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ORIGINAL RESEARCH

Minimally invasive esophagectomy versus open esophagectomy for esophageal cancer: a meta-analysis

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Background and objectives: The safety and effectiveness of minimally invasive esophagectomy (MIE) in comparison with the open esophagectomy (OE) remain uncertain in esophageal cancer treatment. The purpose of this meta-analysis is to compare the outcomes of the two surgical modalities.

Methods: Searches were conducted in MEDLINE, EMBASE, and ClinicalTrials.gov with the following index words: "esophageal cancer", "VATS", "MIE", "thoracoscopic esophagectomy", and "open esophagectomy" for relative studies that compared the effects between MIE and OE. Random-effect models were used, and heterogeneity was assessed.

Results: A total of 20 studies were included in the analysis, consisting of four randomized controlled trials and 16 prospective studies. MIE has reduced operative blood loss (P=0.0009) but increased operation time (P=0.009) in comparison with OE. Patients get less respiratory complications (risk ratio =0.74, 95% CI =0.58–0.94, P=0.01) and better overall survival (hazard ratio =0.54, 95% CI =0.42–0.70, $P<0.00001$) in the MIE group than the OE group. No statistical difference was observed between the two groups in terms of lymph node harvest, R0 resection, and other major complications.

Conclusion: MIE is a better choice for esophageal cancer because patients undergoing MIE may benefit from reduced blood loss, less respiratory complications, and also improved overall survival condition compared with OE. However, more randomized controlled trials are still needed to verify these differences.

Keywords: thoracoscopic esophagectomy, laparoscopic esophagectomy, postoperative prognosis

Introduction

Esophageal cancer is one of the most common malignant tumors of the digestive system that has a poor prognosis.[1] Surgery remains to be the primary treatment for esophageal cancer; however, the open esophagectomy (OE) is a relatively high invasive surgery, which may lead to several morbidities and prominent mortality as well.[2] As a supplement to the traditional open surgery, minimally invasive esophagectomy (MIE) was first introduced to treat esophageal cancer ~20 years ago.[3] With the developing skills and increasing experiences in laparoscopy and thoracoscopy in thoracic and stomach surgery, MIE has become a frequent choice for esophageal cancer nowadays. Minimally invasive surgery is assumed to reduce surgical injury on the one hand and improve patients' prognosis on the other. Guo et al[4] had conducted a prospective randomized study and their results indicated that MIE had some short-term benefits such as less hemorrhage, better recovery, and fewer complications but no difference in long-term

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survival rate in comparison with open surgery. A recently randomized trial conducted by Maas et al[5] suggests that MIE is associated with a better one-year quality of life compared with OE. Both studies were performed based on a small sample size, so that more evidences are needed to prove that MIE is an applicable alternative from which patients can gain more benefits compared with the open surgery. Several relevant meta-analyses had been performed to evaluate the safety and effectiveness of the two surgeries, while most of them were based on retrospective studies. Therefore, this meta-analysis was conducted through only randomized controlled trials and prospective studies in order to clarify whether MIE could improve the short-term outcomes and overall survival of patients with esophageal cancer.

Methods

Data sources and literature search strategy

Literature review was conducted by two investigators (LL and YCR) through online data sources MEDLINE, EMBASE, and ClinicalTrials.gov (up to Jan 2016), using the search terms "esophageal cancer", "VATS", "MIE", "thoracoscopic esophagectomy", "laparoscopic esophagectomy", and "Open esophagectomy".

Study selection

Inclusion criteria were: 1) randomized controlled trials or prospective studies; 2) patients who underwent esophagectomy for esophageal cancer; 3) comparing MIE with OE on interest outcomes such as surgical results, postoperative complications, and survival rate; 4) research of human beings; and 5) written in English language.

Study quality assessment

The quality of the studies was assessed by The Newcastle-Ottawa quality assessment Scale (NOS), and the total score of each study should not be <6, which is considered as high quality and eligible for the research.

Data extraction

The data on characteristics of studies, surgical outcomes, postoperative complications, and overall survival were extracted from the selected studies by one author (LL) and checked by another author (XXW). Information included are study name, publication year, study design, number of patients, interventions, age, sex, tumor stage, tumor location, pathology, operative time, operation blood loss, numbers of lymph node harvest, R0 resection, reoperation, in-hospital mortality, respiratory complications, cardiovascular complications, anastomotic leakage, anastomotic stricture, chylothorax recurrent laryngeal paralysis, and overall survival.

Statistical analysis

Review Manager Version 5.3 was used to perform meta-analysis, and the estimated survival data were obtained from the Kaplan–Meier curves using GetData Graph Digitizer software. The data can be synthesized only when the number of studies exceeds two. Measurement data reported as mean ± SD were adopted, and odds ratio (OR) or risk ratio (RR) was calculated. Pooled weighted mean difference (WMD) was used in enumeration data and hazard ratio in survival data. All the statistical results use random-effect models. Heterogeneity was assessed by χ^2 and I^2 and publication bias by funnel plots. The subgroup analysis was performed based on the study design.

Results

Eligible studies and characteristics of studies

In this meta-analysis, 20 studies were included, four randomized controlled trials and 16 prospective studies (Figure 1). A total of 6,025 patients were joined into research, of whom 2,091(35%) underwent MIE and 3,934 (65%) underwent OE. The characteristics of the studies are shown in Table 1.

Meta-analysis of postoperative outcomes

Surgical outcomes

MIE group has lower operative blood loss (WMD = –283.61, 95% CI =–451.69 to –115.52, P=0.0009; Figure 2A) and longer operation time (WMD =44.42, 95% CI =10.95–77.88, P=0.009; Figure 2B) than the OE group. There are no statistical significances of lymph node harvest (WMD =–0.80, 95% CI =–4.63–3.03, P=0.68; Figure 2C), R0 resection (RR =1.03, 95% CI =0.98–1.08, P=0.21; Figure 2D) between the two groups.

Postoperative complications

Patients in the MIE group get less respiratory complications than in the OE group (RR =0.74, 95% CI =0.58–0.94, P=0.01) and in the randomized-controlled trial (RCT) studies subgroup (RR =0.34, 95% CI =0.21–0.53, P=0.01, P<0.00001), while in the prospective studies subgroup (RR =0.83, 95% CI =0.67–1.04, P=0.11; Figure 3). There are no statistical significances of anastomotic leakage (OR=0.84, 95% CI =0.59–1.18, P=0.32; Figure 4), anastomotic stricture (OR =1.76, 95% CI =0.78–3.97, P=0.18; Figure 5A), in-hospital mortality (OR =0.84, 95% CI =0.60–1.19, P=0.33;

