ottawa Scale.

High heterogeneity was detected among studies (I^2=55.1%). A RemL univariate meta-regression according to a country or publication year was performed, and the result indicated that only country (China/non-China) was related to the heterogeneity (P=0.02), which could show 81.17% of between-study variance. In addition, we performed a sensitivity analysis, namely, the leave-one-out approach, by removing each study to compare the OR [95% CI] pooled from the remaining 12 studies with the overall OR [95% CI] to evaluate the stability of the result. As shown in Figure 3, the result was relatively stable.

Luketich et al[9] as well as Brown et al[10] reported an anastomotic leak that needed surgery (CD grade ≥3). These reports suggest that anastomotic leak requires surgical or endoscopic intervention,[29] so we pooled these data and found that the incidence of severe anastomotic leak was not significantly different (OR =1.28, 95% CI =0.73–2.24, P=0.39), as shown in Figure 4.

Other complications

It was also revealed that MIME was associated with higher incidence of vocal cord injury/palsy (OR =5.62, 95% CI =3.46–9.14, P=0.00), as shown in Figure 5, as well as a higher stricture rate (OR =2.07, 95% CI =1.05–4.07, P=0.04). On the other hand, there was no evidence of significantly different incidence of Chyle leak between the 2 groups (OR =1.42, 95% CI =0.54–3.69, P=0.48).

Mortality

Ten studies involving 3,034 cases addressed the 30-day/in-hospital mortality. The mortality risk was 1.8% (28/1,537) in the MIME group and 1.0% (15/1,497) in the MILE group. As shown in Figure 6, no statistically significant difference existed between the 2 groups (OR =1.76, 95% CI =0.92–3.36, P=0.08), with statistical homogeneity (I^2=0%). Additionally, 3 studies containing 499 cases reported 90-day mortality,[21,27,28] and no statistically significant difference was found between the 2 groups (OR =2.22, 95% CI =0.71–6.98, P=0.17), as shown in Figure 7.

Publication bias analysis

Publication bias was assessed by Egger's test. Significant statistical publication bias was detected with operating time,

Table 3 Difference between MIME and MILE

Variables	Number of studies	Pooled MIME	Data MILE	Data type	WMD/OR (95% CI)	Test for overall effect	Heterogeneity		Egger's test	Favors group
Age, years	10 (n=2,598)	–	–	Continuous	0.77 (−0.21, 1.75)	Z=1.54, P=0.12	P=0.209	I²=25.4%	P=0.947	None
Male sex	10 (n=2,598)	78.7% (931/1,183)	75.8% (1,073/1,415)	Binary	1.13 (0.93, 1.37)	Z=1.25, P=0.21	P=0.461	I²=0%	P=0.760	None
AJCC stage (0, I, and II)	7 (n=1,132)	62.8% (325/517)	66.8% (407/615)	Binary	0.87 (0.63, 1.22)	Z=0.80, P=0.42	P=0.220	I²=26.9%	P=0.460	None
Operating time (minutes)	10 (n=1,666)	–	–	Continuous	36.49 (7.12, 65.86)	Z=2.44, P=0.01	P=0	I²=98.5%	P=0.008	MILE
Blood loss (mL)	9 (n=1,613)	–	–	Continuous	16.9 (3.22, 30.58)	Z=2.42, P=0.02	P=0	I²=73.2%	P=0.175	MILE
Transfusion	4 (n=511)	11.1% (34/305)	6.8% (14/206)	Binary	1.25 (0.29, 5.38)	Z=0.30, P=0.76	P=0.015	I²=71.4%	–	None
Lymph nodes retrieved	7 (n=2,419)	–	–	Continuous	3.22 (−0.95, 7.40)	Z=1.51, P=0.130	P=0	I²=96.7%	P=0.120	None
R0 resection	4 (n=1,687)	97.5% (702/720)	94.0% (909/967)	Binary	1.34 (0.36, 5.02)	Z=0.43, P=0.67	P=0.015	I²=71.2%	–	None
Length of hospital stay (days)	9 (n=2,439)	–	–	Continuous	1.29 (0.27, 2.31)	Z=2.48, P=0.013	P=0	I²=88%	P=0.246	MILE
Length of ICU stay (days)	4 (n=1,496)	–	–	Continuous	−0.3 (−1.28, 0.67)	Z=0.61, P=0.542	P=0.002	I²=79.8%	–	None
Pulmonary	10 (n=1,866)	17.3% (177/1,026)	12.0% (101/840)	Binary	1.96 (1.28, 3.00)	Z=3.10, P=0.002	P=0.106	I²=37.9%	P=0.589	MILE
Cardiac arrhythmia	5 (n=824)	7.6% (29/381)	5.0% (22/443)	Binary	1.20 (0.65, 2.21)	Z=0.58, P=0.56	P=0.941	I²=0%	–	None
Anastomotic leak	13 (n=2,457)	12.9% (131/1,292)	5.7% (63/1,165)	Binary	2.55 (1.40, 4.63)	Z=3.06, P=0.002	P=0.008	I²=55.1%	P=0.100	MILE
Severe anastomotic leak	2 (n=1,121)	5.2% (28/542)	4.1% (24/579)	Binary	1.28 (0.73, 2.23)	Z=0.86, P=0.39	P=0.841	I²=0%	–	None
Vocal cord injury/palsy	10 (n=2,553)	9.2% (108/1,169)	1.4% (20/1,384)	Binary	5.62 (3.46, 9.14)	Z=6.96, P=0.0	P=0.825	I²=0%	P=0.017	MILE
Chyle leak	7 (n=1,000)	2.5% (12/485)	1.4% (7/515)	Binary	1.42 (0.54, 3.69)	Z=0.71, P=0.48	P=0.510	I²=0%	P=0.779	None
Stricture	9 (n=1,682)	8.3% (79/950)	6.0% (44/732)	Binary	2.07 (1.05, 4.07)	Z=2.10, P=0.04	P=0.043	I²=49.9%	P=0.976	MILE
30-day/in-hospital mortality	10 (n=3,034)	1.8% (28/1,537)	1.0% (15/1,497)	Binary	1.76 (0.92, 3.36)	Z=1.72, P=0.08	P=0.758	I²=0%	P=0.250	None
90-day mortality	3 (n=499)	3.7% (9/241)	1.6% (4/258)	Binary	2.22 (0.71, 6.98)	Z=1.36, P=0.17	P=0.990	I²=0.0%	–	None

