

RESEARCH ARTICLE

Superiority of Minimally Invasive Oesophagectomy in Reducing In-Hospital Mortality of Patients with Resectable Oesophageal Cancer: A Meta-Analysis

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Abstract

Background

Compared with open oesophagectomy (OE), minimally invasive oesophagectomy (MIO) proves to have benefits in reducing the risk of pulmonary complications for patients with resectable oesophageal cancer. However, it is unknown whether MIO has superiority in reducing the occurrence of in-hospital mortality (IHM).

Objective

The objective of this meta-analysis was to explore the effect of MIO vs. OE on the occurrence of in-hospital mortality (IHM).

Data Sources

Sources such as Medline (through December 31, 2014), Embase (through December 31, 2014), Wiley Online Library (through December 31, 2014), and the Cochrane Library (through December 31, 2014) were searched.

Study Selection

Data of randomized and non-randomized clinical trials related to MIO versus OE were included.

Interventions

Eligible studies were those that reported patients who underwent MIO procedure. The control group included patients undergoing conventional OE.

Study Appraisal and Synthesis Methods

Fixed or random -effects models were used to calculate summary odds ratios (ORs) or relative risks (RRs) for quantification of associations. Heterogeneity among studies was evaluated by using Cochran's Q and I^2 statistics.

Results

A total of 48 studies involving 14,311 cases of resectable oesophageal cancer were included in the meta-analysis. Compared to patients undergoing OE, patients undergoing MIO had statistically reduced occurrence of IHM (OR=0.69, 95%CI =0.55 -0.86). Patients undergoing MIO also had significantly reduced incidence of pulmonary complications (PCs) (RR=0.73, 95%CI = 0.63-0.86), pulmonary embolism (PE) (OR=0.71, 95%CI= 0.51-0.99) and arrhythmia (OR=0.79, 95%CI = 0.68-0.92). Non-significant reductions were observed among the included studies in the occurrence of anastomotic leak (AL) (OR=0.93, 95%CI =0.78-1.11), or Gastric Tip Necrosis (GTN) (OR=0.89, 95%CI =0.54-1.49).

Limitation

Most of the included studies were non-randomized case-control studies, with a diversity of study designs, demographics of participants and surgical intervention.

Conclusions

Minimally invasive oesophagectomy (MIO) has superiority over open oesophagectomy (OE) in terms of the occurrence of in-hospital mortality (IHM) and should be the first-choice surgical procedure in esophageal surgery.

Introduction

Surgical resections remain the mainstay of potentially curative treatment for resectable oesophageal cancer [1–6]. However, resections for esophageal cancer are invasive, and various surgical techniques for open oesophagectomy (OE) have been considered to have high mortality and morbidity rates [7]. Previous studies found that the occurrence of in-hospital mortality was between 1.2 and 8.8% [7–11], even as high as 29% [12]. Therefore, in-hospital mortality has often been considered as an outcome indicator for esophageal surgery and used to analyze and compare surgical outcomes among different medical centres [13]. Therefore, the exploration for measures to prevent in-hospital death and relevant factor are the hotter and more discussed issues in current studies of esophageal surgery, and any achievement in this aspect may have a deep impact on the clinical treatment of oesophageal cancer.

Minimally invasive oesophagectomy (MIO), first described in 1990s [14–16], has superiority in reducing the risk of postoperative morbidity without compromising oncological outcomes through avoiding thoracotomy and laparotomy [4, 17–20]. Theoretically, MIO has an advantage over OE in reduction the risk of IHM to a larger extent. Nevertheless, this theoretical assumption has never been subjected to empirical verification [20–33]. Instead, previous meta-analyses [22–33], relevant studies [4–6] and even randomized controlled trials [3] of available evidences have suggested a potential advantage of MIO in reducing the incidence of morbidity, rather than in reducing mortality.

Thus, at least two critical questions concerning esophageal surgery are of considerable interest and remain unanswered: i) does MIO have superiority in reducing the occurrence of IHM?; ii) what are the factors affecting the occurrence of IHM? These questions are important for both future research and current clinical practice. For this reason, we conducted a systematic review and meta-analysis to comprehensively assess the superiority of MIO in reducing the occurrence of IHM, with the aim to provide meaningful clues for esophageal surgery.

Methods

Data sources and searches

Medline (through December 31, 2014), Embase (through December 31, 2014), Wiley Online Library (through December 31, 2014), and the Cochrane Library, (through December 31, 2014) were searched, using the terms “Minimally invasive oesophagectomy, oesophageal cancer, oesophageal carcinoma, open oesophagectomy”. This review protocol was registered and published in the International Prospective Register of Systematic Reviews, PROSPERO (Registration No. CRD42014012901), following the prescribed steps [34]. This report complies with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [35–36].

Study Selection and Eligibility Criteria

Included studies had to meet the following criteria: i) research articles published in English; ii) randomized or non-randomized controlled studies with parallel controls; iii) studies comparing MIO with OE; iv) grey literature such as conference proceedings, reports and other peer-reviewed research.

Publications were excluded: i) if the outcomes of interest was not reported or it was impossible to calculate the outcomes from the published results; ii) if a distinct group of patients was not mentioned or the outcomes of interest were not compared; iii) if publications belong to systematic reviews or meta-analysis.

Data collection and Quality Assessment

All eligible studies were retrieved and evaluated by two independent reviewers. Disagreements on inclusion were discussed, if necessary, with the guidance of the corresponding authors of these studies via E-mail. If no response was received, a second E-mail was sent one week later.

To ascertain the validity of eligible studies, study quality was appraised in reference to the 12 items described in methodological index for non-randomized studies (MINORS) [37]. The total quality scores ranged from 0 (low quality) to 24 (high quality). Disagreement on study quality was resolved by discussion with corresponding authors of these studies via E-mail or personal interview.

Outcomes Definition

IHM was defined as hospital mortality, inpatient mortality, mortality within 30 days of hospitalization, in-patient death, death in hospital, or mortality. The broad definition of MIO was thoracoscopic/laparotomy assisted oesophagectomy, hybrid minimally invasive oesophagectomy and total thoracoscopic/ laparoscopic oesophagectomy, or minimally invasive oesophagectomy (MIE). Pulmonary complications were defined as respiratory complications, pulmonary infection, pneumonia, respiratory failure, adult respiratory distress syndrome, atelectasis, etc., but did not include adult respiratory distress syndrome. Arrhythmia was defined as atrial arrhythmia or atrial fibrillation.

Data synthesis and analysis

In-hospital mortality was the primary outcome measure, as it was considered an outcome indicator for esophageal surgery and has been used to analyze and compare surgical outcomes among different medical centres. Secondary outcome measures included pulmonary complications, pulmonary embolism, anastomotic leak, gastric tip necrosis, and arrhythmia, for the reason that they are underlying causes of in-hospital mortality. Fixed or random-effects models [38] were used in this meta-analysis. Forest plots were provided to illustrate pooled relative risks (RRs) or odds ratios (ORs), and corresponding 95% confidence intervals (CIs). The consistency of results (effect sizes) among studies was investigated by means of I^2 statistics [39]. When the heterogeneity test was statistically significant, a random effects model was used, otherwise, a fixed effects model was used. Heterogeneity was interpreted according to the thresholds outlined in the Cochrane Handbook: 0% to 40%- low heterogeneity, 30% to 60%- moderate heterogeneity, 50% to 90%-possible substantial heterogeneity, 75% to 100%- considerable heterogeneity. If the heterogeneity was high [40] ($I^2 > 50\%$ or $P < 0.10$), sensitivity analysis and subgroup analysis were performed to find out potential origin of heterogeneity.