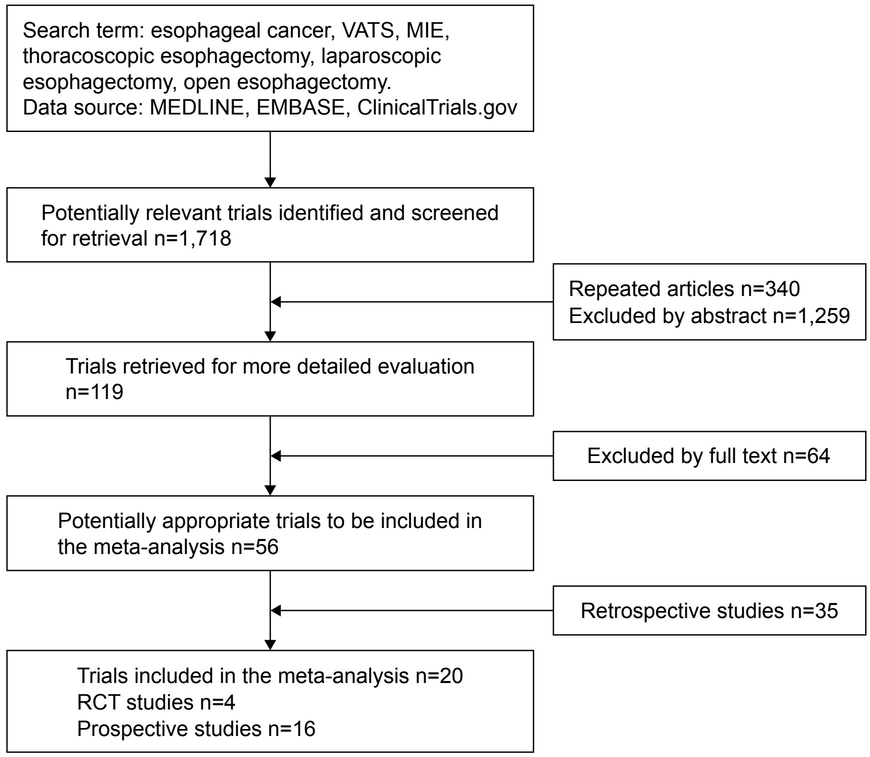


Figure 1 Stages of the systematic review of the trials.
Abbreviations: MIE, minimally invasive esophagectomy; RCT, randomized controlled trial.

Figure 5B), reoperation (OR =1.10, 95% CI =0.59–2.04, *P*=0.77; Figure 5C), cardiovascular complications (OR =0.90, 95% CI =0.64–1.28, *P*=0.57; Figure 6A), chylothorax (OR =0.90, 95% CI =0.47–1.74, *P*=0.76; Figure 6B), and recurrent laryngeal paralysis (OR =1.31, 95% CI =0.67–2.55, *P*=0.43; Figure 6C) between the two groups.

Survival outcome

The MIE group has a better overall survival than the open group (hazard ratio =0.54, 95% CI =0.42–0.70, $P<0.00001$; Figure 7).

All outcomes of interest are listed in Table 2, and the funnel plots display the publication bias of respiratory complications (Figure 8A), cardiovascular complications (Figure 8B), in-hospital mortality (Figure 8C), and anastomotic leakage (Figure 8D).

Discussion

The MIE was first introduced in 1980s, and the study of Cuschieri et al[3] indicated that MIE was as effective as open surgery. In the last 20 years, with the sophisticated technique of thoracoscope and laparoscope, minimally invasive surgery shows significant superiority in reducing surgical injury and increasing survival rate in thoracic and abdominal operations.[6,7] Now, MIE has been used more and more frequently in esophageal cancer, as it has been considered as a good method to reduce the high morbidity and mortality compared with the traditional OE. There are two major operation methods of MIE, including combined thoracoscopic–laparoscopic esophagectomy, which is also known as total MIE and thoracoscopic-assisted esophagectomy or laparoscopic-assisted esophagectomy – the so-called hybrid MIE. This study compared the open surgery with both hybrid MIE and total MIE. Due to the complexity of the esophagectomy, different surgery modalities might lead to various surgical complications, but the main morbidities are pulmonary complications, cardiac complications, anastomotic complications, and so forth. Therefore, the focus was on comparing the postoperative outcomes as mentioned earlier.

The studies about the comparison of the two surgeries are primarily retrospective studies as most of the clinical trials that are registered in ClinicalTrials.gov are still unfinished. So far, only four randomized studies have done their jobs and that is the reason why the majority of the existed meta-analyses were based on retrospective studies. Among those meta-analyses that had been done before us: Sgourakis et al[8] compared postoperative outcomes and survival between MIE and OE and revealed that both groups have the same