Note: "–" means no data.
Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; ICU, intensive care unit; MILE, minimally invasive Ivor Lewis esophagectomy; MIME, minimally invasive McKeown esophagectomy; OR, odds ratio; WMD, weighted mean difference.
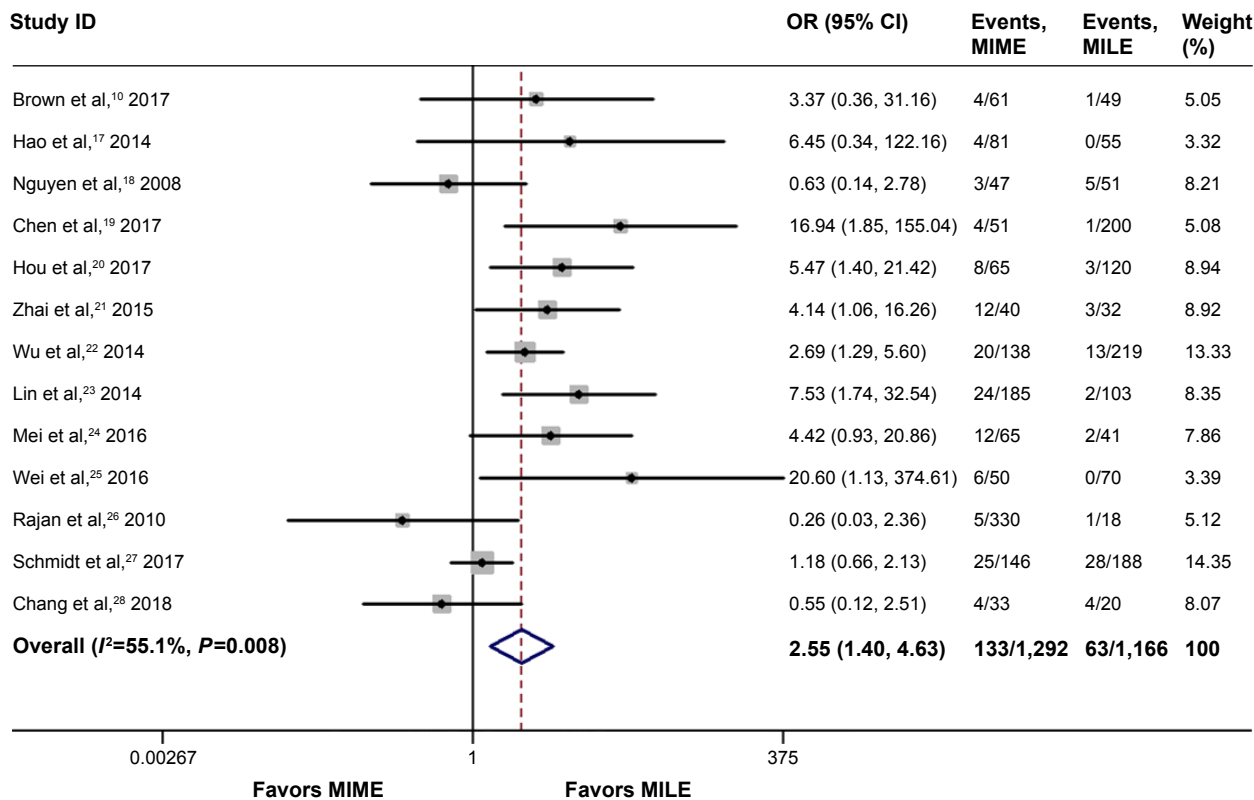
Study ID	OR (95% CI)	Events, MIME	Events, MILE	Weight (%)
Brown et al,[10] 2017	3.37 (0.36, 31.16)	4/61	1/49	5.05
Hao et al,[17] 2014	6.45 (0.34, 122.16)	4/81	0/55	3.32
Nguyen et al,[18] 2008	0.63 (0.14, 2.78)	3/47	5/51	8.21
Chen et al,[19] 2017	16.94 (1.85, 155.04)	4/51	1/200	5.08
Hou et al,[20] 2017	5.47 (1.40, 21.42)	8/65	3/120	8.94
Zhai et al,[21] 2015	4.14 (1.06, 16.26)	12/40	3/32	8.92
Wu et al,[22] 2014	2.69 (1.29, 5.60)	20/138	13/219	13.33
Lin et al,[23] 2014	7.53 (1.74, 32.54)	24/185	2/103	8.35
Mei et al,[24] 2016	4.42 (0.93, 20.86)	12/65	2/41	7.86
Wei et al,[25] 2016	20.60 (1.13, 374.61)	6/50	0/70	3.39
Rajan et al,[26] 2010	0.26 (0.03, 2.36)	5/330	1/18	5.12
Schmidt et al,[27] 2017	1.18 (0.66, 2.13)	25/146	28/188	14.35
Chang et al,[28] 2018	0.55 (0.12, 2.51)	4/33	4/20	8.07
Overall (I^2=55.1%, *P*=0.008)	**2.55 (1.40, 4.63)**	**133/1,292**	**63/1,166**	**100**

