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Systematic Review and Meta-analysis

Totally minimally invasive esophagectomy versus hybrid minimally invasive esophagectomy: systematic review and meta-analysis

Frans van Workum,[1] Bastiaan R Klarenbeek,[1] Nikolaj Baranov,[1] Maroeska M Rovers,[2] Camiel Rosman[1]

[1]*Department of Surgery, Radboudumc, Nijmegen, The Netherlands, and* [2]*Department of Health Evidence and Operating Rooms, Radboudumc, Nijmegen, The Netherlands*

SUMMARY. **Minimally invasive esophagectomy is increasingly performed for the treatment of esophageal cancer, but it is unclear whether hybrid minimally invasive esophagectomy (HMIE) or totally minimally invasive esophagectomy (TMIE) should be preferred. The objective of this study was to perform a meta-analysis of studies comparing HMIE with TMIE. A systematic literature search was performed in MEDLINE, Embase, and the Cochrane Library. Articles comparing HMIE and TMIE were included. The Newcastle–Ottawa scale was used for critical appraisal of methodological quality. The primary outcome was pneumonia. Sensitivity analysis was performed by analyzing outcome for open chest hybrid MIE versus total TMIE and open abdomen MIE versus TMIE separately. Therefore, subgroup analysis was performed for laparoscopy-assisted HMIE versus TMIE, thoracoscopy-assisted HMIE versus TMIE, Ivor Lewis HMIE versus Ivor Lewis TMIE, and McKeown HMIE versus McKeown TMIE. There were no randomized controlled trials. Twenty-nine studies with a total of 3732 patients were included. Studies had a low to moderate risk of bias. In the main analysis, the pooled incidence of pneumonia was 19.0% after HMIE and 9.8% after TMIE which was not significantly different between the groups (RR: 1.46, 95% CI: 0.97–2.20). TMIE was associated with a lower incidence of wound infections (RR: 1.81, 95% CI: 1.13–2.90) and less blood loss (SMD: 0.78, 95% CI: 0.34–1.22) but with longer operative time (SMD:-0.33, 95% CI: −0.59—-0.08). In subgroup analysis, laparoscopy-assisted HMIE was associated with a higher lymph node count than TMIE, and Ivor Lewis HMIE was associated with a lower anastomotic leakage rate than Ivor Lewis TMIE. In general, TMIE was associated with moderately lower morbidity compared to HMIE, but randomized controlled evidence is lacking. The higher leakage rate and lower lymph node count that was found after TMIE in sensitivity analysis indicate that TMIE can also have disadvantages. The findings of this meta-analysis should be considered carefully by surgeons when moving from HMIE to TMIE.**

KEY WORDS: **esophageal cancer, totally minimally invasive esophagectomy, hybrid minimally invasive esophagectomy.**

INTRODUCTION

Esophagectomy is the cornerstone for curative treatment of esophageal cancer. Open esophagectomy is increasingly being replaced by minimally invasive esophagectomy (MIE). Currently it is estimated that nearly 45% of patients are operated using a minimally invasive approach worldwide.[1] MIE can be performed by hybrid minimally invasive esophagectomy (HMIE, laparotomy and thoracoscopy or laparoscopy and thoracotomy) or totally minimally invasive esophagectomy (TMIE, laparoscopy and thoracoscopy). In the Western world, laparoscopy-assisted HMIE is increasingly replaced by TMIE, in an attempt to further decrease postoperative morbidity without compromising patients' safety.[1]

Systematic reviews of retrospective studies comparing the results of open esophagectomy to TMIE and open esophagectomy to HMIE have found that both HMIE and TMIE have advantages over the open approach in terms of blood loss, length of stay, and pulmonary complications.[2,3] In addition, these positive effects of MIE have been shown in a randomized controlled trial for HMIE[4] and for TMIE.[5] Because these beneficial effects seem to be comparable between HMIE and TMIE in these randomized controlled trials, HMIE and TMIE are currently considered to be surgical techniques with equivalently beneficial outcomes. However, no randomized controlled trials have compared HMIE and TMIE and no meta-analysis comparing HMIE and TMIE have been performed.

Address correspondence to: Frans van Workum, Radboud University Medical Centre, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands. Email: frans.vanworkum@radboudumc.nl

Therefore, the aim of this article was to perform a systematic review and meta-analysis of studies comparing HMIE with TMIE in patients undergoing esophagectomy.

MATERIALS AND METHODS

Literature search

The review protocol is registered in the PROSPERO international prospective register of systematic reviews (number CRD 42016043291).[6] PRISMA guidelines for systematic reviews were followed, and the PRISMA checklist is available in online Appendix I.[7]

The electronic databases of MEDLINE, Embase, and the Cochrane central register of controlled trials were systematically searched. The search strategy was composed in collaboration with a medical librarian, and the exact (MEDLINE) search strategy was (minimal invasive[tiab] OR minimally invasive[tiab] OR laparo-thoracoscop*[tiab] OR laparothoracoscop*[tiab] OR thoracolaparoscop*[tiab] OR thoraco-laparoscop*[tiab] OR laparoscop*[tiab] OR hybrid[tiab] OR VATS[tiab] OR video-assisted[tiab] OR video assisted[tiab] OR thoracoscop*[tiab]) AND (esophagectom*[tiab] OR oesophagectom*[tiab] OR (resection*[tiab] AND (oesophagus[tiab] OR oesophageal[tiab] OR oesophagal[tiab] OR esophagus[tiab] OR esophageal[tiab] OR esophagal[tiab]))). A cited reference search and hand search were additionally performed. No language restrictions were applied and all results up to April 2019 were included.

Criteria for selecting studies for this review

Comparative cohort studies or randomized controlled trials comparing patients undergoing HMIE versus TMIE were included. We suspected that articles on 'outcome after MIE' could contain data on both HMIE and TMIE without this being explicitly described in the abstract. Therefore, we liberally included abstracts that contained outcome data after any form of MIE for full text screening.