Table 1 Characteristics and demographics of included studies

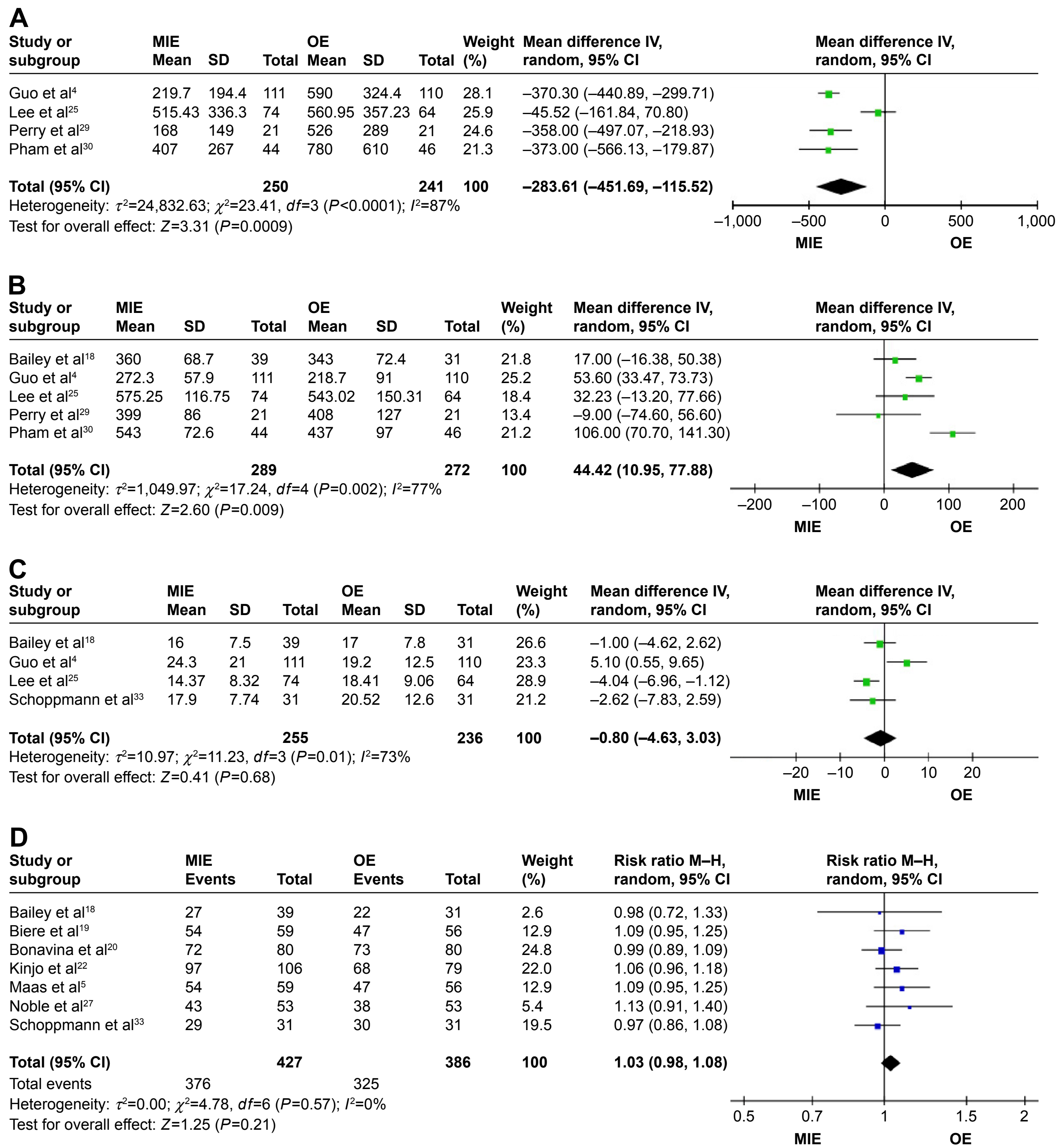
Study	Year	Country/district	Design	NOS score	Intervention	Cases	Age, years median (IQ range) and mean ± SD	Sex (m/f)	TNM stage (0/I/II/III/IV)	Pathology (adeno/spuam/other)
Bailey et al[18]	2013	UK	Prospective	7	Laparoscopically assisted esophagectomy	39	65 (37–78)	32/7	NA	31/6/2
					Open esophagectomy	31	62 (38–78)	27/4		27/3/1
Biere et al[19]	2012	the Netherlands	RCT	8	Minimally invasive esophagectomy	59	62 (34–75)	43/16	1/4/26/11/4/9	24/35/0
					Open esophagectomy	56	62 (42–75)	46/10	0/4/22/14/5/7	36/19/1
Bonavina et al[20]	2015	Italy	Prospective	6	Thoracoscopic-prone esophagectomy	80	61.5 (53–70)	46/34	0/25/25/23/7	9/68/3
					Hybrid Ivor Lewis	80	63.5 (55.4–68.5)	71/9	0/15/22/31/12	63/15/2
Guo et al[4]	2013	People's Republic of China	RCT	8	Thoracoscopy combined laparoscopy	111	57.3±11.8	68/43	0/24/7/80/0	NA
					Open transthoracic esophagectomy	110	60.8±12.4	72/38	0/31/5/74/0	
Hamouda et al[21]	2010	UK	Prospective	7	Laparoscopic of Ivor-Lewis esophagectomy	26	62	25/1	NA	21/4/1
					Open Ivor Lewis esophagectomy	24	60	23/1		21/3/0
Kinjo et al[22]	2012	Japan	Prospective	7	Thoracoscopic–laparoscopic esophagectomy	72	62.7±7.4	58/14	0/21/26/16/9	0/71/1
					Thoracoscopic esophagectomy	34	64.2±8.8	29/5	0/11/7/9/7	3/31/0
					Open esophagectomy	79	63.3±8.6	70/9	0/18/27/20/14	3/71/5
Kothari et al[23]	2011	India	Prospective	7	Minimally invasive surgery	34	NA	NA	NA	NA
					Ivor Lewis esophagectomy	28				
Law et al[24]	1997	Hong Kong	Prospective	6	Thoracoscopy	18	66 (43–80)	13/5	1/1/3/13/0	NA
					Thoracotomy	63	63 (36–84)	55/8	0/4/11/45/3	
Lee et al[25]	2011	Taiwan	Prospective	7	Total minimally invasive esophagectomy	30	59.73±10.32	30/0	2/3/11/12/2	1/29/0
					Hybrid minimally invasive esophagectomy	44	59.70±11.17	43/1	12/13/14/5/1	1/43/0
					Open esophagectomy	64	56.58±11.60	61/3	7/17/25/14/1	5/59/0
Maas et al[26]	2014	the Netherlands	RCT	8	Minimally invasive esophagectomy	14	65 (56–75)	10/4	NA	13/1/0
					Open esophagectomy	13	62 (52–74)	12/1		11/2/0
Maas et al[5]	2015	the Netherlands	RCT	8	Minimally invasive esophagectomy	59	62 (34–75)	43/16	1/4/26/11/4	35/24/0
					Open esophagectomy	56	62 (42–75)	46/10	0/4/22/14/5	36/19/1
Noble et al[27]	2013	UK	Prospective	7	Minimally invasive esophagectomy	53	66 (45–85)	43/10	NA	47/4/1
					Ivor Lewis esophagectomy	53	64 (36–81)	45/8		48/3/0
Parameswaran et al[28]	2013	UK	Prospective	7	Total minimally invasive esophagectomy	36	64 (45–84)	24/12	6/6/13/10/0	22/8/5
					Laparoscopic-assisted esophagectomy	31	67 (48–79)	23/8	1/5/12/13/0	27/3/0
					Open esophagectomy	19	64 (51–77)	15/4	0/0/8/11/0	16/3/0
Perry et al[29]	2009	USA	Prospective	6	Laparoscopic inversion esophagectomy	21	69±8	18/3	NA	NA
					Open transhiatal esophagectomy	21	61±9	17/4		
Pham et al[30]	2010	USA	Prospective	7	Thoracoscopic–laparoscopic esophagectomy	44	63±8.6	41/3	0/6/14/18/2	34/8/0
					Ivor Lewis esophagectomy	46	61±10.7	33/13	0/7/13/18/1	34/6/2

Safranek et al[31]	2010	UK	Prospective	6	Total minimally invasive esophagectomy	41	64 (41–74)	25/16	2/7/17/15/0	23/17/1
					Hybrid minimally invasive esophagectomy	34	63 (44–76)	28/6	2/2/14/16/0	29/3/2
					Open esophagectomy	46	60 (44–77)	38/8	0/6/11/29/0	43/3/0
Scarpa et al[32]	2015	Italy	Prospective	7	Hybrid minimally invasive esophagectomy	34	62 (52–70)	25/9	11/5/13/5/0	24/10/0
					Open esophagectomy	34	64 (56–70)	27/7	5/6/18/4/1	24/10/0
Schoppmann et al[33]	2010	Austria	Prospective	7	Minimally invasive esophagectomy	31	61.5 (35.7–74.8)	6/25	0/9/9/11/0	17/14/0
					Open esophagectomy	31	58.6 (33.7–76.8)	10/21	0/3/16/11/0	12/19/0
Sihag et al[34]	2015	USA	Prospective	6	Minimally invasive esophagectomy	814	63.3±10.7	658/156	NA	NA
					Open esophagectomy	2,966	63.2±10.2	2,492/474		
Smithers et al[35]	2007	Australia	Prospective	6	Total minimally invasive esophagectomy	23	61 (38–77)	20/3	1/3/5/10/0	16/3/4
					Thoracoscopic-assisted esophagectomy	309	64 (27–85)	248/61	21/66/96/100/8	199/74/18
					Open esophagectomy	114	62.5 (29–81)	104/10	2/6/28/73/2	100/7/4

Abbreviations: m/f, male/female; NOS, Newcastle-Ottawa quality assessment Scale; RCT, randomized controlled trial; IQ, interquartile; SD, standard deviation; TNM, tumor node metastasis; NA, not available.

in-hospital results and prognosis; Nagpal et al[9] analyzed postoperative outcomes, including the 30-day mortality and anastomotic leakage of MIE and OE and revealed that there was no significant difference in the mortality; Zhou et al[10,11] compared anastomotic leakage and in-hospital mortality between the two groups, and the outcome showed that MIE has superiority over OE as the former could reduce the in-hospital mortality rate; however, there was no evidence that MIE could decrease the anastomotic leakage; and Guo et al[12] indicated that MIE can achieve significant long-term survival rates and reduce perioperative complications.