0.00267   1   375

Favors MIME   Favors MILE

Figure 2 Meta-analysis for anastomotic leak.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; MILE, minimally invasive Ivor Lewis esophagectomy; MIME, minimally invasive McKeown esophagectomy; OR, odds ratio.

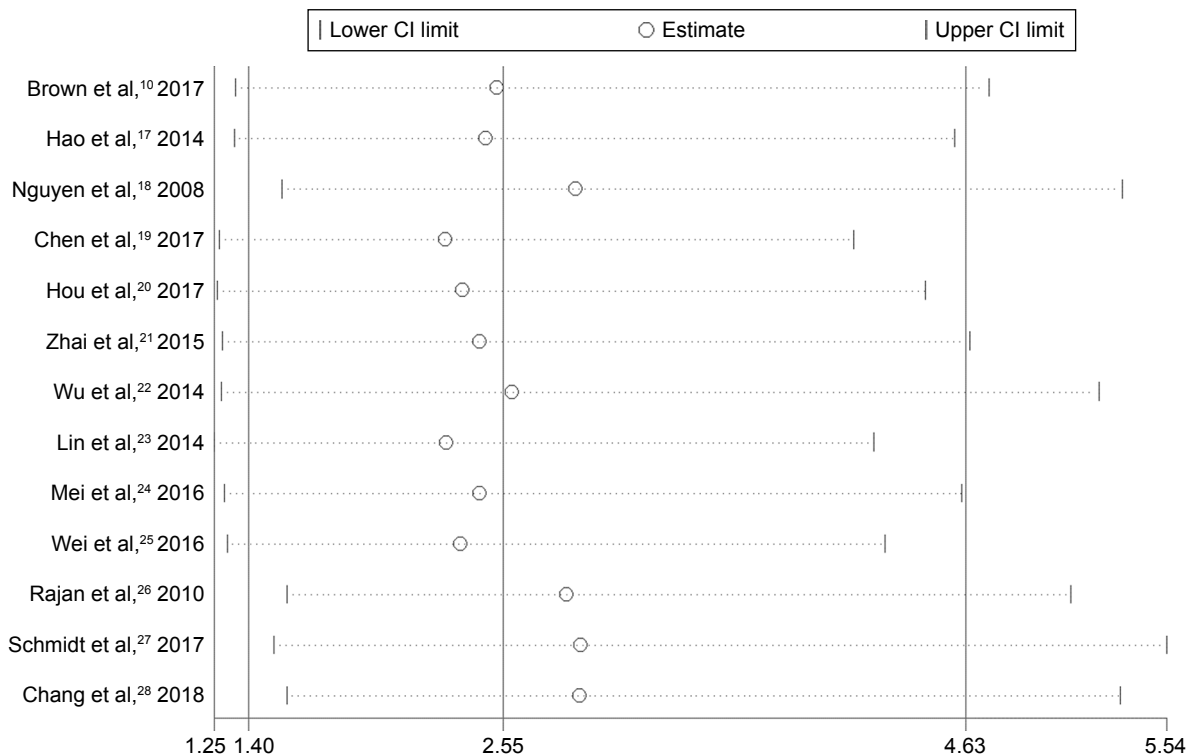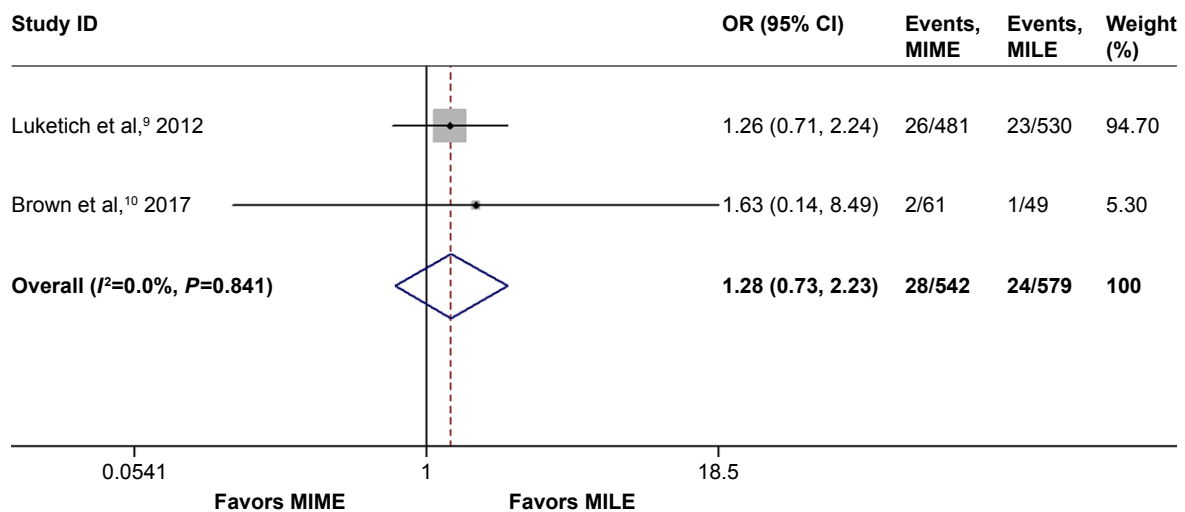## Meta-analysis estimates, given named study is omitted