Egger's test and Begg's funnel plot were used for diagnosis of potential publication bias [41]. In addition, the possible effect of publication bias in our meta-analysis was further assessed using Duval and Tweedie nonparametric "trim and fill" procedure [42]. This method considers the possibility of hypothetical "missing" studies that might exist, imputes their RRs, and recalculates a pooled RR that incorporates the hypothetical "missing" studies as though they actually existed.

All statistical processes were performed with Stata version 12.0 software (Stata Corp LP, College Station, TX, USA).

Results

Selected studies and methodological quality

The steps of our literature search are shown in Fig 1. A total 3,326 unique records were identified from the electronic databases. Of these, 1,075 records were excluded for duplicated ones, 2,175 records were excluded for meeting the exclusion criteria. After an initial screening of titles and abstracts, 76 potential articles were included for full-text view [3, 4, 6, 21–33, 43–102]. Twenty-eight articles were excluded after additional screening, with the reasons that: i) 12 studies were meta-analyses or systematic overviews [22–33]; ii) 14 studies did not compare the outcomes of interest [89–102]; iii) 2 studies were retrieved from the same registry [53,62] and contained an overlapping group of patients with the recent publications [75,78]. Thus, in total, 48 articles with 14,311 patients undergoing MIO versus OE were included in this systematic review and meta-analysis.

The evaluation results of the methodological quality of the studies are shown in Table 1. The quality scores of the included studies ranged from 16 to 20 (Table 1). None of the included studies performed a prospective calculation of the study size or an unbiased assessment of study outcomes. A randomized controlled design was done in only one study [4].

Characteristics of studies and patients

The 48 studies totaling in 14,311 patients included in this meta-analysis contained 4,509 (30.5%) cases undergoing MIO and 9,793 (69.5%) undergoing OE (Table 1). Of the 48 studies, only 1 was a randomized controlled trial (RCT) [4]. Eight studies [54,56,58,59,72,76,79,80,85] were done in the United Kingdom (UN), 8 in the USA [21,44,52,55,64,73,74,88], 11 in Japan [6,45,46,50,66,68,70,75,77,78,81], 7 in China [43,63,65,82,84,86, 87], 4 in Australia [3,57,60,67], 3

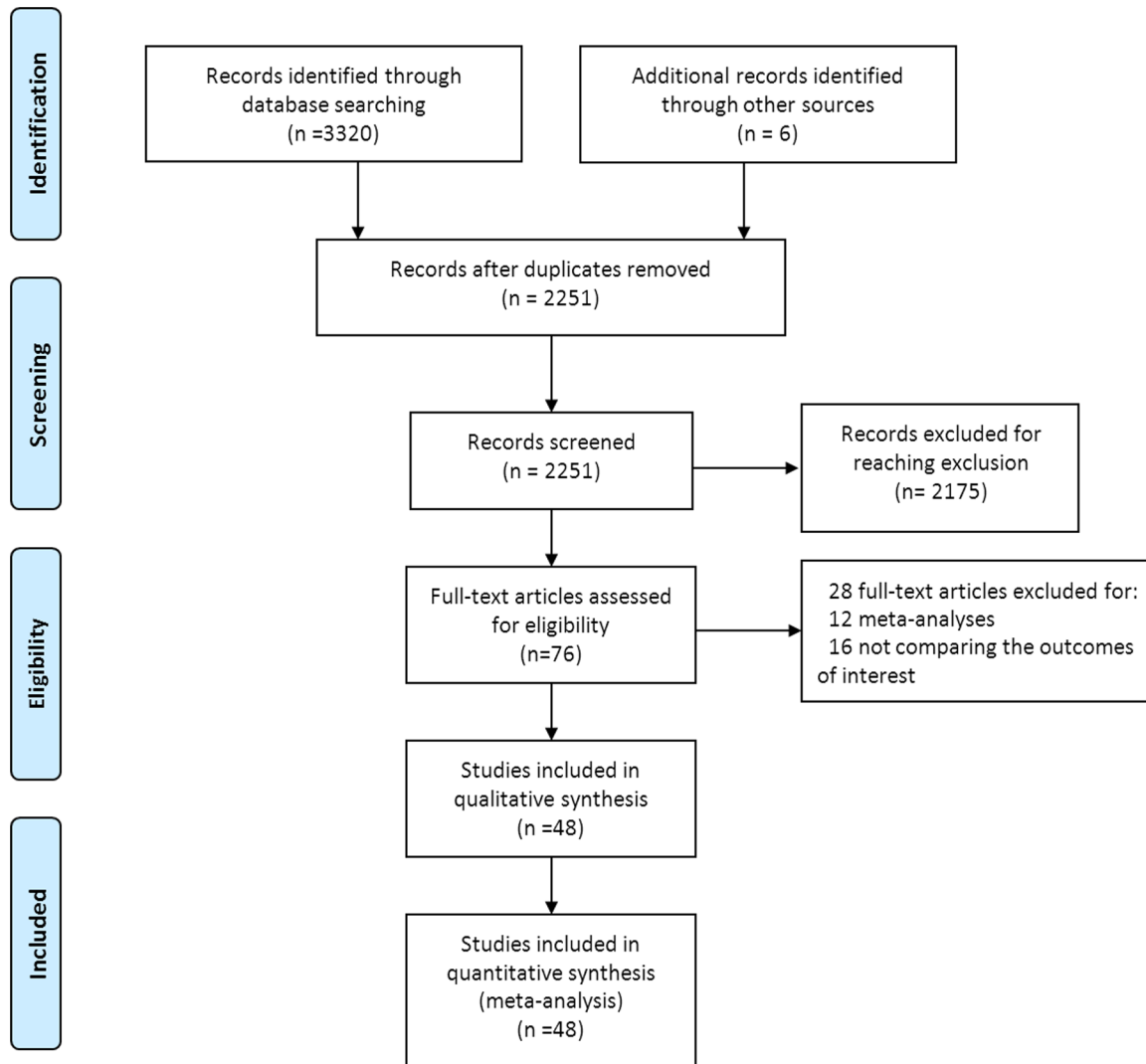


Fig 1. Flow Diagram of the search and selection method.

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in Netherlands [4,47,71], and 2 in Italy [49,51], and the remaining studies were conducted in Germany [61], France [69], Chile [48], and Finland [83]. Key methodological characteristics are shown in Table 1. Thirty-one studies investigated in-hospital mortality (IHM) as an outcome measure, 42 studies for pulmonary complications (PCs), 17 studies for pulmonary embolism (PE), 25 studies for Arrhythmia, 41 studies for Anastomotic Leak (AL) and 17 studies for Gastric Tip Necrosis (GTN) (Table 2).

Large variations existed in the pathological types of the tumors: 32 studies reported the cases of adenocarcinoma, with the proportions ranging from 0% to 86.8%, whereas 16 studies failed to mention the pathological types. In addition, 31 studies involved total MIE, 11 studies thoroscopic- assisted MIE (TA), and 6 studies Hybrid (some cases underwent TA while some underwent MIE). In addition, TNM stage were reported in 31 studies totaling in 4440 cases, of whom 63.5% (1,346/2,119) were early stage (stage I and II) of esophageal cancer in the MIO group, and only 54.2% (1,257/2,321) were early stage in the OE group.

Table 1. Characteristics and Demographics of Included Studies.