In this study, only randomized trials and prospective studies were included, totally 20 studies were pooled to compare the outcomes between MIE and OE. Though Xiong et al[13] had done a similar work before us, they included only three RCTs and two prospective studies. Therefore, our evidence is more sufficient and reliable. The results showed that MIE had advantage in reducing the operative blood loss, but the outcome has great heterogeneity (I^2=87%) that may be attributable to the following reasons: first, there are various approaches in both MIE and OE, and the surgery styles vary from one operation team to another as well. Second, most of the studies use the median ± interquartile range, instead of mean ± SD, which is unavailable to run meta-analysis, that in turn influences the result of synthesis. Patients undergoing MIE get less respiratory complications than OE. In order to figure out the source of its heterogeneity (I^2=67%) we did a subgroup analysis. The heterogeneity is much more significant in the subgroup of prospective studies (I^2=57%) than that in the prospective studies (I^2=0%), and it suggests that the study design is the main cause of heterogeneity. Respiratory morbidities, especially pulmonary complications, which are the most important factors, could impact the prognosis of the patients. A lot of patients get dysfunctions of respiratory system after esophagectomy.[14–17] The reasons that MIE can reduce respiratory complications might be as follows: first, the exquisite operation procedure could decrease the surgical trauma and do less harm to the chest wall or pulmonary tissues. Next, less surgical injury can free the patients from the pain followed by and postoperative pain makes patients less willing to cough, which aggravates the pulmonary infection. The results demonstrated that there are no statistical differences with respect to number of lymph nodes harvest, R0 resection, reoperation, in-hospital mortality, cardiovascular complications, anastomotic leakage, anastomotic stricture, chylothorax, and recurrent laryngeal paralysis between the two groups, but the MIE group has a better overall survival than the open group. The reason could be explained by the



A

Study or subgroup	MIE Mean	MIE SD	MIE Total	OE Mean	OE SD	OE Total	Weight (%)	Mean difference IV, random, 95% CI
Guo et al[4]	219.7	194.4	111	590	324.4	110	28.1	–370.30 (–440.89, –299.71)
Lee et al[25]	515.43	336.3	74	560.95	357.23	64	25.9	–45.52 (–161.84, 70.80)
Perry et al[29]	168	149	21	526	289	21	24.6	–358.00 (–497.07, –218.93)
Pham et al[30]	407	267	44	780	610	46	21.3	–373.00 (–566.13, –179.87)
Total (95% CI)			**250**			**241**	**100**	**–283.61 (–451.69, –115.52)**

Heterogeneity: τ^2=24,832.63; χ^2=23.41, *df*=3 (*P*<0.0001); I^2=87%
Test for overall effect: *Z*=3.31 (*P*=0.0009)

B

Study or subgroup	MIE Mean	MIE SD	MIE Total	OE Mean	OE SD	OE Total	Weight (%)	Mean difference IV, random, 95% CI
Bailey et al[18]	360	68.7	39	343	72.4	31	21.8	17.00 (–16.38, 50.38)
Guo et al[4]	272.3	57.9	111	218.7	91	110	25.2	53.60 (33.47, 73.73)
Lee et al[25]	575.25	116.75	74	543.02	150.31	64	18.4	32.23 (–13.20, 77.66)
Perry et al[29]	399	86	21	408	127	21	13.4	–9.00 (–74.60, 56.60)
Pham et al[30]	543	72.6	44	437	97	46	21.2	106.00 (70.70, 141.30)
Total (95% CI)			**289**			**272**	**100**	**44.42 (10.95, 77.88)**

Heterogeneity: τ^2=1,049.97; χ^2=17.24, *df*=4 (*P*=0.002); I^2=77%
Test for overall effect: *Z*=2.60 (*P*=0.009)

C

Study or subgroup	MIE Mean	MIE SD	MIE Total	OE Mean	OE SD	OE Total	Weight (%)	Mean difference IV, random, 95% CI
Bailey et al[18]	16	7.5	39	17	7.8	31	26.6	–1.00 (–4.62, 2.62)
Guo et al[4]	24.3	21	111	19.2	12.5	110	23.3	5.10 (0.55, 9.65)
Lee et al[25]	14.37	8.32	74	18.41	9.06	64	28.9	–4.04 (–6.96, –1.12)
Schoppmann et al[33]	17.9	7.74	31	20.52	12.6	31	21.2	–2.62 (–7.83, 2.59)
Total (95% CI)			**255**			**236**	**100**	**–0.80 (–4.63, 3.03)**

Heterogeneity: τ^2=10.97; χ^2=11.23, *df*=3 (*P*=0.01); I^2=73%
Test for overall effect: *Z*=0.41 (*P*=0.68)

D

Study or subgroup	MIE Events	MIE Total	OE Events	OE Total	Weight (%)	Risk ratio M–H, random, 95% CI
Bailey et al[18]	27	39	22	31	2.6	0.98 (0.72, 1.33)
Biere et al[19]	54	59	47	56	12.9	1.09 (0.95, 1.25)
Bonavina et al[20]	72	80	73	80	24.8	0.99 (0.89, 1.09)
Kinjo et al[22]	97	106	68	79	22.0	1.06 (0.96, 1.18)
Maas et al[5]	54	59	47	56	12.9	1.09 (0.95, 1.25)
Noble et al[27]	43	53	38	53	5.4	1.13 (0.91, 1.40)
Schoppmann et al[33]	29	31	30	31	19.5	0.97 (0.86, 1.08)
Total (95% CI)		**427**		**386**	**100**	**1.03 (0.98, 1.08)**
Total events	376		325			

Heterogeneity: τ^2=0.00; χ^2=4.78, *df*=6 (*P*=0.57); I^2=0%
Test for overall effect: *Z*=1.25 (*P*=0.21)

Figure 2 Forest plots of surgical outcomes.
Notes: (**A**) Forest plots of blood loss. (**B**) Forest plots of operation time. (**C**) Forest plots of number of lymph nodes harvest. (**D**) Forest plots of R0 resection.
Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; MIE, minimally invasive esophagectomy; OE, open esophagectomy.

amplification effect of the thoracoscope or laparoscope, through which the tumor tissues and relevant lymph nodes could be dissected more accurately; therefore, the MIE can get a better prognosis.