| Lower CI limit   ○ Estimate | Upper CI limit

Brown et al,[10] 2017
Hao et al,[17] 2014
Nguyen et al,[18] 2008
Chen et al,[19] 2017
Hou et al,[20] 2017
Zhai et al,[21] 2015
Wu et al,[22] 2014
Lin et al,[23] 2014
Mei et al,[24] 2016
Wei et al,[25] 2016
Rajan et al,[26] 2010
Schmidt et al,[27] 2017
Chang et al,[28] 2018

1.25 1.40   2.55   4.63   5.54

Figure 3 Sensitivity analysis for anastomotic leak.
Abbreviation: CI, confidence interval.

Study ID		OR (95% CI)	Events, MIME	Events, MILE	Weight (%)
Luketich et al,[9] 2012		1.26 (0.71, 2.24)	26/481	23/530	94.70
Brown et al,[10] 2017		1.63 (0.14, 8.49)	2/61	1/49	5.30
Overall (*I²*=0.0%, *P*=0.841)		1.28 (0.73, 2.23)	28/542	24/579	100

0.0541   1   18.5

Favors MIME   Favors MILE

Figure 4 Meta-analysis for severe anastomotic leak.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; MILE, minimally invasive Ivor Lewis esophagectomy; MIME, minimally invasive McKeown esophagectomy; OR, odds ratio.

anastomotic leak, and vocal cord injury/palsy. The trim-and-fill computation was carried out to estimate the effect of publication bias on the result, which indicated the result was consistent and stable.