Exclusion criteria were less than 10 patients per treatment arm and unclear description of operative technique rendering classification into HMIE or TMIE impossible. Studies that incorporated results of a transhiatal approach in the TMIE group were also excluded, because transhiatal resection cannot be performed as a hybrid procedure and inclusion would therefore be a source of selection bias. Video-assisted thoracic surgery (VATS) procedures and hand-assisted laparoscopic surgery (HALS) procedures were classified as minimally invasive and were also included.

Articles were selected for inclusion using a three-step review process. First, the titles and abstracts of all identified studies were examined by three reviewers (FvW, BK, and NB) independently, and studies that failed to meet the inclusion criteria were excluded. Second, reviewers (FvW, BK, and NB) independently examined the full text of potentially relevant articles. In the event of disagreement regarding the eligibility of a study during this phase, the opinion of a fourth reviewer (CR) was sought, and the parameters of the study's inclusion were discussed until consensus was reached. Third, all articles cited in and cited by the remaining eligible and relevant articles were independently assessed for inclusion.

Quality assessment

The Newcastle–Ottawa quality assessment scale was used to assess bias in studies included in this review.[8] This scale rates studies on three sources of bias based on eight criteria. Each criterion is worth one star except confounding, which is worth two stars. For this systematic review, studies scoring seven to nine stars were considered to be of high methodological quality, studies scoring four to six stars were considered to be of moderate methodological quality, and studies scoring one to three stars were considered to be of low methodological quality.

Outcome parameters and data extraction

The primary outcome parameter was pneumonia. Secondary outcome parameters were all complications, severe complications (Clavien–Dindo>2),[9] pulmonary complications, anastomotic leakage, chyle leakage, RLN palsy, wound infection, reoperation, hospital length of stay, ICU length of stay, postoperative mortality, operating time, blood loss, R0 resection rate, number of lymph nodes, and quality of life. Data was extracted and was entered into Review Manager (version 5.3).

In case continuous variables were expressed as median and interquartile range or range, the mean and SD were estimated from the available data by methods described elsewhere.[10,11]

Analysis

Since studies were homogeneous enough to pool, meta-analyses were performed, and statistical heterogeneity was assessed. The Mantel–Haenszel method was used for dichotomous data, presented as relative risks (RR) with 95% confidence intervals (CIs). The inverse variance method was used for meta-analysis of continuous data; results are presented as standardized mean difference (SMD) with 95% CIs. A random effects model was used for all analyses. The statistical heterogeneity was assessed with I^2. A funnel plot with the effect measures on the x-axis and standard error

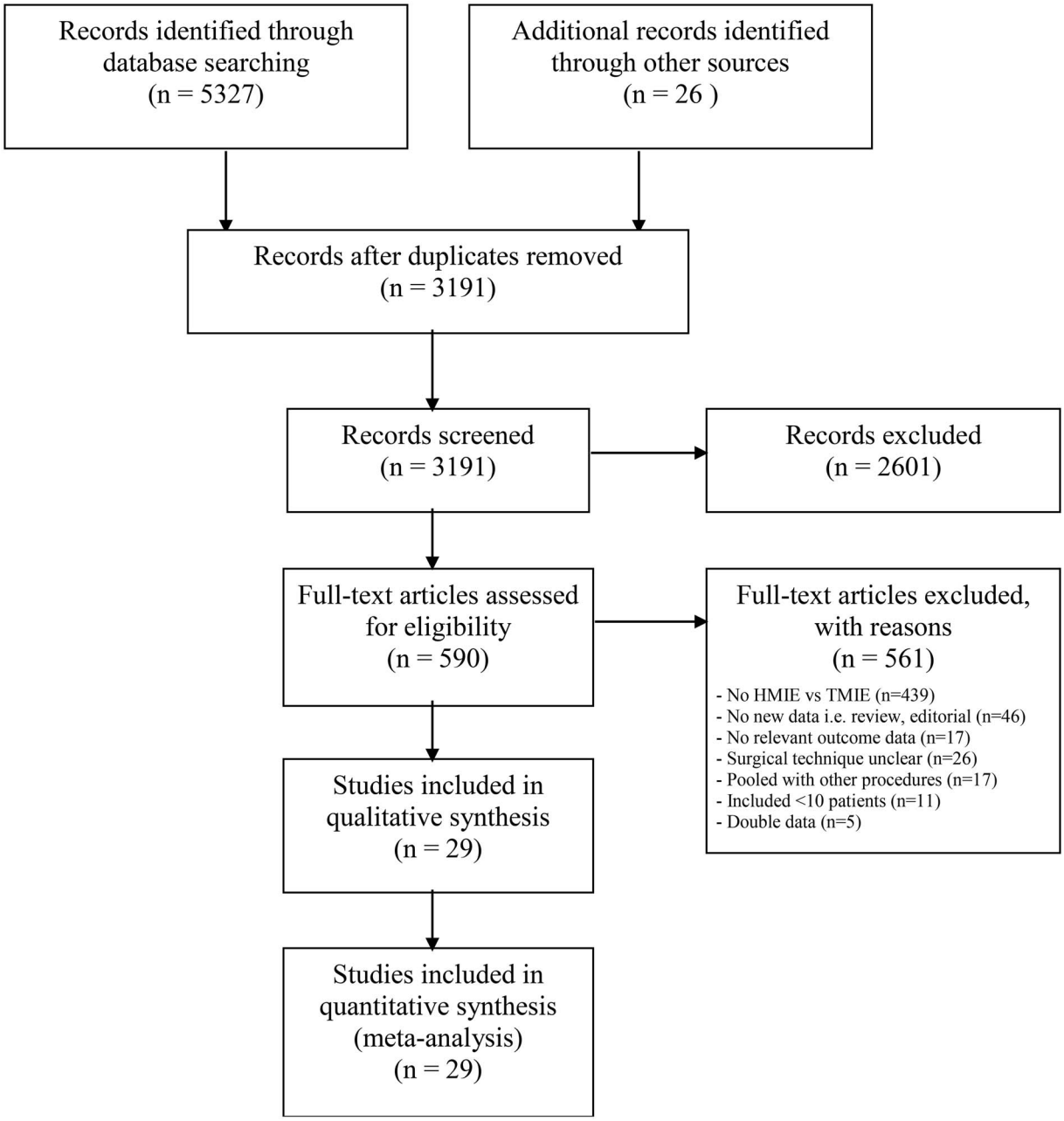

Fig. 1 Summary of screening and selection process—PRISMA diagram.

of the log for the effect measures on the *y*-axis was created for the primary outcome parameter in order to assess publication bias.