This study has also some limitations. In the first place, except for operation blood loss and operative time, there were significant heterogeneities in number of lymph nodes harvest, reoperation, and anastomotic stricture. The reasons resemble those explained in operation blood loss. In the second place, several included studies did not report the outcomes completely, yet access to the original data was unavailable. Finally, lack of large, multiple center, randomized-controlled trials might reduce the effectiveness of the research. Therefore, the work needs to be improved when there are more RCTs.

Study or subgroup	MIE Events	Total	OE Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
RCT studies						
Biere et al[19]	12	59	35	56	6.9	0.33 (0.19, 0.56)
Guo et al[4]	3	111	9	110	2.7	0.33 (0.09, 1.19)
Maas et al[26]	3	14	7	13	3.2	0.40 (0.13, 1.22)
Subtotal (95% CI)		**184**		**179**	**12.8**	**0.34 (0.21, 0.53)**
Total events	18		51			
Heterogeneity: τ^2=0.00; χ^2=0.10, *df*=2 (*P*=0.95); I^2=0%						
Test for overall effect: *Z*=4.66 (*P*<0.00001)						
Prospective studies						
Bailey et al[18]	15	39	18	31	7.4	0.66 (0.40, 1.09)
Bonavina et al[20]	11	80	9	80	4.8	1.22 (0.54, 2.79)
Hamouda et al[21]	7	26	5	24	3.8	1.29 (0.47, 3.53)
Kinjo et al[22]	35	106	36	79	8.6	0.72 (0.50, 1.04)
Kothari et al[23]	3	34	4	28	2.3	0.62 (0.15, 2.53)
Law et al[24]	4	18	15	63	3.9	0.93 (0.35, 2.46)
Lee et al[25]	11	74	20	64	6.0	0.48 (0.25, 0.92)
Noble et al[27]	19	53	14	53	6.7	1.36 (0.76, 2.41)
Parameswaran et al[28]	12	67	3	19	3.1	1.13 (0.36, 3.61)
Perry et al[29]	2	21	3	21	1.7	0.67 (0.12, 3.59)
Pham et al[30]	13	44	9	46	5.3	1.51 (0.72, 3.17)
Safranek et al[31]	19	75	13	46	6.4	0.90 (0.49, 1.64)
Scarpa et al[32]	3	34	5	34	2.5	0.60 (0.16, 2.31)
Schoppmann et al[33]	6	31	28	31	5.4	0.21 (0.10, 0.44)
Sihag et al[34]	230	814	762	2,966	10.4	1.10 (0.97, 1.25)
Smithers et al[35]	87	332	35	114	8.9	0.85 (0.61, 1.19)
Subtotal (95% CI)		**1,848**		**3,699**	**87.2**	**0.83 (0.67, 1.04)**
Total events	477		979			
Heterogeneity: τ^2=0.09; χ^2=34.77, *df*=15 (*P*=0.003); I^2=57%						
Test for overall effect: *Z*=1.61 (*P*=0.11)						
Total (95% CI)		**2,032**		**3,878**	**100**	**0.74 (0.58, 0.94)**
Total events	495		1,030			
Heterogeneity: τ^2=0.14; χ^2=54.62, *df*=18 (*P*<0.0001); I^2=67%						
Test for overall effect: *Z*=2.45 (*P*=0.01)						
Test for subgroup differences: χ^2=12.13, *df*=1 (*P*=0.0005); I^2=91.8%						

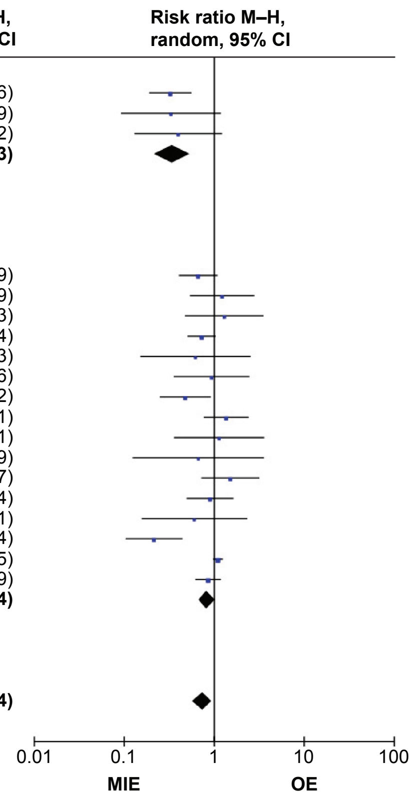


Figure 3 Forest plot of respiratory complications.

Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; MIE, minimally invasive esophagectomy; OE, open esophagectomy; RCT, randomized controlled trial.

Study or subgroup	MIE Events	Total	OE Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
RCT studies						
Biere et al[19]	7	59	4	56	5.7	1.75 (0.48, 6.34)
Guo et al[4]	1	111	2	110	1.9	0.49 (0.04, 5.49)
Maas et al[26]	3	14	1	13	1.9	3.27 (0.29, 36.31)
Subtotal (95% CI)		**184**		**179**	**9.6**	**1.56 (0.56, 4.35)**
Total events	11		7			
Heterogeneity: τ^2=0.00; χ^2=1.28, *df*=2 (*P*=0.53); I^2=0%						
Test for overall effect: *Z*=0.85 (*P*=0.40)						
Prospective studies						
Bonavina et al[20]	3	80	6	80	4.9	0.48 (0.12, 1.99)
Hamouda et al[21]	1	26	2	24	1.8	0.44 (0.04, 5.19)
Kinjo et al[22]	11	106	13	79	10.2	0.59 (0.25, 1.39)
Kothari et al[23]	4	34	3	28	4.1	1.11 (0.23, 5.44)
Law et al[24]	0	18	2	63	1.2	0.66 (0.03, 14.47)
Lee et al[25]	10	74	18	64	10.3	0.40 (0.17, 0.94)
Noble et al[27]	5	53	2	53	3.7	2.66 (0.49, 14.35)
Perry et al[29]	4	21	6	21	4.8	0.59 (0.14, 2.49)
Pham et al[30]	4	44	5	46	5.1	0.82 (0.21, 3.28)
Safranek et al[31]	11	75	1	46	2.5	7.73 (0.96, 62.05)
Scarpa et al[32]	4	34	2	34	3.4	2.13 (0.36, 12.51)
Schoppmann et al[33]	1	31	8	31	2.4	0.10 (0.01, 0.82)
Sihag et al[34]	107	814	366	2,966	25.0	1.08 (0.85, 1.35)
Smithers et al[35]	18	332	10	114	11.2	0.60 (0.27, 1.33)
Subtotal (95% CI)		**1,742**		**3,649**	**90.4**	**0.78 (0.53, 1.15)**
Total events	183		444			
Heterogeneity: τ^2=0.14; χ^2=19.78, *df*=13 (*P*=0.10); I^2=34%						
Test for overall effect: *Z*=1.27 (*P*=0.21)						
Total (95% CI)		**1,926**		**3,828**	**100**	**0.84 (0.59, 1.18)**
Total events	194		451			
Heterogeneity: τ^2=0.11; χ^2=21.96, *df*=16 (*P*=0.14); I^2=27%						
Test for overall effect: *Z*=1.00 (*P*=0.32)						
Test for subgroup differences: χ^2=1.53, *df*=1 (*P*=0.22); I^2=34.4%						