Discussion

MILE with an intrathoracic anastomosis has become increasingly prevalent and feasible because of increasing cases of adenocarcinoma located in the distal esophagus.[10] In addition, MILE was associated with lower incidence of recurrent laryngeal nerve injury and induces anastomotic leak, stricture, and swallowing dysfunction at lower rates in comparison with MIME.[9,10] However, it should be noted that the results for these complications were inconsistent and MILE is not appropriate for patients with esophageal tumors located above the carina, because it might compromise
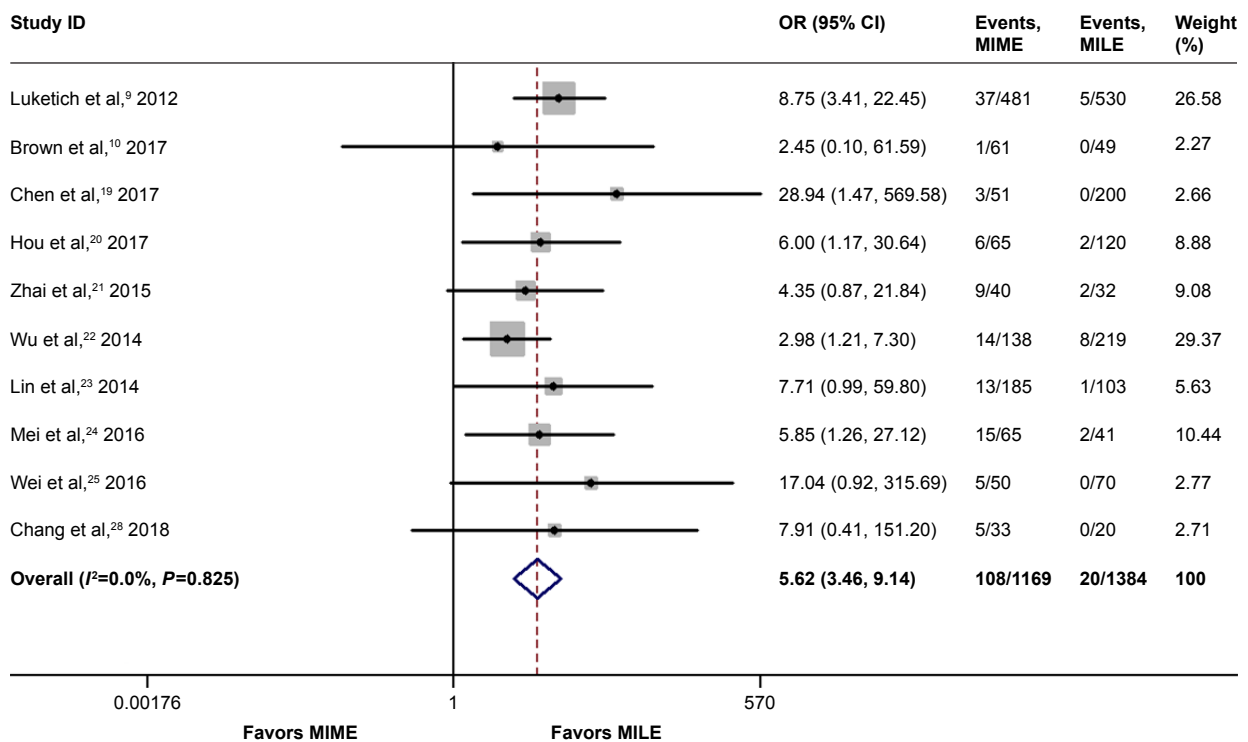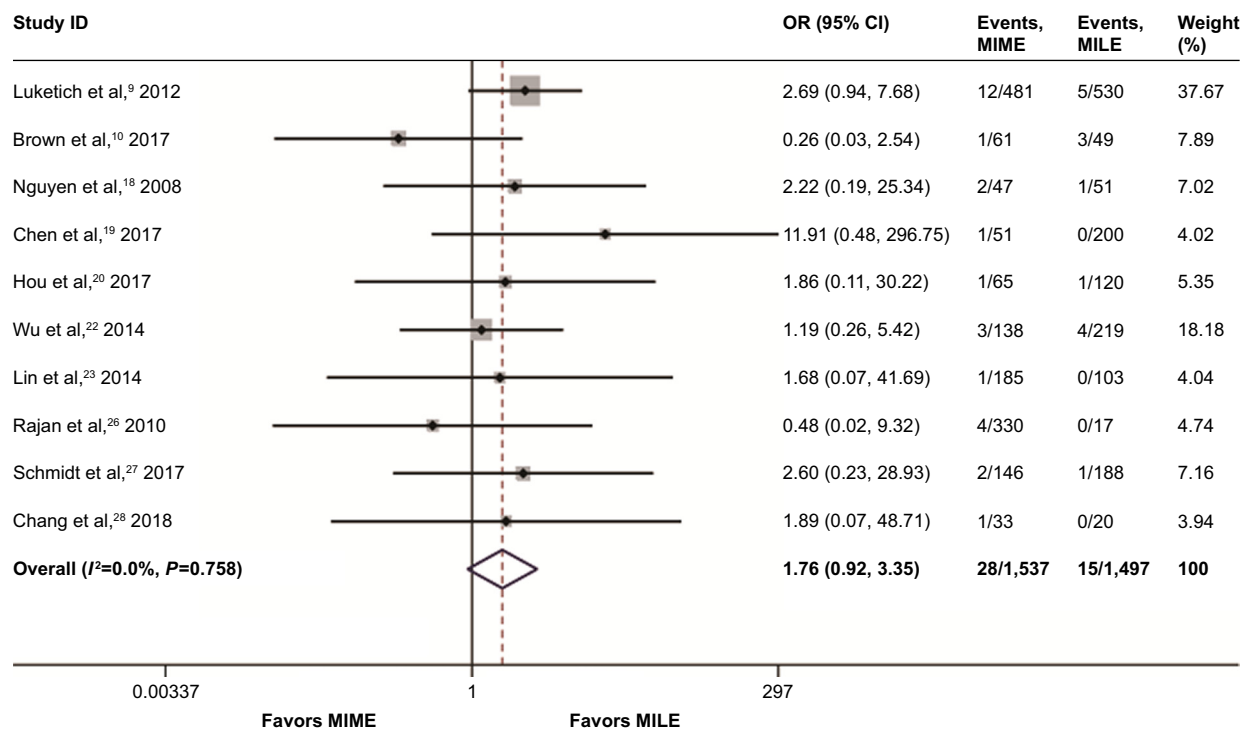
Study ID		OR (95% CI)	Events, MIME	Events, MILE	Weight (%)
Luketich et al,[9] 2012		8.75 (3.41, 22.45)	37/481	5/530	26.58
Brown et al,[10] 2017		2.45 (0.10, 61.59)	1/61	0/49	2.27
Chen et al,[19] 2017		28.94 (1.47, 569.58)	3/51	0/200	2.66
Hou et al,[20] 2017		6.00 (1.17, 30.64)	6/65	2/120	8.88
Zhai et al,[21] 2015		4.35 (0.87, 21.84)	9/40	2/32	9.08
Wu et al,[22] 2014		2.98 (1.21, 7.30)	14/138	8/219	29.37
Lin et al,[23] 2014		7.71 (0.99, 59.80)	13/185	1/103	5.63
Mei et al,[24] 2016		5.85 (1.26, 27.12)	15/65	2/41	10.44
Wei et al,[25] 2016		17.04 (0.92, 315.69)	5/50	0/70	2.77
Chang et al,[28] 2018		7.91 (0.41, 151.20)	5/33	0/20	2.71
Overall (*I²*=0.0%, *P*=0.825)		5.62 (3.46, 9.14)	108/1169	20/1384	100