In addition to comparing all articles reporting on outcome of patients undergoing HMIE versus TMIE, subgroup and sensitivity analyses were performed for (i) laparoscopy-assisted HMIE (minimally invasive abdominal phase and open thoracic phase) versus TMIE; (ii) thoracoscopy-assisted HMIE (minimally invasive thoracic phase and open abdominal phase) versus TMIE; (iii) Ivor Lewis HMIE versus Ivor Lewis TMIE; and (iv) McKeown HMIE versus McKeown TMIE. For the Ivor Lewis HMIE group, we decided to only include the Ivor Lewis laparoscopy-assisted HMIE (therefore excluding one study that compared Ivor Lewis thoracoscopy-assisted HMIE with Ivor Lewis TMIE), since this reflects the predominant change of practice that is currently taking place in the Western world.

RESULTS

Studies

Twenty-nine studies, including a total of 3,732 patients, met the inclusion criteria of this systematic review.[12–40] A summary of the screening and selection process is shown in Figure 1. The individual studies included 29–445 patients. In 14 studies (n = 1,631) laparoscopy-assisted HMIE was compared to TMIE;

in 12 (n = 1,522) studies, thoracoscopy-assisted HMIE was compared to TMIE and 3 studies (n = 579) included both laparoscopy-assisted HMIE and thoracoscopy-assisted HMIE in the HMIE arm. Seven studies (n = 723) compared Ivor Lewis laparoscopy-assisted HMIE with Ivor Lewis TMIE, 15 studies (n = 2142) compared McKeown HMIE versus McKeown TMIE, and 7 studies (n = 867) used different or multiple surgical techniques of HMIE or TMIE and were therefore ineligible for subgroup analysis. These and other characteristics of the included studies are summarized in Table 1.

Quality and publication bias assessment

There were no randomized controlled trials. Studies scored six to nine stars out of nine according to the Newcastle–Ottawa rating scale, corresponding to a moderate to low risk of bias for non-randomized studies. The results of the quality assessment of the included studies are shown in online Appendix II.

By observation of the funnel plot for the primary outcome parameter in the main analysis, we concluded that publication bias may have been present because there appears to be a gap in the lower left quadrant of the funnel plot. However, the limited number of studies (n = 15) that reported the primary outcome parameter limits reliability of the plot [Online Appendix III].

Meta-analysis of all included studies comparing all HMIE with TMIE

A total of 15 studies including 1,492 patients reported the incidence of the primary outcome parameter. The pooled incidence of pneumonia was 19.0% after HMIE and 9.8% after TMIE which was not significantly different between the groups (RR: 1.46, 95% CI: 0.97–2.20). In a post hoc sensitivity analysis in which we excluded studies that included patients with HALS or VATS, these results remained similar (RR: 1.26, 95% CI: 0.85–1.89). Compared to HMIE, TMIE was associated with a lower incidence of wound infections (RR: 1.81, 95% CI: 1.13–2.90) and less blood loss (SMD: 0.78, 95% CI: 0.34–1.22) but with a longer operative time (SMD: -0.33, 95% CI: −0.59—-0.08) (Appendix IV-a). The other parameters were not statistically different between the groups (Table 2).

Subgroup analyses per HMIE type

In the laparoscopy-assisted HMIE versus TMIE subgroup, the incidence of pneumonia was described by 6 studies which included 451 patients. The incidence of pneumonia was 17.1% after laparoscopy-assisted HMIE and 8.5% after TMIE (RR: 1.68, 95% CI: 1.03–3.37). In addition, TMIE was associated with less blood loss (SMD: 0.39, 95% CI: 0.07–0.72) but with longer operative times (SMD: −0.50, 95%CI: −0.74–−0.25) and less extracted lymph nodes (SMD 0.29, 95%CI: 0.29–0.49) (Table 3) (Appendix IV-b).

In the thoracoscopy-assisted HMIE versus TMIE subgroup, the incidence of pneumonia was reported by 8 studies which included 966 patients. The incidence of pneumonia did not differ between the groups (RR: 1.24, 95% CI: 0.66–2.34). The overall complication rate was lower after TMIE compared to thoracoscopy-assisted HMIE (RR: 1.16, 95% CI: 1.02–1.32), and there was less blood loss after TMIE compared to thoracoscopy-assisted HMIE (SMD 1.03, 95%CI: 0.31–1.75) (Table 4) (Appendix IV-c).

Subgroup analyses per resection type

In the Ivor Lewis HMIE versus TMIE subgroup, the incidence of pneumonia was described by four studies (n = 297) and was not statistically different between the groups (RR: 1.83, 95% CI: 0.71–4.71). Compared to Ivor Lewis HMIE, Ivor Lewis TMIE was associated with a lower incidence of wound infections (RR: 7.33, 95% CI: 1.39–38.61) and less blood loss (SMD: 0.66, 95% CI: 0.36–0.95), but with a longer operative time (SMD: −0.47, 95% CI: −0.72–−0.0.23). Anastomotic leakage was reported in seven studies (n = 723), and the pooled incidence was 10.0% after Ivor Lewis HMIE compared to 18.9% after Ivor Lewis TMIE (RR: 0.55, 95% CI: 0.38–0.80) (Table 5) (Appendix IV-d).

In the McKeown HMIE versus McKeown TMIE subgroup, the incidence of pneumonia was reported by 8 studies which included 947 patients. The incidence of pneumonia did not differ between the groups (RR: 1.45, 95% CI: 0.84–2.54). Compared to McKeown HMIE, McKeown TMIE was associated with a lower incidence of pulmonary complications (RR: 1.45, 95% CI: 1.05–1.99), less blood loss (SMD: 1.11, 95% CI: 0.46–1.75), and a shorter hospital length of stay (SMD: 0.38, 95% CI: 0.09–0.66) (Table 6) (Appendix IV-e).