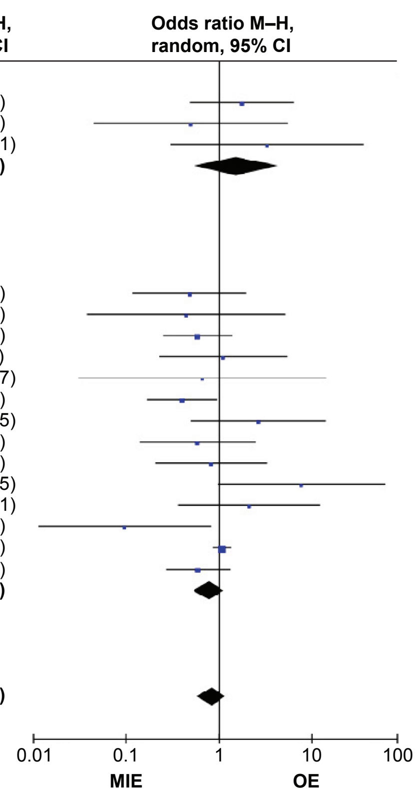


Figure 4 Forest plot of anastomotic leakage.

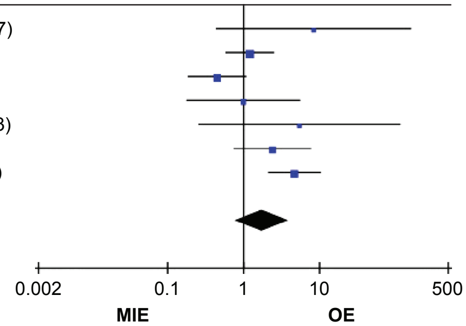
Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; MIE, minimally invasive esophagectomy; OE, open esophagectomy; RCT, randomized controlled trial.

A

Study or subgroup	MIE Events	MIE Total	OE Events	OE Total	Weight (%)	Odds ratio M–H, random, 95% CI
Kothari et al[23]	4	34	0	28	5.8	8.41 (0.43, 163.27)
Maas et al[5]	26	59	22	56	20.8	1.22 (0.58, 2.56)
Noble et al[27]	10	53	18	53	19.3	0.45 (0.19, 1.10)
Perry et al[29]	3	21	3	21	11.8	1.00 (0.18, 5.63)
Pham et al[30]	2	44	0	46	5.5	5.47 (0.26, 117.23)
Safranek et al[31]	14	75	4	46	16.5	2.41 (0.74, 7.83)
Smithers et al[35]	78	332	7	114	20.2	4.69 (2.10, 10.51)
Total (95% CI)		**618**		**364**	**100**	**1.76 (0.78, 3.97)**
Total events	137		54			

Heterogeneity: $\tau^2=0.69$; $\chi^2=18.02$, $df=6$ ($P=0.006$); $I^2=67\%$
Test for overall effect: $Z=1.35$ ($P=0.18$)

Odds ratio M–H, random, 95% CI

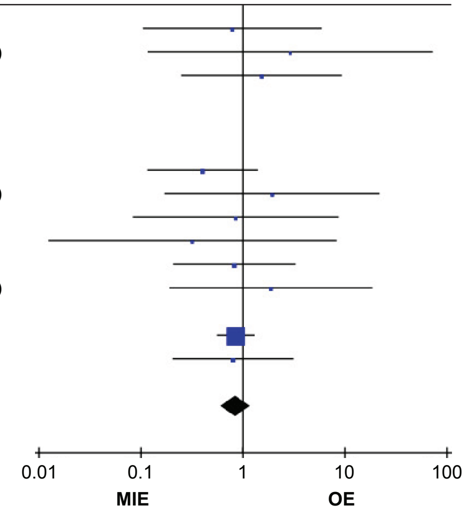


B

Study or subgroup	MIE Events	MIE Total	OE Events	OE Total	Weight (%)	Odds ratio M–H, random, 95% CI
Bailey et al[18]	2	39	2	31	2.9	0.78 (0.10, 5.90)
Biere et al[19]	1	59	0	56	1.1	2.90 (0.12, 72.62)
Bonavina et al[20]	3	80	2	80	3.6	1.52 (0.25, 9.35)
Hamouda et al[21]	0	26	0	24		Not estimable
Kinjo et al[22]	0	106	0	79		Not estimable
Law et al[24]	0	18	0	63		Not estimable
Lee et al[25]	4	74	8	64	7.5	0.40 (0.11, 1.40)
Maas et al[5]	2	59	1	56	2.0	1.93 (0.17, 21.90)
Parameswaran et al[28]	3	67	1	19	2.2	0.84 (0.08, 8.61)
Perry et al[29]	0	21	1	21	1.1	0.32 (0.01, 8.26)
Pham et al[30]	4	44	5	46	6.2	0.82 (0.21, 3.28)
Safranek et al[31]	3	75	1	46	2.2	1.88 (0.19, 18.58)
Schoppmann et al[33]	0	31	0	31		Not estimable
Sihag et al[34]	27	814	115	2,966	64.9	0.85 (0.56, 1.30)
Smithers et al[35]	7	332	3	114	6.3	0.80 (0.20, 3.13)
Total (95% CI)		**1,845**		**3,696**	**100**	**0.84 (0.60, 1.19)**
Total events	56		139			

Heterogeneity: $\tau^2=0.00$; $\chi^2=3.61$, $df=10$ ($P=0.96$); $I^2=0\%$
Test for overall effect: $Z=0.97$ ($P=0.33$)

Odds ratio M–H, random, 95% CI



C

Study or subgroup	MIE Events	MIE Total	OE Events	OE Total	Weight (%)	Odds ratio M–H, random, 95% CI
Bailey et al[18]	3	39	5	21	10.0	0.27 (0.06, 1.25)
Biere et al[19]	8	59	6	56	14.0	1.31 (0.42, 4.04)
Bonavina et al[20]	6	80	5	80	12.9	1.22 (0.36, 4.16)
Hamouda et al[21]	1	26	1	24	4.1	0.92 (0.05, 15.58)
Kinjo et al[22]	5	106	3	79	10.7	1.25 (0.29, 5.41)
Safranek et al[31]	9	75	3	46	11.6	1.95 (0.50, 7.63)
Schoppmann et al[33]	4	29	10	30	12.2	0.32 (0.09, 1.17)
Sihag et al[34]	77	814	131	2,966	24.6	2.26 (1.69, 3.03)
Total (95% CI)		**1,228**		**3,302**	**100**	**1.10 (0.59, 2.04)**
Total events	113		164			

Heterogeneity: $\tau^2=0.39$; $\chi^2=16.24$, $df=7$ ($P=0.02$); $I^2=57\%$
Test for overall effect: $Z=0.29$ ($P=0.77$)