Study	Year	Country	Design	Cases		MINORS	Adeno.%	Hybrid	TNM stage			
				MIO	OE				MIO		OE	
									0+I+II	III+IV	0+I+II	III+IV
Law S ^[43]	1997	China	NA	18	63	16	NA	MIE	5	13	15	48
Nguyen NT ^[44]	2000	USA	R	18	36	16	NA	MIE	NA	NA	NA	NA
Osugi H ^[45]	2003	Japan	P	77	72	20	0	TA	NA	NA	NA	NA
Kunisaki C ^[46]	2004	Japan	P	15	30	16	NA	MIE	NA	NA	NA	NA
Van den Broek WT ^[47]	2004	Netherlands	NA	25	20	19	71.1	TA	8	17	10	10
Braghetto I ^[48]	2006	Chile	R	47	119	20	NA	MIE	41	6	29	90
Bresadola V ^[49]	2006	Italy	NA	14	14	16	NA	MIE	11	3	6	8
Shiraishi T ^[50]	2006	Japan	R	116	37	16	NA	Hybrid	NA	NA	NA	NA
Benzoni E ^[51]	2007	Italy	P	9	13	20	23.8	TA	9	0	7	6
Smithers BM ^[53]	2007	Australia	P	332	114	20	70.6	Hybrid	192	118	36	75
Fabian T ^[52]	2008	USA	R	22	43	20	69.2	MIE	14	7	25	19
Parameswaran R ^[54]	2009	UK	NA	50	30	19	82.5	MIE	27	23	17	15
Perry KA ^[55]	2009	USA	P	21	21	16	45.2	MIE	NA	NA	NA	NA
Saha AK ^[56]	2009	UK	NA	16	28	19	16+	MIE	NA	NA	NA	NA
Zingg U ^[57]	2009	Australia	NA	56	98	20	72.1	MIE	35	21	47	42
Hamouda AH ^[58]	2010	UK	P	51	24	16	80	MIE	NA	NA	NA	NA
Pham TH ^[21]	2010	USA	P	44	46	16	74.4	MIE	20	20	20	19
Safranek PM ^[59]	2010	UK	P	75	46	16	NA	Hybrid	31	44	29	17
Schoppmann SF ^[60]	2010	Australia	P	31	31	20	46.8	MIE	14	15	13	17
Schröder W ^[61]	2010	Germany	R	238	181	16	60.1	TA	NA	NA	NA	NA
Wang H ^[63]	2010	China	NA	27	29	16	5.3	TA	24	3	24	5
Berger AC ^[64]	2011	USA	NA	65	53	16	79.7	MIE	52	13	41	12
Gao Y ^[65]	2011	China	R	96	78	16	5.2	MIE	54	42	40	38
Lee JM ^[66]	2011	Japan	P	74	64	20	5.1	Hybrid	45	20	49	15
Nafteux P ^[67]	2011	Belgium	R	65	101	16	75.3	MIE	NA	NA	NA	NA
Yamasaki M ^[68]	2011	Japan	R	109	107	20	NA	TA	NA	NA	NA	NA
Briez N ^[69]	2012	France	P	140	140	20	40.7	TA	92	48	89	51
Kinjo Y ^[70]	2012	Japan	P	106	79	19	3.2	MIE	65	41	45	34
Maas KW ^[71]	2012	Netherlands	R	50	50	20	69	MIE	19	31	19	31
Mamidanna R ^[72]	2012	UK	P	1155	6347	16	NA	MIE	NA	NA	NA	NA
Sihag S ^[73]	2012	USA	P	38	76	16	85.1	MIE	29	9	53	23
Sundaram A ^[74]	2012	USA	R	47	57	20	78.8	MIE	NA	NA	NA	NA
Tsujimoto H ^[75]	2012	Japan	NA	22	27	16	NA	TA	9	11	19	18
Bailey L ^[76]	2013	UK	P	39	31	20	82.9	TA	NA	NA	NA	NA
Biere SS ^[4]	2013	Netherlands	RCT	59	56	18	61.7	MIE	31	15	26	19
Ichikawa H ^[77]	2013	Japan	NA	153	162	20	66.7	TA	101	51	81	79
Kitagawa H ^[78]	2013	Japan	R	45	47	16	4.3	MIE	NA	NA	NA	NA
Noble F ^[79]	2013	UK	P	53	53	19	NA	MIE	NA	NA	NA	NA
Parameswaran R ^[80]	2013	UK	P	67	19	16	75.6	Hybrid	43	23	8	11
Takeno S ^[81]	2013	Japan	R	91	166	20	3.5	TA	NA	NA	NA	NA
Kubo N ^[6]	2014	Japan	R	135	74	16	NA	Hybrid	112	23	41	33
Mu J ^[82]	2014	China	R	176	142	16	NA	MIE	34	18	73	17
Kauppi J ^[83]	2014	Finland	R	74	79	20	NA	MIE	28	46	25	54
Meng F ^[84]	2014	China	R	94	89	20	4.4	MIE	56	38	50	39

(Continued)

Table 1. (Continued)

Study	Year	Country	Design	Cases		MINORS	Adeno.%	Hybrid	TNM stage			
				MIO	OE				MIO		OE	
									0+I+II	III+IV	0+I+II	III+IV
Schneider C ^[85]	2014	UK	R	19	61	16	78.8	MIE	16	2	36	24
Zhang J ^[86]	2014	China	R	60	61	16	NA	MIE	NA	NA	NA	NA
Li J ^[87]	2014	China	R	89	318	20	NA	MIE	64	25	188	126
Javidfar J ^[88]	2012	USA	R	92	165	20	86.8	MIE	65	27	96	69

Note: Adeno.: adenocarcinoma; NA: not applicable; MIO: minimally invasive oesophagectomy, including MIE,TA and Hybrid MIE; OE: open esophagectomy; MIE: total minimally invasive esophagectomy; TA: thoracoscopic-assisted MIE; Hybrid: Hybrid minimally invasive oesophagectomy.

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Results

MIO and Risk of In-hospital Mortality (IHM)

Thirty-one trials including a total of 13,117 patients were included, with an overall in-hospital mortality (IHM) rate of 4.0% (528/13,117). Of the 13,267 patients, 4.6% (413/8,968) were allocated to OE group and 3.0% (115/3,774) were allocated to MIO group. As shown in Fig 2, the pooled OR of 0.69 (95%CI = 0.55–0.86) indicated a significant reduction in the risk of IHM after treated with MIO, with no heterogeneity among the included studies ($I^2 = 0\%$, $p = 0.953$).

MIO and Risk of Pulmonary complications (PCs)

Data for pulmonary complications (PCs) was available for 42 studies or 13,267 cases. Of the 13,267 patients included in these studies, 17.8% (715/4,006) of the patients were allocated to MIO group and 20.4% (1,888/9,261) of the patients allocated to OE group developed PCs, with an overall morbidity of 19.6% (2,603/13,267).

As shown in Fig 3, due to a statistically significant heterogeneity ($I^2 = 52.0\%$, $p < 0.001$), random-effects model as well as subgroup analysis was performed. The pooled RR of 0.73 (95% CI = 0.62–0.86) revealed a significant effect of MIO in reducing the risk of PCs. A consistent result from the subgroup analysis (RR = 0.69, 95% CI: 0.61–0.77) after removing two studies [67, 72], which might be the source of heterogeneity, demonstrated that MIO intervention was associated with a difference in the occurrence of PCs (Fig 3), with no significant heterogeneity ($I^2 = 0\%$, $p = 0.501$).