DISCUSSION

This meta-analysis showed that a clinically relevant difference in the incidence of pneumonia between HMIE and TMIE might exist, but we were unable to demonstrate this since this difference did not reach statistical significance. Interestingly, in the subgroup analysis in which different types of HMIE were compared to TMIE, the incidence of pneumonia was lower after TMIE when it was compared with laparoscopy-assisted HMIE but not when it was compared with thoracoscopy-assisted HMIE. Although laparoscopy-assisted HMIE has clearly been shown to reduce pulmonary complications,[4] this finding may implicate that a further reduction of postoperative pneumonia is possible by moving from laparoscopy-assisted HMIE to TMIE. In general,

Table 1 Characteristics of included studies

Study	Study design	N	Type of HMIO	Type of TMIO	Surgery type HMIO	Surgery type TMIO	Outcome parameters
Berlth 2018	Retrospective cohort	60	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	Ivor Lewis	Pneumonia, pulm complications, AL, severe compl, all compl, RLN palsy, mortality, R0, WI, ICU LOS, hosp LOS, LN, OT, blood loss
Bizekis 2006	Retrospective cohort	50	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	Ivor Lewis	Pneumonia, pulm compl, AL, chyle leak, mortality
Blazeby 2011	Prospective cohort	124	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	Ivor Lewis & McKeown	Severe compl, reoperation, mortality, hosp LOS, LN, OT, blood loss
Bonavina 2016	Retrospective cohort, PSMA	160	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	McKeown	Severe compl, pulm compl, AL, reoperation, chyle leak, RLN palsy, mortality, R0, WI, ICU LOS, hosp LOS, LN, OT, blood loss
Daiko 2015	Cohort (not specified)	64	TA; thoracoscopy	Laparoscopy and thoracoscopy	McKeown	McKeown	All compl, pneumonia, pulm compl, AL, chyle leak, RLN palsy, mortality, R0, WI, hospital LOS, LN, OT, blood loss.
Elshaer 2017	Prospective cohort	26	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	Ivor Lewis	AL, chyle leak, mortality, hosp LOS, LN, OT.
Findlay 2017	Prospective cohort	162	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	McKeown	AL, mortality, hosp LOS, LN.
Fumagalli 2019	Prospective cohort	349	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	Ivor Lewis	AL.
Grimminger 2018	Prospective cohort	50	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	Ivor Lewis	Pneumonia, AL, reoperation, chyle leakage, mortality, R0, WI, ICU LOS, hosp LOS, LN, OT
Hamouda 2010	Prospective cohort	51	LA; laparoscopy	Laparoscopy and VATS	Ivor Lewis	Ivor Lewis	Pulm compl, AL, reoperation, chyle leak, R0
Ichikawa 2013	Prospective cohort	315	TA; thoracoscopy	HALS and thoracoscopy	McKeown	McKeown	All compl, pulm compl, AL, chyle leak, RLN palsy, mortality, R0, ICU LOS, LN, OT, blood loss
Kinjo 2012	Cohort (not specified)	106	TA; thoracoscopy	HALS or laparoscopy and thoracoscopy	McKeown	McKeown	All compl, pneumonia, pulm compl, AL, reoperation, chyle leak, RLN palsy, mortality, R0, WI, ICU LOS, hosp LOS, blood loss
Kitagawa 2016	Retrospective cohort	105	LA, laparoscopy	Laparoscopy and thoracoscopy	McKeown	McKeown	Pneumonia, AL, RLN palsy, mortality, WI, ICU LOS, hosp LOS, LN, blood loss.
Kubo 2014	Cohort (not specified)	135	LA; HALS	HALS and VATS	McKeown	McKeown	All compl, pneumonia, pulm compl, AL, chyle leak, RLN palsy, mortality, ICU LOS, hosp LOS, OT, blood loss
Lee 2011	Prospective cohort	74	TA; VATS	HALS and VATS	McKeown	McKeown	Pulm compl, AL, mortality, ICU LOS, hosp LOS, LN, OT, blood loss
Lee 2015	Cohort (not specified)	98	TA; VATS	Laparoscopy and VATS	Ivor Lewis	Ivor Lewis	Pneumonia, pulm compl, AL, mortality, hosp LOS, LN, OT, blood loss
Li 2018	Retrospective cohort	172	TA; thoracoscopy	Laparoscopy and thoracoscopy	McKeown	McKeown	Pneumonia, pulm compl, AL, chyle leak, RLN palsy, WI, hosp LOS, LN, OT, blood loss
Mao 2015	Retrospective cohort	59	LA and TA; laparoscopy and thoracoscopy	Laparoscopy and thoracoscopy	McKeown	McKeown	AL, mortality
Martin 2005	Prospective cohort	36	TA; thoracoscopy	HALS and thoracoscopy	McKeown	McKeown	OT.
Mu 2015	Retrospective cohort	445	LA and TA; laparoscopy & thoracoscopy	Laparoscopy and thoracoscopy	McKeown	McKeown	All compl, pulm compl, AL, mortality, R0, hosp LOS, LN, OT, blood loss
Nilsson 2017	Cohort (not specified)	173	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	Ivor Lewis and McKeown	Pulm compl, AL, severe compl
Nozaki 2017	Prospective cohort	101	TA; thoracoscopy	HALS/laparoscopy and thoracoscopy	Ivor Lewis and McKeown (94% McKeown)	Ivor Lewis and McKeown (94% McKeown)	Pneumonia, pulm compl, AL, RLN palsy, mortality, hosp LOS, LN, OT, blood loss
Oshikiri 2016	Cohort (not specified)	64	TA, thoracoscopy	HALS and thoracoscopy	McKeown	McKeown	Pneumonia, AL, RLN palsy, mortality, hosp LOS, OT, blood loss
Safranek 2010	Prospective cohort	75	LA & TA; laparoscopy and thoracoscopy	Laparoscopy and thoracoscopy	McKeown	McKeown	Pneumonia AL, reoperation, RLN palsy, mortality, R0, ICU LOS, hosp LOS, LN, OT
Smithers 2007	Prospective cohort	332	TA; thoracoscopy	Laparoscopy and thoracoscopy	McKeown	McKeown	All compl, pneumonia, pulm compl, AL, chyle leak, RLN palsy, mortality, R0, ICU LOS, hosp LOS, LN, OT, blood loss
Souche 2019	Prospective cohort	137	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	Ivor Lewis	Pneurmonia, pulm compl, AL, severe compl, reoperation, all compl, RLN palsy, mortality, R0, WI, hosp LOS, LN, OT, blood loss
Tsujimoto 2012	Retrospective cohort	49	LA; laparoscopy	Laparoscopy and thoracoscopy	Ivor Lewis	Ivor Lewis & McKeown	All compl, pulm compl, AL, chyle leak, RLN palsy, mortality, WI, ICU LOS, hosp LOS, OT, blood loss
Yanasoot 2017	Cohort (not specified)	29	TA; thoracoscopy	Laparoscopy and thoracoscopy	McKeown	McKeown	Pneumonia, AL, RLN palsy, mortality, WI, ICU LOS, Hosp LOS, OT, blood loss
Yao 2017	Prospective cohort	131	TA; thoracoscopy	Laparoscopy and thoracoscopy	McKeown	McKeown	Pulm compl, AL, chyle leak, RLN palsy, mortality, R0, WI, hosp LOS, LN, OT, blood loss