Odds ratio M–H, random, 95% CI

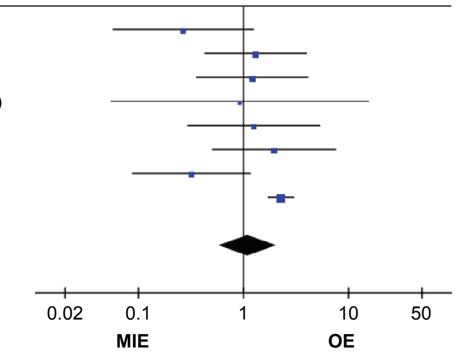
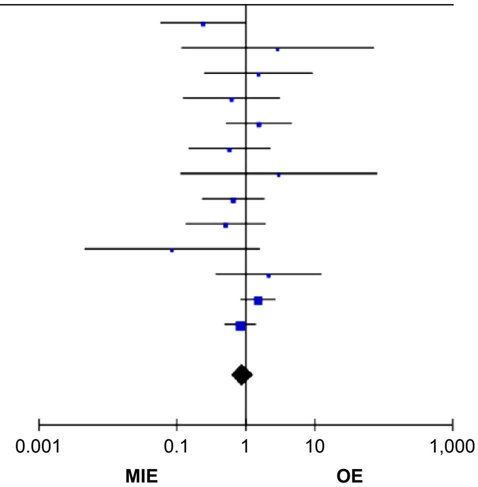


Figure 5 Forest plots of anastomotic stricture, in-hospital mortality, and reoperation.
Notes: (**A**) Forest plots of anastomotic stricture. (**B**) Forest plots of in-hospital mortality. (**C**) Forest plots of reoperation.
Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; MIE, minimally invasive esophagectomy; OE, open esophagectomy.

A

Study or subgroup	MIE Events	Total	OE Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Bailey et al[18]	3	39	8	31	5.5	0.24 (0.06, 1.00)
Biere et al[19]	1	59	0	56	1.2	2.90 (0.12, 72.62)
Bonavina et al[20]	3	80	2	80	3.5	1.52 (0.25, 9.35)
Hamouda et al[21]	3	26	4	23	4.4	0.62 (0.12, 3.12)
Kinjo et al[22]	10	106	5	79	8.6	1.54 (0.51, 4.70)
Law et al[24]	3	16	18	63	5.9	0.58 (0.15, 2.27)
Maas et al[26]	1	14	0	13	1.1	3.00 (0.11, 80.39)
Noble et al[27]	7	53	10	53	9.5	0.65 (0.23, 1.87)
Perry et al[29]	5	21	8	21	6.2	0.51 (0.13, 1.93)
Pham et al[30]	0	44	5	46	1.4	0.08 (0.00, 1.58)
Scarpa et al[32]	4	34	2	34	3.7	2.13 (0.36, 12.51)
Sihag et al[34]	16	814	39	2,966	22.9	1.50 (0.84, 2.71)
Smithers et al[35]	60	332	24	114	26.0	0.83 (0.49, 1.41)
Total (95% CI)		**1,638**		**3,579**	**100**	**0.90 (0.64, 1.28)**
Total events	116		125			

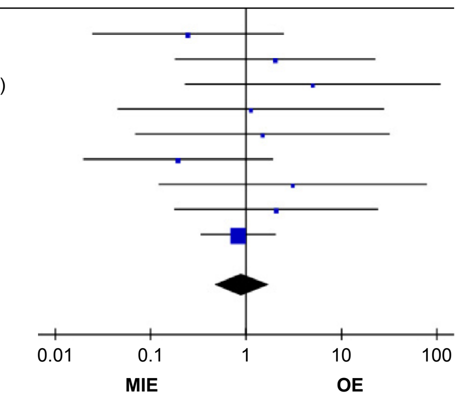
Heterogeneity: $\tau^2=0.05$; $\chi^2=13.70$, $df=12$ ($P=0.32$); $I^2=12\%$
Test for overall effect: $Z=0.56$ ($P=0.57$)



B

Study or subgroup	MIE Events	Total	OE Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Bailey et al[18]	1	39	3	31	8.0	0.25 (0.02, 2.49)
Bonavina et al[20]	2	80	1	80	7.3	2.03 (0.18, 22.80)
Hamouda et al[21]	2	26	0	24	4.5	5.00 (0.23, 109.62)
Kinjo et al[22]	1	106	0	39	4.1	1.12 (0.04, 28.15)
Parameswaran et al[28]	2	67	0	19	4.5	1.49 (0.07, 32.33)
Safranek et al[31]	1	75	3	46	8.2	0.19 (0.02, 1.92)
Scarpa et al[32]	1	34	0	34	4.1	3.09 (0.12, 78.55)
Schoppmann et al[33]	2	31	1	31	7.1	2.07 (0.18, 24.07)
Smithers et al[35]	17	332	7	114	52.1	0.82 (0.33, 2.04)
Total (95% CI)		**790**		**418**	**100**	**0.90 (0.47, 1.74)**
Total events	29		15			

Heterogeneity: $\tau^2=0.00$; $\chi^2=5.70$, $df=8$ ($P=0.68$); $I^2=0\%$
Test for overall effect: $Z=0.30$ ($P=0.76$)



C

Study or subgroup	MIE Events	Total	OE Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Guo et al[4]	0	111	1	110	4.2	0.33 (0.01, 8.12)
Kinjo et al[22]	17	72	18	79	57.2	1.05 (0.49, 2.23)
Law et al[24]	4	18	8	63	22.3	1.96 (0.52, 7.47)
Perry et al[29]	1	21	2	21	7.0	0.47 (0.04, 5.68)
Pham et al[30]	6	44	0	46	5.1	15.70 (0.86, 287.64)
Safranek et al[31]	1	41	0	46	4.2	3.44 (0.14, 86.92)
Total (95% CI)		**307**		**365**	**100**	**1.31 (0.67, 2.55)**
Total events	29		29			

Heterogeneity: $\tau^2=0.05$; $\chi^2=5.32$, $df=5$ ($P=0.38$); $I^2=6\%$
Test for overall effect: $Z=0.80$ ($P=0.43$)

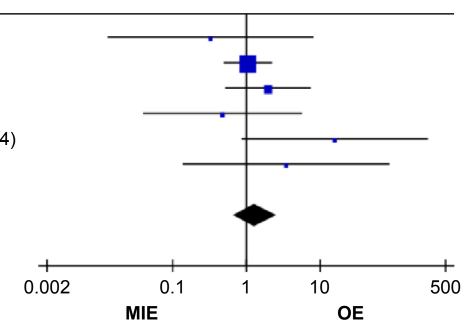


Figure 6 Forest plots of cardiovascular complications, chylothorax, and recurrent laryngeal paralysis.
Notes: (**A**) Forest plots of cardiovascular complications. (**B**) Forest plots of chylothorax. (**C**) Forest plots of recurrent laryngeal paralysis.
Abbreviations: CI, confidence interval; M–H, Mantel–Haenszel; MIE, minimally invasive esophagectomy; OE, open esophagectomy.