0.00176   1   570

Favors MIME   Favors MILE

Figure 5 Meta-analysis for vocal cord injury/palsy.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; MILE, minimally invasive Ivor Lewis esophagectomy; MIME, minimally invasive McKeown esophagectomy; OR, odds ratio.

Study ID		OR (95% CI)	Events, MIME	Events, MILE	Weight (%)
Luketich et al,[9] 2012		2.69 (0.94, 7.68)	12/481	5/530	37.67
Brown et al,[10] 2017		0.26 (0.03, 2.54)	1/61	3/49	7.89
Nguyen et al,[18] 2008		2.22 (0.19, 25.34)	2/47	1/51	7.02
Chen et al,[19] 2017		11.91 (0.48, 296.75)	1/51	0/200	4.02
Hou et al,[20] 2017		1.86 (0.11, 30.22)	1/65	1/120	5.35
Wu et al,[22] 2014		1.19 (0.26, 5.42)	3/138	4/219	18.18
Lin et al,[23] 2014		1.68 (0.07, 41.69)	1/185	0/103	4.04
Rajan et al,[26] 2010		0.48 (0.02, 9.32)	4/330	0/17	4.74
Schmidt et al,[27] 2017		2.60 (0.23, 28.93)	2/146	1/188	7.16
Chang et al,[28] 2018		1.89 (0.07, 48.71)	1/33	0/20	3.94
Overall (I^2=0.0%, P=0.758)		1.76 (0.92, 3.35)	28/1,537	15/1,497	100

0.00337   1   297

Favors MIME   **Favors MILE**

Figure 6 Meta-analysis for 30-day/in-hospital mortality.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; MILE, minimally invasive Ivor Lewis esophagectomy; MIME, minimally invasive McKeown esophagectomy; OR, odds ratio.

adequate resection margins.[8] Potential advantages of MIME mainly include improved lymph node dissection and a more proximal resection margin.[19] Additionally, MIME adopts cervical anastomosis, which is less technically challenging, and if an anastomotic leak occurs, it can be managed more easily than an intrathoracic leak.[8] Therefore, it has caused a

controversy about which one is preferred for patients with resectable esophageal or junctional cancer.