TMIE, totally minimally invasive esophagectomy; HMIE, hybrid minimally invasive esophagectomy; LA, laparoscopy assisted (thus: minimally invasive abdominal and open thoracic stage); TA, thoracoscopy assisted (thus: minimally invasive thoracic and open abdominal stage); PSMA, propensity score matched analysis; VATS, video-assisted thoracic surgery; HALS, hand-assisted laparoscopic surgery; compl, complications; pulm compl, pulmonary complications; AL, anastomotic leakage; RLN, recurrent laryngeal nerve; R0, R0 resection rate; WI, wound infection; ICU, intensive care unit; LOS, length of stay; LN, lymph nodes examined; OT, operating time

Table 2 All hybrid minimally invasive esophagectomy versus totally minimally invasive esophagectomy

	No of studies	No of patients	RR/SMD (95% CI)	I^2 (%)
Pneumonia (RR)	15	1492	1.46 (0.97–2.20)	39
Pulmonary complications (RR)	18	2653	1.24 (0.97–1.58)	31
Anastomotic leakage (RR)	27	3572	0.94 (0.73–1.21)	32
Chyle leakage (RR)	13	1641	1.13 (0.62–2.04)	0
RLN palsy (RR)	16	2035	0.90 (0.65–1.25)	22
Wound infection (RR)	11	1003	***1.81 (1.13–2.90)***	0
Severe complications (RR)	5	654	0.95 (0.72–1.25)	24
All complications (RR)	9	1643	1.10 (0.99–1.23)	0
Reoperation (RR)	7	703	0.86 (0.51–1.46)	0
Postoperative mortality (RR)	24	2951	1.33 (0.73–2.41)	0
Irradical resection (RR)	13	2066	1.22 (0.93–1.60)	0
Intensive care LOS (SMD)	12	1490	0.19 (0.00–0.38)	59
Hospital LOS (SMD)	23	2699	0.19 (0.00–0.39)	79
Extracted lymph nodes (SMD)	19	2630	−0.01 (−0.24–0.22)	85
Operating time (SMD)	23	2782	***−0.33 (−0.59–−0.08)***	88
Blood loss (SMD)	71	2701	***0.78 (0.34–1.22)***	96

RR, relative risk; SMD, standardized mean difference; CI, confidence interval. For dichotomous parameters, RR > 1 favors TMIE and RR < 1 favors HMIE. For continuous parameters, SMD >0 favors TMIE and SMD <0 favors HMIE, except for the parameter 'Extracted lymph nodes', in which SMD >0 favors HMIE and SMD <0 favors TMIE

Table 3 Laparoscopy-assisted hybrid minimally invasive esophagectomy versus totally minimally invasive esophagectomy

	No of studies	No of patients	RR/SMD (95% CI)	I^2 (%)
Pneumonia (RR)	6	451	***1.86 (1.03–3.37)***	9
Pulmonary complications (RR)	9	889	1.15 (0.78–1.71)	44
Anastomotic leakage (RR)	14	1581	0.79 (0.57–1.11)	30
Chyle leakage (RR)	5	521	1.10 (0.48–2.53)	0
RLN palsy (RR)	6	646	0.68 (0.35–1.35)	23
Wound infection (RR)	5	501	1.69 (0.96–2.96)	0
Severe complications (RR)	5	654	0.95 (0.72–1.25)	24
All complications (RR)	4	381	1.00 (0.82–1.22)	0
Reoperation (RR)	5	522	0.79 (0.43–1.46)	0
Postoperative mortality (RR)	12	1132	1.28 (0.61–2.67)	0
Irradical resection (RR)	6	620	1.44 (0.91–2.29)	0
Intensive care LOS (SMD)	7	633	0.28 (−0.06–0.61)	75
Hospital LOS (SMD)	12	1082	0.16 (−0.08–0.39)	69
Extracted lymph nodes (SMD)	10	898	***0.29 (0.10–0.49)***	47
Operating time (SMD)	11	920	***−0.50 (−0.74–−0.25)***	65
Blood loss (SMD)	9	844	***0.39 (0.07–0.72)***	79

RR, relative risk; SMD, standardized mean difference; CI, confidence interval. For dichotomous parameters, RR > 1 favors TMIE and RR < 1 favors HMIE. For continuous parameters, SMD >0 favors TMIE and SMD <0 favors HMIE, except for the parameter 'Extracted lymph nodes', in which SMD >0 favors HMIE and SMD <0 favors TMIE

parameters regarding postoperative morbidity showed moderately improved outcome after TMIE compared to HMIE. However, we additionally found that anastomotic leakage was higher after Ivor Lewis TMIE compared to Ivor Lewis HMIE and that laparoscopy-assisted HMIE was associated with higher numbers of extracted lymph nodes compared to TMIE, and this suggests that TMIE can also have disadvantages regarding clinically important outcome parameters.