Study or subgroup	MIE Events	Total	OE Events	Total	O–E	Variance	Weight (%)	Hazard ratio exp ([O–E]/V), fixed, 95% CI
Schoppmann et al[33]	8	31	14	31	−0.17	0.67	1.2	0.78 (0.07, 8.51)
Noble et al[27]	20	53	25	53	−1.36	4.38	7.8	0.73 (0.29, 1.87)
Smithers et al[35]	166	309	84	114	−32.72	50.76	91.0	0.52 (0.40, 0.69)
Total (95% CI)		**393**		**198**			**100**	**0.54 (0.42, 0.70)**
Total events	194		123					

Heterogeneity: χ^2=0.54, *df*=2 (*P*=0.76); I^2=0%
Test for overall effect: *Z*=4.58 (*P*<0.00001)

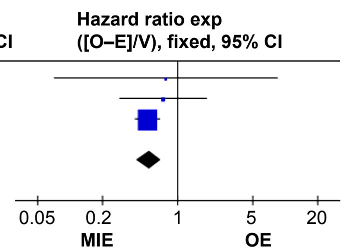


Figure 7 Forest plot of overall survival.
Abbreviations: CI, confidence interval; MIE, minimally invasive esophagectomy; OE, open esophagectomy.

Table 2 All outcomes of interest

Outcome	Number of studies	Cases	MD/RR/OR/HR	95% CI	Heterogeneity	Test for overall effect	Favors group
Operative blood loss	4	491	MD =–283.61	–451.69, –115.52	*P*<0.0001, I^2=87%	*Z*=3.31, *P*=0.0009	MIE
Operation time	5	561	MD =44.42	10.95, 77.88	*P*=0.002, I^2=77%	*Z*=2.60, *P*=0.009	OE
Number of lymph node harvest	4	491	MD =–0.80	–4.63, 3.03	*P*=0.01, I^2=73%	*Z*=0.41, *P*=0.68	None
R0 resection	7	813	RR =1.03	0.98, 1.08	*P*=0.57, I^2=0%	*Z*=1.25, *P*=0.21	None
Reoperation	8	4,530	OR =1.10	0.59, 2.04	*P*=0.02, I^2=57%	*Z*=0.29, *P*=0.77	None
In-hospital mortality	15	5,541	OR =0.84	0.60, 1.19	*P*=0.96, I^2=0%	*Z*=0.97, *P*=0.33	None
Respiratory complication	19	5,910	RR =0.74	0.58, 0.94	*P*<0.0001, I^2=67%	*Z*=2.45, *P*=0.01	MIE
Cardiovascular complication	13	5,217	OR =0.90	0.64, 1.28	*P*=0.32, I^2=12%	*Z*=0.56, *P*=0.57	None
Anastomotic leakage	17	5,754	OR =0.84	0.59, 1.18	*P*=0.14, I^2=27%	*Z*=1.00, *P*=0.32	None
Anastomotic stricture	7	982	OR =1.76	0.78, 3.97	*P*=0.0006, I^2=67%	*Z*=1.35, *P*=0.18	None
Chyle leakage	9	1,208	OR =0.90	0.47, 1.74	*P*=0.68, I^2=0%	*Z*=0.30, *P*=0.76	None
Recurrent laryngeal paralysis	6	672	OR =1.31	0.67, 2.55	*P*=0.38, I^2=6%	*Z*=0.80, *P*=0.43	None
Overall survival	3	591	HR =0.54	0.42, 0.70	*P*=0.76, I^2=0%	*Z*=4.58, *P*<0.00001	MIE

Abbreviations: CI, confidence interval; RR, relative ratio; OR, odds ratio; HR, hazard ratio; MD, mean difference; MIE, minimally invasive esophagectomy; OE, open esophagectomy.

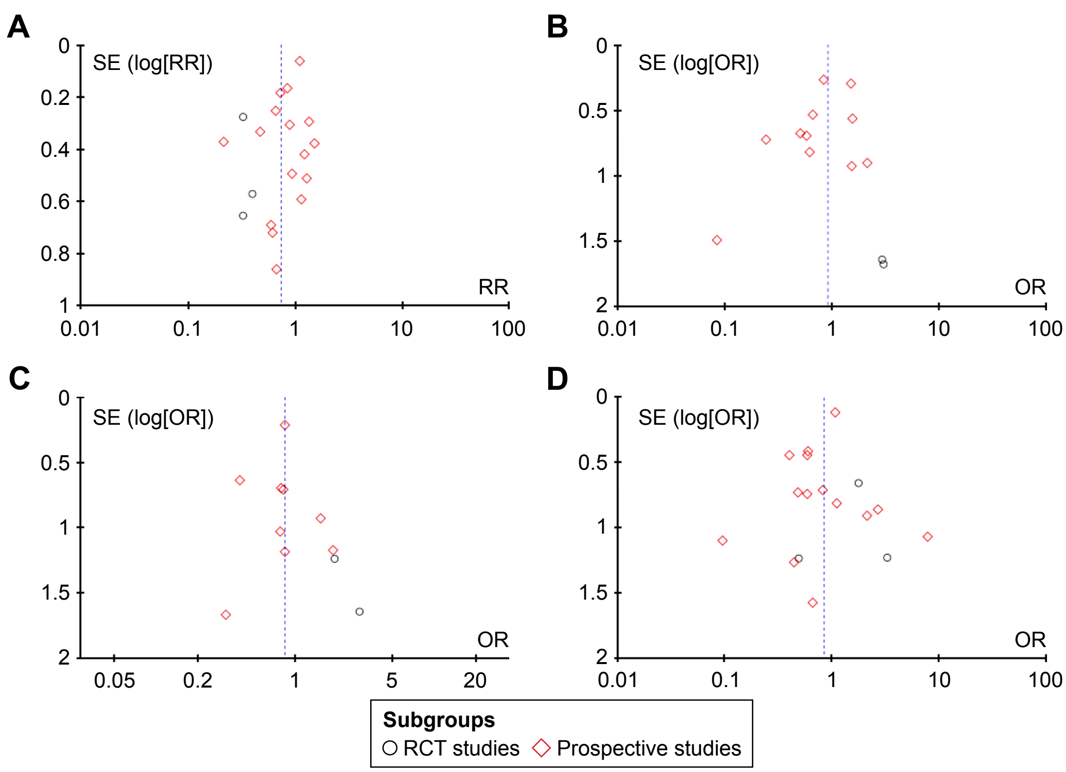


Figure 8 Funnel plots of postoperative complications.
Notes: (**A**) Funnel plots of respiratory complications. (**B**) Funnel plots of cardiovascular complications. (**C**) Funnel plots of in-hospital mortality. (**D**) Funnel plots of anastomotic leakage.
Abbreviations: OR, odds ratio; RR, relative ratio; RCT, randomized controlled trial; SE, standard error.

Conclusion

Patients who have undergone the MIE have lower blood loss and less respiratory complications in comparison with the OE. They can also gain the same benefits of postoperative outcomes composing lymph node harvest and margin of resection as the open group. The estimated overall survival rate is improved in the MIE group. That being said, MIE is a better choice for esophageal cancer patients.

Disclosure

The authors report no conflicts of interest in this work.

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