MIO and Risk of Pulmonary Embolism (PE)

Seventeen studies, including a total of 9,585 patients, evaluated the efficacy of MIO in reducing the risk of pulmonary embolism (PE). Of the 9,585 patients, 2,045 underwent OE and 7,540 underwent MIO, with an overall PE morbidity of 2.3% (217/9,585). As shown in Fig 4, the pooled OR of 0.71 (95% CI = 0.51–0.99) showed an obvious downward trend of the PE morbidity, with no heterogeneity ($I^2 = 18.1\%$, $p = 0.242$).

MIO and Risk of Arrhythmia

Twenty five trials, including a total of 11,115 participants, of whom 2,983 underwent OE and 8,132 underwent MIO, evaluated the efficacy of MIO in reducing the risk of arrhythmia. Of these participants, 10.2% (305/2,983) of the patients in MIO group and 11.0% (900/8,132) in OE group developed arrhythmia, with an overall morbidity of 10.8% (1,205/11,115). It can be

Table 2. Outcomes of interest in Included Studies.

Study	Endpoints											
	Hospital Mortality		Pulmonary complications		Pulmonary embolism		Arrhythmia		Anastomotic Leak		Gastric Tip Necrosis	
	MIO	OE	MIO	OE	MIO	OE	MIO	OE	MIO	OE	MIO	OE
Law S ^[43]	NA	NA	3/18	11/63	NA	NA	NA	NA	NA	NA	NA	NA
Nguyen NT ^[44]	NA	NA	2/18	6/36	1/18	1/36	NA	NA	2/18	4/40	0/18	1/36
Osugi H ^[45]	NA	NA	NA	NA	12/149	3/72	2/77	2/77	1/149	2/53	NA	NA
Kunisaki C ^[46]	NA	NA	0/15	1/30	NA	NA	NA	NA	2/15	1/30	NA	NA
Van den Broek WT ^[47]	NA	NA	2/25	2/20	NA	NA	NA	NA	2/25	3/20	NA	NA
Braghetto J ^[48]	3/47	13/119	7/47	22/119	0/47	1/119	NA	NA	4/47	26/119	NA	NA
Bresadola V ^[49]	NA	NA	1/14	2/14	1/14	0/14	NA	NA	1/14	2/14	NA	NA
Shiraishi T ^[50]	6/116	5/37	25/116	12/37	NA	NA	3/116	4/37	13/116	9/56	NA	NA
Benzoni E ^[51]	NA	NA	0/8	1/13	NA	NA	NA	NA	1/8	1/13	0/8	1/13
Smithers BM ^[5]	7/332	3/114	87/332	35/114	NA	NA	55/332	21/114	18/332	10/114	5/332	2/114
Fabian T ^[52]	1/22	4/43	3/22	18/43	1/22	0/43	4/22	8/43	3/22	3/43	1/22	0/43
Parameswaran R ^[54]	NA	NA	4/50	2/30	0/50	1/30	0/50	2/30	4/50	1/30	5/50	2/30
Perry KA ^[55]	NA	NA	2/21	3/21	NA	NA	5/21	8/21	4/21	6/21	NA	NA
Saha AK ^[56]	0/16	2/28	NA	NA	NA	NA	NA	NA	2/16	3/28	NA	NA
Zingg U ^[57]	2/56	6/98	17/56	33/98	NA	NA	NA	NA	11/56	11/98	NA	NA
Hamouda AH ^[58]	NA	NA	15/51	5/24	NA	NA	3/51	6/24	4/51	2/24	3/51	1/24
Pham TH ^[21]	3/44	2/46	13/44	9/46	0/44	2/46	18/44	11/46	4/44	5/46	1/44	1/46
Safranek PM ^[59]	3/75	1/46	19/75	13/46	NA	NA	NA	NA	11/75	1/46	2/75	0/46
Schoppmann SF ^[60]	NA	NA	5/31	17/31	NA	NA	NA	NA	1/31	8/31	0/31	1/31
Schröder W ^[61]	7/238	11/181	NA	NA	NA	NA	NA	NA	18/238	17/181	NA	NA
Wang H ^[63]	NA	NA	1/27	5/29	0/27	1/29	2/27	1/29	5/27	4/29	NA	NA
Berger AC ^[64]	5/65	4/53	5/65	12/53	NA	NA	NA	NA	9/65	6/53	NA	NA
Gao Y ^[65]	2/96	3/78	13/96	11/78	NA	NA	NA	NA	7/96	6/47	NA	NA
Lee JM ^[66]	4/74	8/64	11/74	20/64	NA	NA	NA	NA	10/74	18/60	NA	NA
Nafteux P ^[67]	2/65	2/101	47/65	17/101	NA	NA	NA	NA	5/65	10/101	NA	NA
Yamasaki M ^[68]	0/109	2/107	7/109	15/107	NA	NA	3/109	6/107	6/109	4/166	0/109	2/107
Briez N ^[69]	2/140	10/140	22/140	60/140	NA	NA	NA	NA	8/140	6/140	0/140	1/140
Kinjo Y ^[70]	NA	NA	22/106	31/79	NA	NA	10/106	4/79	8/106	10/29	NA	NA
Maas KW ^[71]	0/50	1/50	9/50	13/50	NA	NA	3/50	6/50	4/50	3/50	NA	NA
Mamidanna R ^[72]	46/1155	274/6347	230/1155	1181/6347	19/1155	92/6347	102/1155	611/6347	NA	NA	NA	NA
Sihag S ^[73]	0/38	2/76	1/38	33/76	0/38	2/76	5/38	12/76	0/38	2/76	NA	NA
Sundaram A ^[74]	2/47	1/57	5/47	19/57	5/47	19/57	9/47	19/57	4/47	4/57	NA	NA
Tsujimoto H ^[75]	1/22	5/27	2/22	10/27	NA	NA	3/22	14/27	7/22	3/31	1/22	0/27
Bailey L ^[76]	2/39	2/31	15/39	18/31	NA	NA	3/39	8/31	NA	NA	NA	NA
Biere SS ^[4]	2/59	1/56	7/59	19/56	1/59	9/56	NA	NA	7/59	4/56	NA	NA
Ichikawa H ^[77]	0/153	8/153	20/153	33/153	NA	NA	17/153	38/153	14/153	27/153	4/153	5/153
Kitagawa H ^[78]	1/45	2/47	6/45	14/47	NA	NA	NA	NA	NA	NA	NA	NA
Noble F ^[79]	NA	NA	18/53	14/53	0/53	1/53	6/53	6/53	5/53	2/53	NA	NA
Parameswaran R ^[80]	3/67	1/19	NA	NA	11/67	2/19	1/67	2/19	NA	NA	9/67	2/19
Takeno S ^[81]	4/91	15/166	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kubo N ^[6]	2/135	2/74	13/135	16/74	NA	NA	NA	NA	10/135	7/74	0/135	2/74
Mu J ^[82]	1/176	1/142	6/176	4/142	NA	NA	NA	NA	12/176	4/142	NA	NA
Kauppi J ^[83]	NA	NA	13/74	15/79	5/74	5/79	14/74	20/79	5/74	5/79	0/74	2/79

(Continued)

Table 2. (Continued)

Study	Endpoints											
	Hospital Mortality		Pulmonary complications		Pulmonary embolism		Arrhythmia		Anastomotic Leak		Gastric Tip Necrosis	
	MIO	OE	MIO	OE	MIO	OE	MIO	OE	MIO	OE	MIO	OE
Meng F ^[84]	1/94	4/89	9/49	24/89	NA	NA	4/94	11/89	6/94	7/89	NA	NA
Schneider C ^[85]	0/19	2/61	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Zhang J ^[86]	NA	NA	4/60	7/61	NA	NA	3/60	5/61	3/60	2/61	NA	NA
Li J ^[87]	3/89	16/318	15/89	76/318	1/89	3/318	7/89	29/318	19/89	45/318	NA	NA
Javidfar J ^[88]	NA	NA	9/92	29/165	3/92	4/165	22/92	46/165	5/92	7/165	2/92	2/165

Note: NA: not applicable; MIO: minimally invasive oesophagectomy, including MIE, thoracoscopic-assisted MIE and Hybrid MIE; OE: open esophagectomy.