The major strength of this systematic review and meta- analysis is that this is the first study that directly compares the effectiveness of HMIE with TMIE. Some possible limitations should also be discussed. First, although statistical heterogeneity was limited, supporting our decision to pool results of the included studies in a meta-analysis, clinical heterogeneity (i.e. variations in surgical technique of HMIE and TMIE) was present. The variations in surgical technique of the included studies reflect the current lack of robust evidence on the optimal surgical technique for resection of esophageal cancer.[1] In order to address this, we performed subgroup-and sensitivity analyses for which we included studies that only compared similar types of surgery, and this indeed resulted in lower heterogeneity for most parameters. Additionally, there was heterogeneity in our primary outcome parameter definition across studies. Second, selection bias could not be excluded since TMIE was most frequently implemented after HMIE and compared retrospectively, possibly favoring outcome in the TMIE group. However, the fact that the anastomotic leakage rate was higher after TMIE cannot be explained by this type of selection bias

Table 4 Thoracoscopy-assisted hybrid minimally invasive esophagectomy versus totally minimally invasive esophagectomy

	No of studies	No of patients	RR/SMD (95% CI)	I^2 (%)
Pneumonia (RR)	8	966	1.24 (0.66–2.34)	57
Pulmonary complications (RR)	8	1319	1.33 (0.95–1.86)	30
Anastomotic leakage (RR)	10	1412	1.28 (0.81–2.03)	29
Chyle leakage (RR)	6	1120	1.16 (0.50–2.69)	0
RLN palsy (RR)	9	1314	1.16 (0.92–1.45)	0
Wound infection (RR)	5	502	2.13 (0.88–5.14)	0
Severe complications (RR)	0	0	N/A	N/A
All complications (RR)	4	817	***1.16 (1.02–1.32)***	0
Reoperation (RR)	1	106	3.18 (0.56–18.14)	N/A
Postoperative mortality (RR)	9	1240	1.34 (0.36–5.08)	12
Irradical resection (RR)	5	926	0.90 (0.57–1.42)	0
Intensive care LOS (SMD)	4	782	0.17 (0.00–0.34)	0
Hospital LOS (SMD)	9	1097	0.31 (−0.12–0.74)	88
Extracted lymph nodes (SMD)	7	1212	−0.37 (−0.81–0.07)	91
Operating time (SMD)	10	1342	0.21 (−0.65–0.23)	91
Blood loss (SMD)	10	1412	***1.03 (0.31–1.75)***	97

RR, relative risk; SMD, standardized mean difference; CI, confidence interval. For dichotomous parameters, RR > 1 favors TMIE and RR < 1 favors HMIE. For continuous parameters, SMD >0 favors TMIE and SMD <0 favors HMIE, except for the parameter 'Extracted lymph nodes', in which SMD >0 favors HMIE and SMD <0 favors TMIE

Table 5 Laparoscopy-assisted hybrid minimally invasive Ivor Lewis esophagectomy versus totally minimally invasive Ivor Lewis esophagectomy

	No of studies	No of patients	RR/SMD (95% CI)	I^2 (%)
Pneumonia (RR)	4	297	1.83 (0.71–4.71)	32
Pulmonary complications (RR)	4	298	1.45 (0.98–2.15)	4
Anastomotic leakage (RR)	7	723	***0.55 (0.38–0.80)***	0
Chyle leakage (RR)	4	177	1.05 (0.21–5.28)	0
RLN palsy (RR)	2	197	4.18 (0.52–33.57)	0
Wound infection (RR)	2	187	***7.33 (1.39–38.61)***	0
Severe complications (RR)	2	197	0.85 (0.57–1.27)	0
All complications (RR)	2	197	1.02 (0.79–1.32)	0
Reoperation (RR)	3	238	2.21 (0.44–11.06	0
Postoperative mortality (RR)	5	323	0.85 (0.17–4.19)	0
Irradical resection (RR)	4	298	1.63 (0.39–6.73)	0
Intensive care LOS (SMD)	2	110	0.45 (−0.77–1.67)	89
Hospital LOS (SMD)	4	273	−0.05 (−0.31–0.21)	9
Extracted lymph nodes (SMD)	4	273	0.17 (−0.09–0.42)	6
Operating time (SMD)	4	273	***−0.47 (−0.72–-0.23)***	0
Blood loss (SMD)	2	197	***0.66 (0.36–0.95***	0

RR, relative risk; SMD, standardized mean difference; CI, confidence interval. For dichotomous parameters, RR > 1 favors TMIE and RR < 1 favors HMIE. For continuous parameters, SMD >0 favors TMIE and SMD <0 favors HMIE, except for the parameter 'Extracted lymph nodes', in which SMD >0 favors HMIE and SMD <0 favors TMIE

since TMIE cases were generally operated on in later time frames. In addition, TMIE has been described to be associated with a significant learning curve, and this might favor outcome in the HMIE group.[41–44] Finally, the Newcastle–Ottawa rating scale was used because high-quality randomized studies were absent. Although this score gives a relevant indication of the quality of non-randomized studies, it generally results in an overestimation of the quality of the included studies, and this should be taken into account when interpreting the results of this study.

Currently, no RCTs have been performed that compared the effectiveness of HMIE versus TMIE, and as far as we are aware, no RCTs are currently being performed on this subject. Although the ROMIO feasibility trial has randomized between open, laparoscopy-assisted HMIE and TMIE, this feasibility study was not designed to identify a difference between HMIE and TMIE,[45] and the definitive ROMIO trial does not randomize patients between open esophagectomy and laparoscopy-assisted HMIE.[46] Therefore, surgeons will have to rely on non-randomized data when making decisions regarding whether to use HMIE or TMIE for surgical resection of esophageal cancer. The current meta-analysis provides an overview of the best available evidence on differences in outcome of HMIE compared to TMIE. From our data, TMIE was generally associated with a (trend towards) lower postoperative morbidity compared to HMIE. This suggests that TMIE has potential benefits over HMIE regarding morbidity. However, anastomotic leakage was higher after Ivor Lewis TMIE compared to Ivor Lewis HMIE. This may be explained by a

Table 6 Hybrid minimally invasive McKeown esophagectomy versus totally minimally invasive McKeown esophagectomy