In the present study, we found that MIME was associated with higher rates of anastomotic leak, stricture, and pulmonary complication, and longer operating time than MILE, which were different from the findings of a previous

Study ID		OR (95% CI)	Events, MIME	Events, MIME	Weight (%)
Zhai et al,[21] 2015		2.49 (0.25, 24.72)	3/62	1/50	24.94
Schmidt et al,[27] 2017		2.19 (0.51, 9.30)	5/146	3/188	62.62
Chang et al,[28] 2018		1.89 (0.07, 48.71)	1/33	0/20	12.45
Overall (I^2=0.0%, P=0.990)		2.22 (0.71, 6.98)	9/241	4/258	100

0.0205   1   48.7

Favors MIME   **Favors MILE**
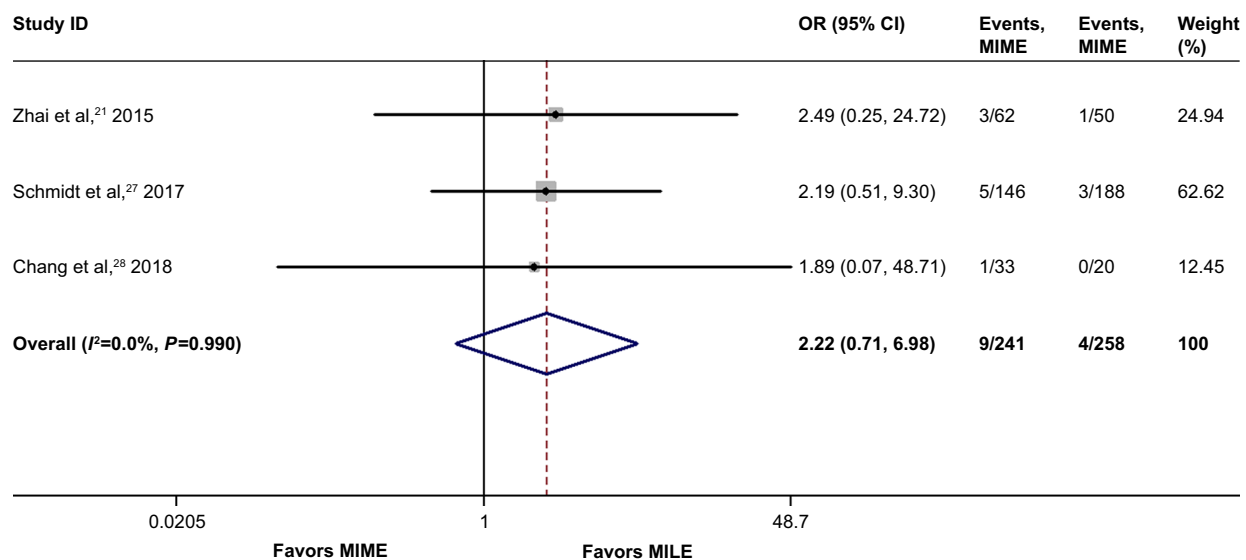
Figure 7 Meta-analysis for 90-day mortality.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; MILE, minimally invasive Ivor Lewis esophagectomy; MIME, minimally invasive McKeown esophagectomy; OR, odds ratio.

meta-analysis.[8] Furthermore, like the previous meta-analysis, we also found that MIME had higher incidence of vocal cord injury/palsy, more blood loss, longer length of hospital stay, equal number of lymph nodes retrieved, and similar ICU stay, similar rates of transfusion, and 30-day/in-hospital mortality compared with MILE. In addition, to our best knowledge, this is the first meta-analysis that reported similar rates of R0 resection, 90-day mortality, severe anastomotic leak, Chyle leak, and cardiac arrhythmia between the 2 procedures.

Because of performing an esophagogastrostomy through the third incision in the left neck, the MIME procedure will take a longer operative time and cause more blood loss. However, similar blood transfusion rates and ICU stay periods between the 2 groups was observed; transfusion of blood products in oncologic surgery is often used to determine the quality of the surgery.[30] Because the number of cases included to make a pooled analysis was not large enough (n=511), we could not conclude whether the 2 procedures are identical in terms of surgical quality.

The oncologic efficacy was evaluated in this review. No difference in total lymph nodes retrieved during surgery and R0 resection rate between the 2 procedures was detected. This may be because most of the included studies adopted standard 2-field lymphadenectomy, including the left gastric and celiac nodes in patients' abdomen, as well as the periesophageal and subcarinal nodes in the chest of patients.[10] In addition, MILE was performed only in the cases of esophageal cancer where clear margins can be obtained after preoperative evaluation. Combined with cautious preoperative evaluation with the clear surgical exposure provided by thoracoscopy and laparoscopy, MILE may have an equal oncologic efficacy as MIME.