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seen that the MIO group, as shown in Fig 5, showed a significant decrease in the morbidity of arrhythmia (OR = 0.79, 95%CI = 0.68–0.92), with no heterogeneity among different studies ($I^2 = 14.5\%$, $P = 0.257$).

MIO and Risk of Anastomotic Leak (AL)

Forty-one studies carried out on 6,188 patients assessed the effect of MIO on anastomotic leak (AL). Of these patients, 3,152 patients underwent MIO and 3,036 patients underwent OE, with an overall AL morbidity of 9.1% (566/6,188). Fig 6 showed that there was no difference in the occurrence of AL between the MIO and OE groups (OR = 0.93, 95%CI = 0.78–1.11). No heterogeneity was detected among the different studies ($I^2 = 14.9\%$, $P = 0.208$).

MIO and Risk of Gastric Tip Necrosis (GTN)

Seventeen studies, including a total of 2,570 participants, investigated gastric tip necrosis (GTN) as an outcome measure. Of the included patients, 2.3% (33/1,423) of the patients in MIO group and 2.0% (23/1,147) in OE group developed GTN, with an overall morbidity of 2.2% (56/2,570). The pooled OR 0.89 (95%CI = 0.54–1.49) in Fig 7 showed that no significant difference was found between the two groups, with no heterogeneity ($I^2 = 0.0\%$, $p = 0.939$).

Publication Bias Analysis

Egger's test and Begg's funnel plots (S1 Fig) were used to assess the publication bias among the included studies. An asymmetric funnel plots figure was shown in S1 Fig, with significantly statistical differences ($P < 0.05$) through Egger's test (S1 Table). This raises the possibility of publication bias. Because of this, we undertook a sensitivity analysis using the trim and fill method, with the aim to impute hypothetically negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry [42]. The pooled analyses after incorporating the hypothetical studies showed consistent results which revealed a statistically significant association between MIO and the risk of IHM.

Sensitivity Analysis

In the analysis of MIO and risk PCs, sensitivity analyses using the “metaninf” Stata command (S2 Fig) indicated that two independent studies [67, 72], were the main origin of heterogeneity. The heterogeneity was vanished after deletion of the two studies above-mentioned, while the

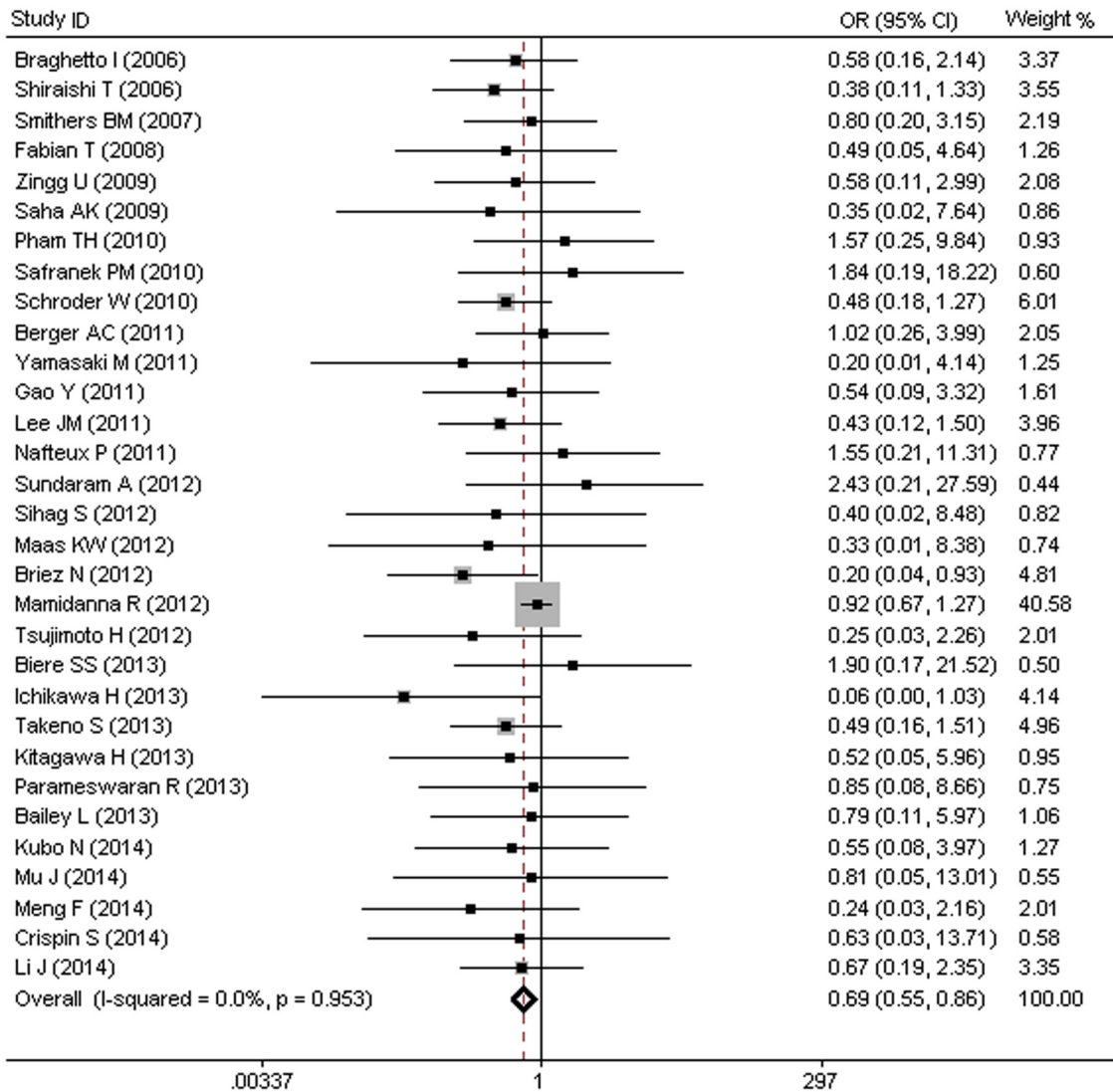


Fig 2. MIO and Risk of In-Hospital Mortality (IHM).

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association still kept significant (Fig 3). In addition, no other single study influenced the pooled ORs or RRs qualitatively, as indicated by sensitivity analyses, suggesting that the results of this meta-analysis are stable.

Discussion

As previously described, minimally invasive oesophagectomy (MIO) has been in existence for almost 20 years and has been used as an option for the curative treatment of esophageal cancer in some centres around the world [28]. Our systematic review and meta-analysis assessed the superiority of MIO in reducing IHM in 14,302 patients from 48 published studies. The major findings of the current meta-analysis provide proof that administration of MIO can significantly decrease the IHM rate in patients with resectable esophageal cancer.