	No of studies	No of patients	RR/SMD (95% CI)	I^2 (%)
Pneumonia (RR)	8	947	1.46 (0.84–2.54)	52
Pulmonary complications (RR)	9	1774	***1.45 (1.05–1.99)***	21
Anastomotic leakage (RR)	14	2106	1.26 (0.93–1.72)	19
Chyle leakage (RR)	7	1255	1.14 (0.58–2.25)	0
RLN palsy (RR)	11	1528	0.82 (0.56–1.22)	36
Wound infection (RR)	6	607	1.65 (0.98–2.78)	0
Severe complications (RR)	0	0	N/A	N/A
All complications (RR)	6	1397	1.13 (1.00–1.27)	0
Reoperation (RR)	2	181	1.25 (0.25–6.28)	55
Postoperative mortality (RR)	13	1934	1.74 (0.68–4.48)	0
Irradical resection (RR)	7	1446	1.12 (0.81–1.57)	0
Intensive care LOS (SMD)	8	1171	0.12 (−0.02–0.26)	7
Hospital LOS (SMD)	12	1732	***0.38 (0.09–0.66)***	83
Extracted lymph nodes (SMD)	9	1712	−0.18 (−0.46–0.10)	83
Operating time (SMD)	13	1977	−0.26 (−0.62–0.10)	91
Blood loss (SMD)	12	1972	***1.11 (0.46–1.75)***	83

RR, relative risk; SMD, standardized mean difference; CI, confidence interval. For dichotomous parameters, RR > 1 favors TMIE and RR < 1 favors HMIE. For continuous parameters, SMD >0 favors TMIE and SMD <0 favors HMIE, except for the parameter 'Extracted lymph nodes', in which SMD >0 favors HMIE and SMD <0 favors TMIE

surgical learning curve, which has been described to be long for Ivor Lewis TMIE (>100 cases, which can correspond to years of practice),[41,43,44] since intrathoracic anastomosis can be difficult to perform safely with minimally invasive techniques. Although no studies have been published that directly compare learning curves of HMIE and TMIE, it is assumed that HMIE is associated with a shorter learning curve and less associated morbidity because it is technically less complex. However, literature also shows that favorable results of TMIE can be achieved after the learning curve has been completed,[43,44] but this might not have been the case in most included studies. Another important finding is that laparoscopy-assisted HMIE was associated with higher numbers of extracted lymph nodes compared to TMIE. This suggests that surgeons performing thoracoscopic instead of open thoracic resection performed a more limited lymph node dissection, although other factors (e.g. pathology department related) may have also influenced lymph node count. In general, higher lymph node count is associated with improved survival after esophagectomy, and this is therefore an important finding.[47] However, similar rates of extracted lymph nodes after minimally invasive versus open surgery and even higher numbers of extracted lymph nodes after thoracoscopic versus open transthoracic resection have been reported.[48,49]

Clinical implications

Currently, HMIE and TMIE are regarded as equally effective, and safe surgical approaches and both procedures are used to treat patients with esophageal cancer worldwide. In this meta-analysis, a moderate benefit for TMIE regarding morbidity was found. Because outcomes between HMIE and TMIE are only moderately different, the learning curve of HMIE and TMIE procedures and its associated morbidity may also be important arguments in choosing which type of procedure to implement.[50] Therefore, surgeons moving from HMIE to TMIE should carefully consider this, since this study showed that TMIE can also have disadvantageous effects and randomized controlled evidence supporting the benefits of TMIE over HMIE is lacking.

CONCLUSIONS

In general, TMIE was associated with moderately lower morbidity compared to HMIE, but randomized controlled evidence is lacking. The higher leakage rate and lower lymph node count that was found after TMIE in sensitivity analysis indicate that TMIE can also have disadvantages. The findings of this meta-analysis should be considered carefully by surgeons when moving from HMIE to TMIE.

DETAILS OF CONTRIBUTIONS

All authors contributed to the design of the work; F. Van Workum and B.R. Klarenbeek and N. Baranov were involved in acquisition of the data. Analysis was performed by F. van Workum, and all other authors were involved in interpretation of the work. F. Van Workum and B.R. Klarenbeek were involved in drafting the manuscript. All other authors were involved in critically revising the manuscript for intellectual content. All authors approve of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

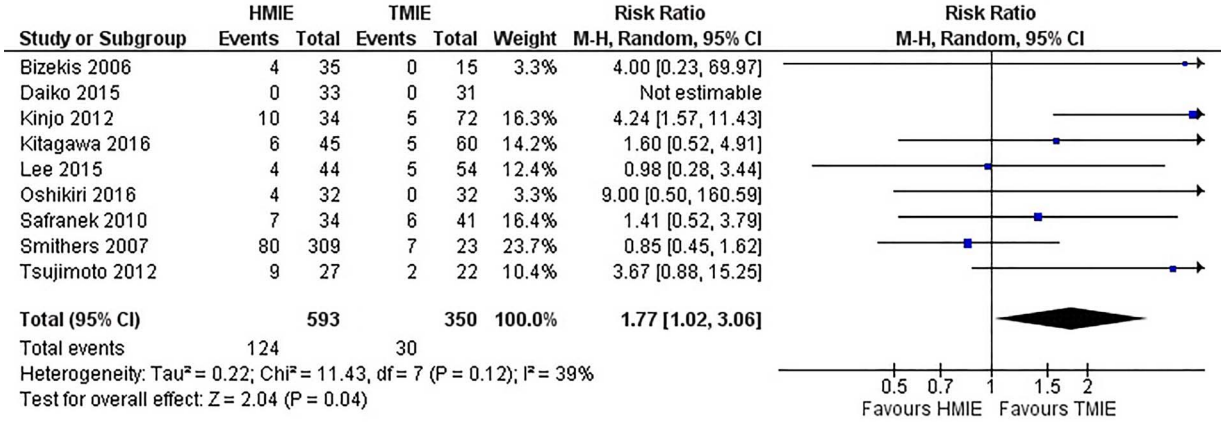

Fig. 2 All hybrid minimally invasive esophagectomy (HMIE) versus totally minimally invasive esophagectomy (TMIE) for primary outcome parameter pneumonia.