After esophagectomy, anastomotic leakage is one of the most severe complications.[31] Our findings showed that the MILE procedure caused less anastomotic leak than MIME, which differs from the result of the previous meta-analysis.[8] This may be mainly due to the fact that MILE is able to remove the potentially ischemic gastric tip and reduce the tension at the anastomosis; thus, anastomosis can be created with a better vascularization and a lower level of the gastric tube, facilitating healing of intrathoracic anastomosis.[19,32] In contrast, MIME requires a longer gastric tube for cervical anastomosis, which demands more vascular supply and causes higher tension and potential ischemic gastric tip existed at a higher rate at the anastomosis; also, there was oppression of thoracic outlet on the gastric tube leading to a poorly vascularized anastomosis in the neck.[21] Two previous systematic reviews also reported that cervical anastomosis was associated with a higher rate of anastomotic leak.[33,34] Significant heterogeneity was detected among studies, and meta-regression analysis found that country (China and non-China) was related to the heterogeneity. This might be because the China subgroup included 5 studies that compared MIME and MILE among esophageal cancers located in the middle and low segments. This may also be a factor that partly resulted from different anastomotic leakage between the 2 procedures. Hence, sensitivity analysis indicated that this result was stable. In addition, the 2 procedures were found to be associated with similar incidence of severe anastomotic leakage, probably because cervical leakages are easier to treat to prevent the deterioration of the leakage condition, despite higher rates in the MIME group.[8] On the contrary, once the intrathoracic leakages occurs in MILE, it is much more difficult to deal with.

The incidence of anastomotic strictures was also higher in the MIME group, just as van Workum et al[32] reported, it may also be caused by relatively more ischemia of the tip of the gastric tube in MIME. The 2 procedures induced chylothorax at similar rates. We found that MIME was associated with higher incidence of vocal cord injury/palsy; this may be explained by the fact that the MIME procedure necessitates a cervical dissection close to recurrent laryngeal nerve, so it is easier to cause nerve injury.[8] Recurrent laryngeal nerve injury may result in aspiration and cough reflex disorders, and so MIME procedure causes more pulmonary complications.[21] In addition, the 2 procedures had an equal rate of cardiac arrhythmia. Taken together, MIME was associated with higher incidence of total anastomotic leakage, stricture, vocal cord injury/palsy, and pulmonary complications, and as a result, MIME led to longer duration of hospital stay.

Despite the higher complications caused by MIME, a similar 30-day/in-hospital mortality was observed in the 2 groups, which is in concordance with the 2 latest studies.[27,32] This may partly be explained by our previous result that the 2 procedures had similar incidence of causing severe anastomotic leakage. Walters et al[35] suggested that 90-day mortality may provide a better understanding on true death risk for the surgery and patient. Here, the 90-day mortality between MIME and MILE was not significantly different. Therefore, MIME and MILE are comparable with respect to clinical safety.

Compared with the previous meta-analysis in methodology,[8] our study included a larger number of cases (3,468 vs 1,681) and made a more comprehensive and rational comparison of short-term outcomes between minimally invasive McKeown and Ivor Lewis esophagectomy for

esophageal or junctional cancer. In addition, we compared the preoperative parameters, including age, sex, and stage of the disease, and found that the 2 groups were comparable in terms of these parameters, which could increase the comparability between MIME and MILE procedures in this meta-analysis. It is worth noting that in this meta-analysis, we were not able to make a pooled analysis of other important baseline factors such as comorbidity, neoadjuvant therapy, pathology type, locations of tumors, body mass index, and smoking, all of which have been identified as risks factors for the anastomotic leak,[36,37] because only few of included studies reported these parameters or because of the fact that these parameters were recorded in very different ways. This prevented us from getting a more comprehensive understanding of the comparability between the 2 groups.

There are some limitations in this meta-analysis. Some of them are as follows: 1) No randomized controlled trials were found and included in this meta-analysis; most of studies we included were retrospective cohorts, which are often subjected to considerable selection bias. 2) Definitions of outcome parameters and certain surgical details were often heterogeneous among the studies in this meta-analysis. The Esophagectomy Complications Consensus Group has proposed standardized definitions for complications after esophagectomy, which will standardize the definitions of complications in future studies.[30]

Overall, the present evidence indicated that MILE was associated with improved outcomes in terms of anastomotic leak, stricture, vocal cord injury/palsy, pulmonary complications, blood loss, and duration of hospital stay, but the 2 procedures had similar rates of 30-day/in-hospital and 90-day mortality, severe anastomotic leak, and oncologic efficacy. Many surgeons think that the MILE approach is only suitable for tumors located up to 5 cm distal of the carina, so that MILE can achieve similar oncologic efficacy as MIME does.[38] Therefore, we may conclude that the 2 procedures are comparable with respect to perioperative safety. MILE may be a better option when oncologically and clinically suitable, and MIME is still a safe alternative procedure when clinically indicated.

Conclusion

In conclusion, the present meta-analysis suggests that MIME and MILE are comparable with respect to clinical safety. MILE may be a better option when oncologically and clinically suitable, and MIME is still a safe alternative procedure when clinically indicated; however, these findings are at risk for bias, and so randomized controlled trials are needed to validate or correct them.

Author contribution

Jianqing Deng, Qingqing Su, and Xiangyang Chu conceived and designed the study. Jianqing Deng, Qingqing Su, Zhipeng Ren, and Jiaxin Wen helped with the collection and assembly of data. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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