As we have mentioned before, in-hospital mortality (IHM) is an objective, reliable, precise, and bias-free measurement for patients with surgery in hospital databases. The overall IHM

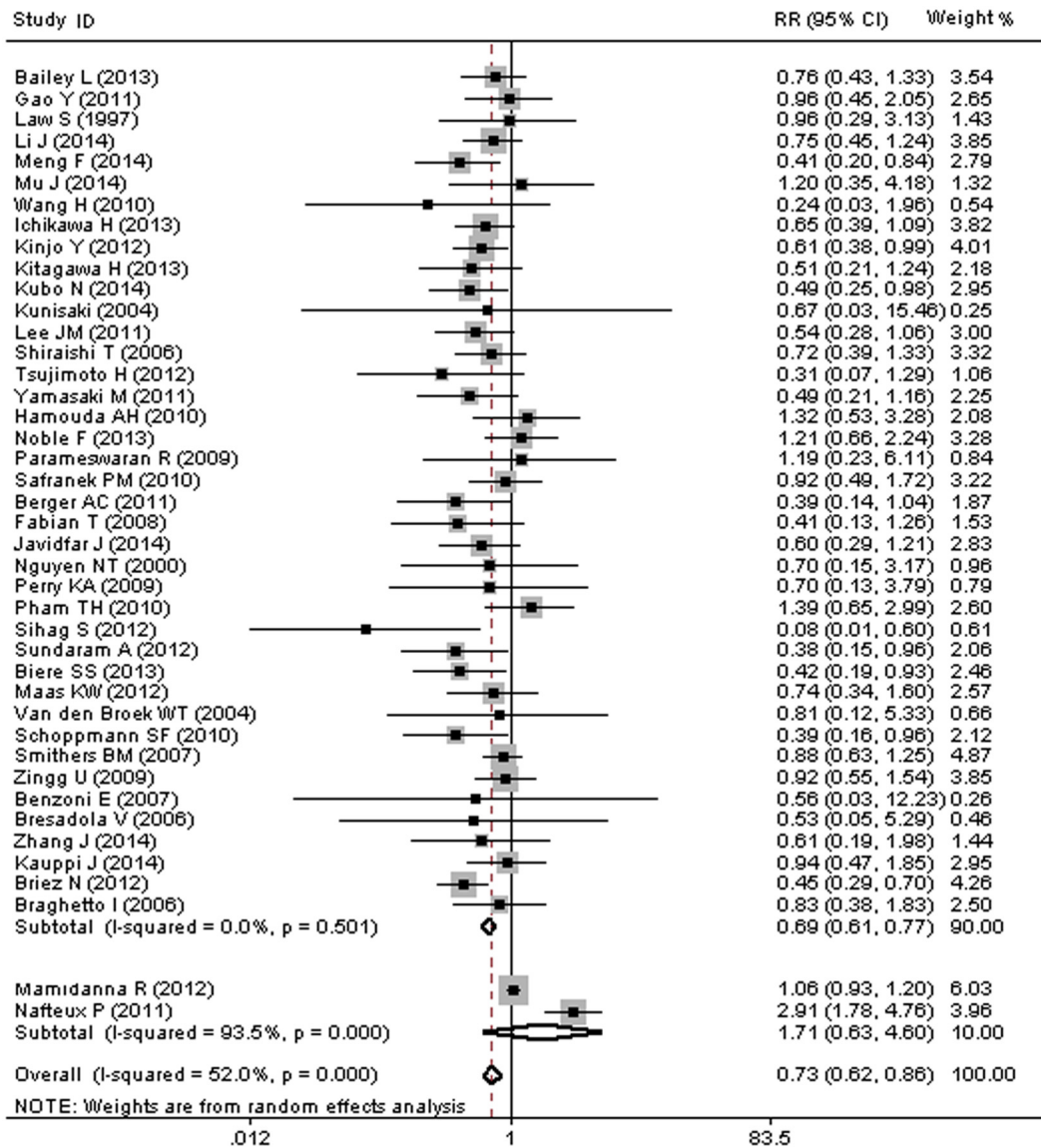


Fig 3. MIO and Risk of Pulmonary Complications (PCs).

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rate of 4.0% we found in our meta-analysis was slightly lower than 5% documented in other studies [9, 11]. The underlying reason for the diverse results may be the difference in the surgical procedures for the included patients in the included studies. The pooled OR 0.69 demonstrated that MIO could significantly reduce the risk of IHM, when compared with OE, which was consistent with the results from other studies [4, 68]. The main superiority of MIO over conventional OE was minimal trauma, since in MIO, the operation could be done through small incision, avoiding the trauma of open operation [9]. Moreover, the bias in the selection of patients should be taken into consideration, that is, patients selected for MIO were always in early stages of esophageal cancer, with smaller tumors and lower risk in the occurrence of post-operative complications than patients of late stages.

Pulmonary complications (PCs) are the most frequent morbidity event after oesophagectomy. At least half the patients are at risk for developing PCs after open oesophagectomy

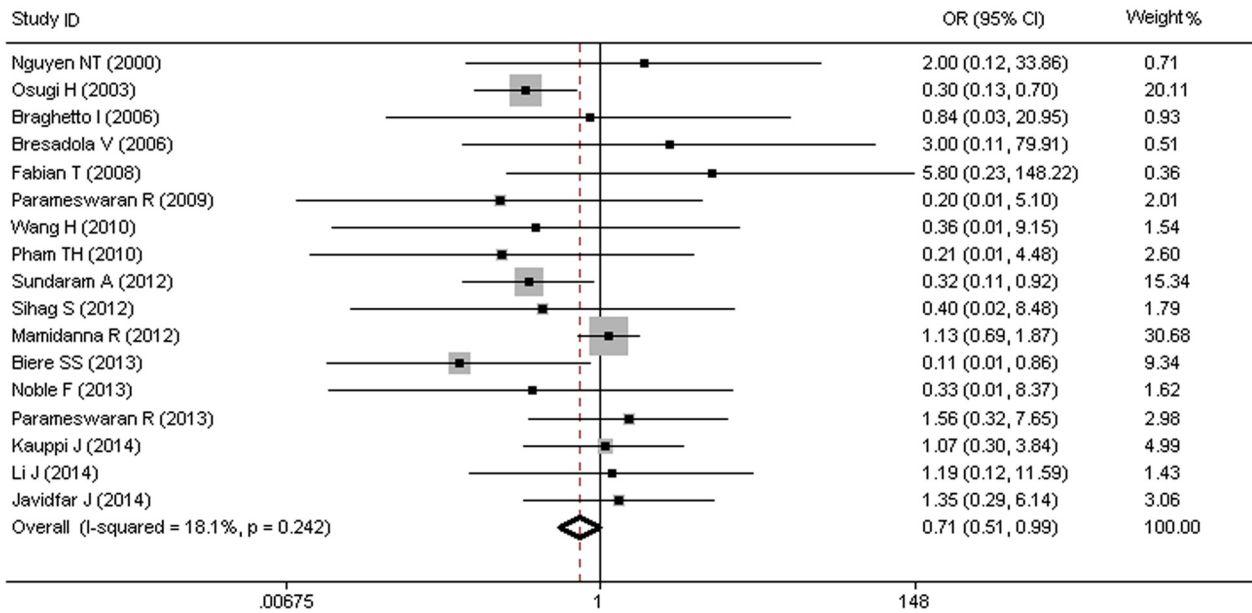


Fig 4. MIO and Risk of Pulmonary Embolism (PE).

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performed through a right thoracotomy and laparotomy [9]. In addition, researchers even have reported that the occurrence of PCs are correlated with in-hospital mortality and prolonged hospital stay [6,103]. Therefore, theoretically, we hypothesize that MIO can reduce the rate of PCs and thereby reduce the risk of IHM. The most basic reasons for this hypothesis are the less invasive nature of the procedure and reduced deterioration of the ventilatory mechanism than is observed after the open procedure through avoiding thoracotomy and laparotomy [9,104]. The hypothesis was confirmed in a recently reported multicentre, randomised controlled trial, which found the occurrence of PCs in OE group (29%) was three times more than the MIO group (9%) [3]. In our analysis, when compared to the OE group, the MIO group showed a reduced morbidity of PCs, with the overall PCs morbidity of 19.2% (2,613/13,585). This was consistent with the result of 3.1%-37.0% from other studies [3, 68, 103]. Moreover, the pooled RR of 0.73 indicated that sufficient evidence was available for validation of the superiority of MIO in reducing PCs, with a statistically significant heterogeneity. We also found that two studies reported by Nafteux [67] and Mamidanna [72] due to not taking the TNM stage into account, were the source of heterogeneity. A consistent result from the subgroup analysis after removing the two above- mentioned studies [67, 72] further confirmed the superiority of MIO in reducing the risk of PCs.

We know that cancer patients have a higher risk of deep venous thrombosis (DVT) and even pulmonary embolism (PE) when compared to the general population [105]. And PE has been considered to be associated with arrhythmia, especially atrial fibrillation (AF). Moreover, PE and arrhythmia are recognized as common problems that cause significant morbidity and mortality in modern societies [106]. Hence prevention of postoperative PE and arrhythmia is crucial in reducing the risk of IHM in patients with esophagus carcinoma. Interestingly, it was found in this study that MIO was associated with decreased incidences of PE and arrhythmia. The most fundamental reason for this association is also the less invasive nature of MIO, after which patients easily comply with doctor's advice and start to ambulate as soon as possible. And early ambulation contributes to prevention of thrombosis and thereby prevents the occurrence of PE [107]. In addition, the perforation of minimally invasive surgery per se could

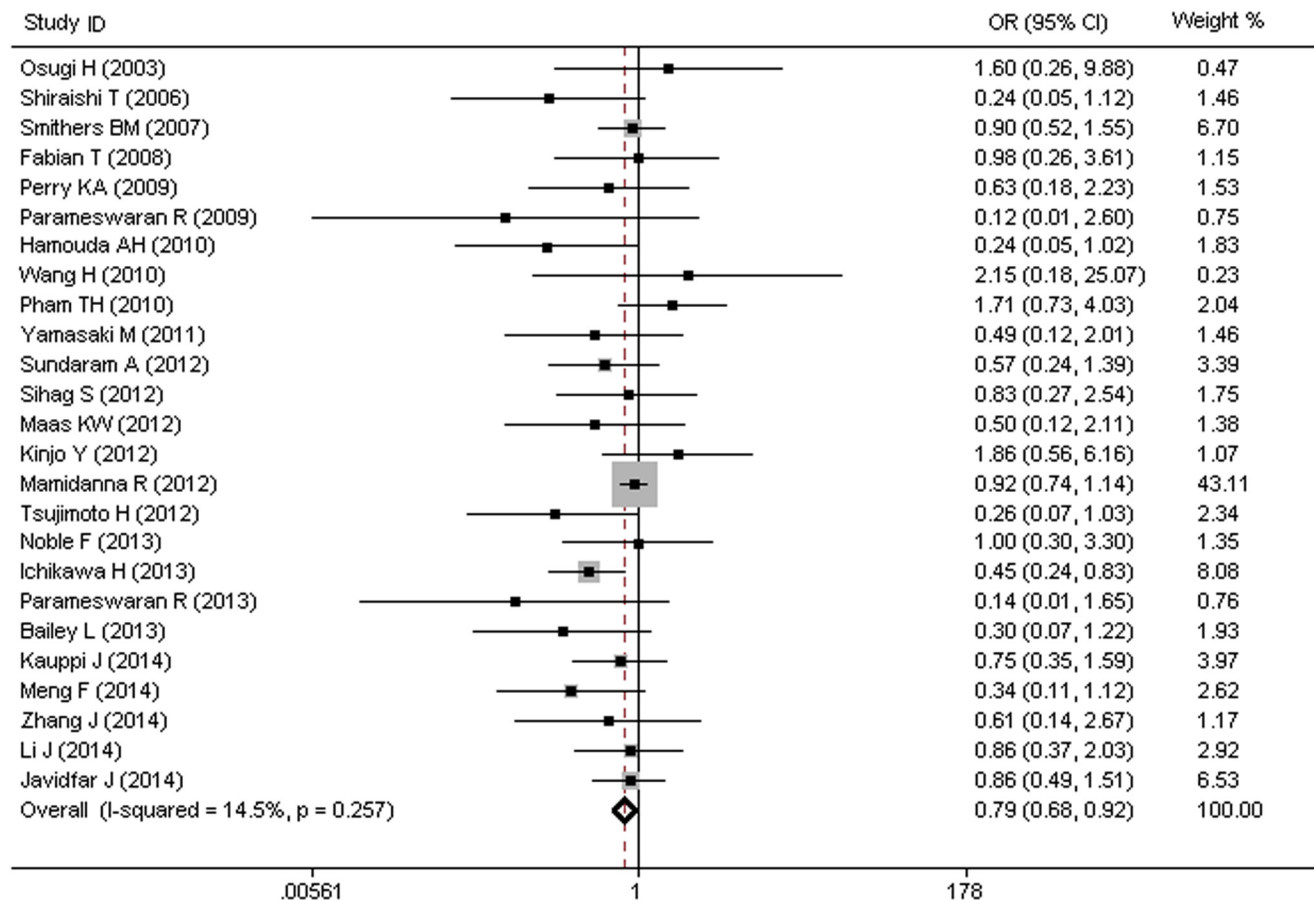


Fig 5. MIO and Risk of Arrhythmia.

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decrease the risk factors leading to postoperative cardiac arrhythmia [108]. Therefore, it is reasonable to assume that minimally invasive surgery can mitigate the risk of hospital mortality by reducing the chances of PE and arrhythmia.

Anastomotic leakages (ALs) and gastric tip necrosis (GTN) are fatal complications after oesophagectomy and can be viewed as catastrophic events [108]. Therefore, the prevention of ALs and GTN appear quite important. In our analysis, no significant difference was found in the occurrence of ALs or GTN between the MIO and OE groups. Such findings indicated that there is still insufficient evidence at present to support the hypothesis that MIO can reduce the occurrence of ALs or GTN for patients with resectable esophageal cancer.

Our meta-analysis has some limitations that might affect the interpretation of the results. First, of the included studies, only one was randomized controlled trial (RCT). The remaining 47 studies used a case-control or cross-sectional design, which is susceptible to recall and selection biases. Therefore, to a certain extent, the included studies cannot provide good evidence for potential treatment effects/ harms, compared to RCTs. Second, the included studies were clinically heterogeneous in some aspects, although the statistical heterogeneity was low. For example, there exists difference in study design, demographics of participants, surgical intervention, operative details, histopathological type, even the outcome reporting after esophageal cancer surgery [103]. Thirdly, we have to emphasize the selection bias in TNM stage of esophageal cancer, that is, patients in MIO group had a higher proportion of early stages when

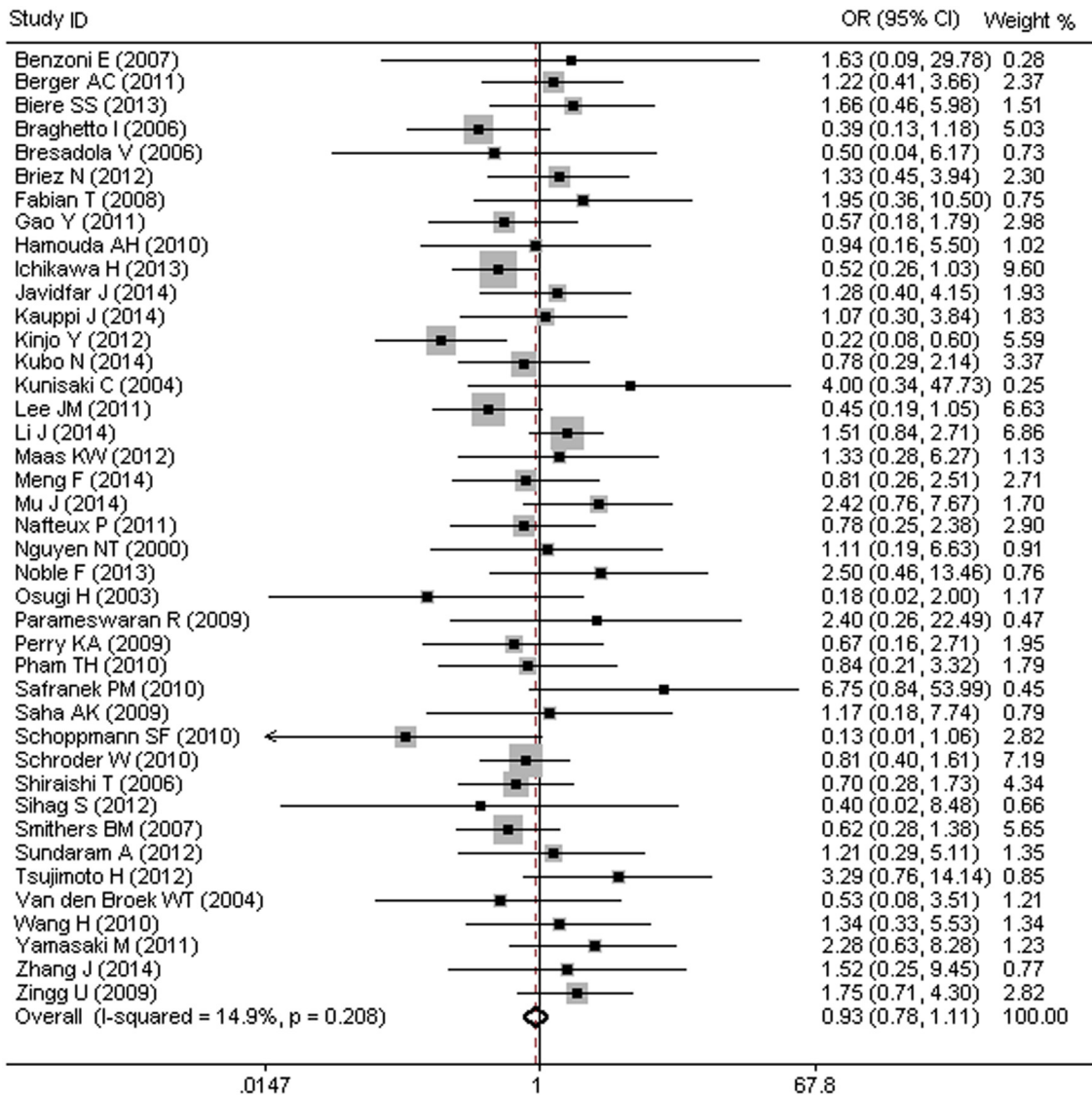


Fig 6. MIO and Risk of Anastomotic Leak (AL).

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compared to that OE group, although only 31 studies totaling in 4440 cases involved TNM stages. Such bias could result in a lower risk in the occurrence of postoperative complications. However, we were unable to account for these differences, despite the use of appropriate meta-analytic techniques. These limitations may result in an overestimation or underestimation of the effect of MIO. In addition, unmeasured or residual confounding is likely to be present, for instance, the intraoperative collateral tissue damage, bleeding, or worsening organ failure due to surgical trauma.

In conclusion, our research has demonstrated that MIO has superiority in decreasing the incidence of in-hospital mortality, which reinforces the idea that this strategy should be considered as a first-line surgical procedure in esophageal surgery. The decrease in in-hospital mortality by MIO was attributed to the reduction in occurrence of PCs, PE and arrhythmia for patients with resectable esophageal cancer. In addition, more proof is needed for the hypothesis

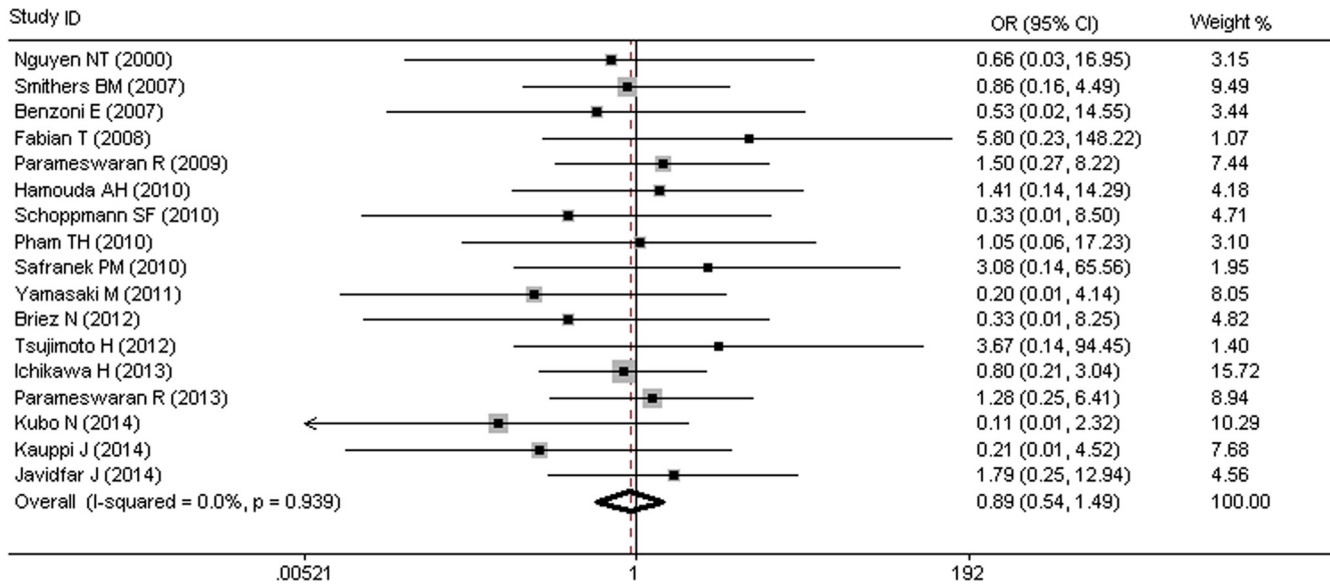


Fig 7. MIO and Risk of Gastric Tip Necrosis (GTN).

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that AL or GTN are two significant contributors to reducing the occurrence of in-hospital mortality.

Supporting Information

S1 Table. Egger's test of interest in Included Studies.
(DOCX)

S1 Fig. Begg's funnel plot of In-Hospital Mortality (IHM).
(TIF)

S2 Fig. Sensitivity Analysis of MIO and risk of PCs.
(TIF)

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Author Contributions

Conceived and designed the experiments: YR CZ. Performed the experiments: CZ YR LZ. Analyzed the data: CZ LZ HW XM BS. Contributed reagents/materials/analysis tools: JH HW XM. Wrote the paper: CZ LZ. Reviewed/Edited the manuscript: KW PL WC.

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