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APPENDIX I—PRISMA checklist

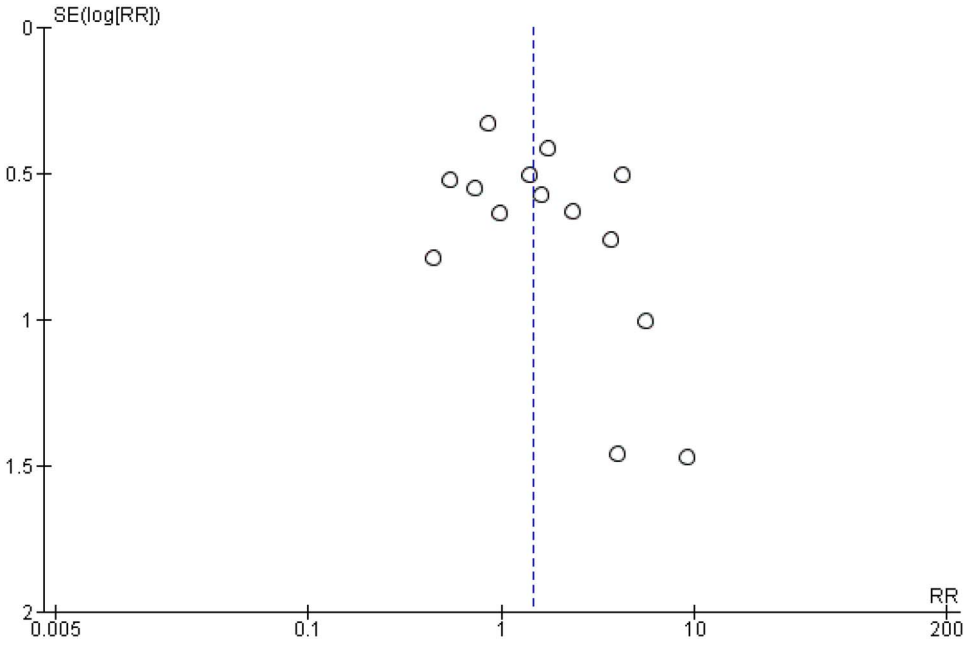
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4,5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7, online appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7,8, Figure 2, Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9, table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7, online appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8,9, table 3-6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11,12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

1. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

APPENDIX II—Risk of bias assessment

Study	Representative	Selection	Ascertainment of exposure	Demonstration	Comparability	Outcome	Follow-up	Adequacy follow-up	Total stars
Berlth 2018	1	1	1	1	2	1	1	1	9
Bizekis 2006	1	0	1	1	0	1	1	1	6
Blazeby 2011	1	0	1	1	0	1	1	1	6
Bonavina 2016	1	0	1	1	2	1	1	1	8
Daiko 2015	1	0	1	1	0	1	1	1	6
Elshaer 2017	1	0	1	1	0	1	1	1	6
Findlay 2017	1	0	1	1	0	1	1	1	6
Fumagalli 2019	1	0	1	1	0	1	1	1	6
Grimminger 2018	1	0	1	1	0	1	1	1	6
Hamouda 2009	1	1	1	1	0	1	1	1	7
Kinjo 2012	1	0	1	1	2	1	1	1	8
Kitagawa 2016	1	1	1	1	0	1	1	1	7
Kubo 2014	1	0	1	1	0	1	1	1	6
Ichikawa 2013	1	1	1	1	0	1	1	1	7
Lee 2011	1	1	1	1	0	1	1	1	7
Lee 2015	1	1	1	1	0	1	1	1	7
Li 2018	1	0	1	1	2	1	1	1	8
Mao 2015	1	0	1	1	0	1	1	1	6
Martin 2005	1	0	1	1	0	1	1	1	6
Mu 2015	1	0	1	1	0	1	1	1	6
Nilsson 2017	1	0	1	1	0	1	1	1	6
Nozaki 2017	1	1	1	1	0	1	1	1	7
Oshikiri 2016	1	0	1	1	2	1	1	1	8
Safranek 2010	1	0	1	1	0	1	1	1	6
Smithers 2007	1	1	1	1	0	1	1	1	7
Souche 2019	1	1	1	1	0	1	1	1	7
Tsujimoto 2012	1	1	1	1	0	1	1	1	7
Yanasoot 2017	1	0	1	1	0	1	1	1	6
Yao 2017									

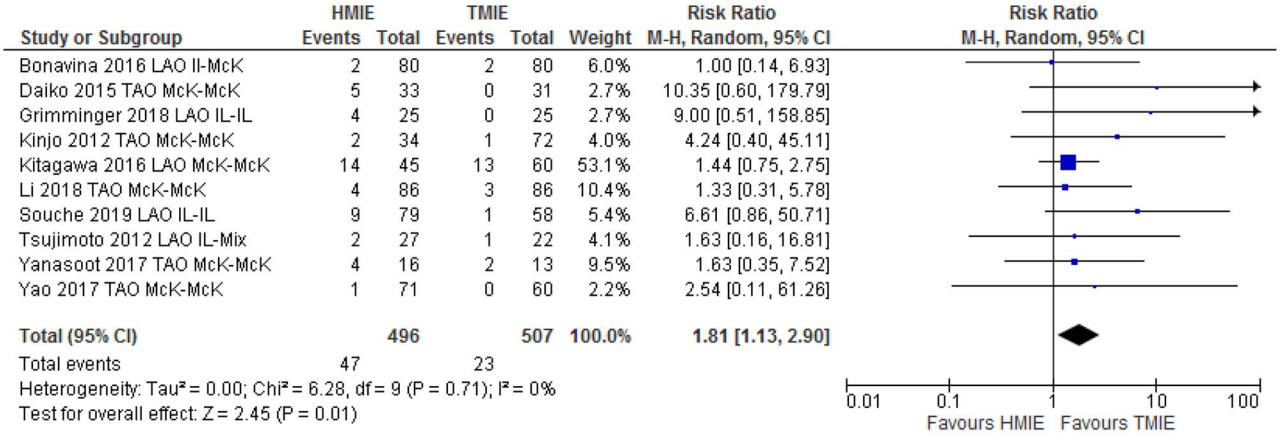
APPENDIX III—Funnel plot for primary outcome parameter pneumonia



APPENDIX IV. Forest plots for parameters showing significant differences between hybrid and total MIE groups

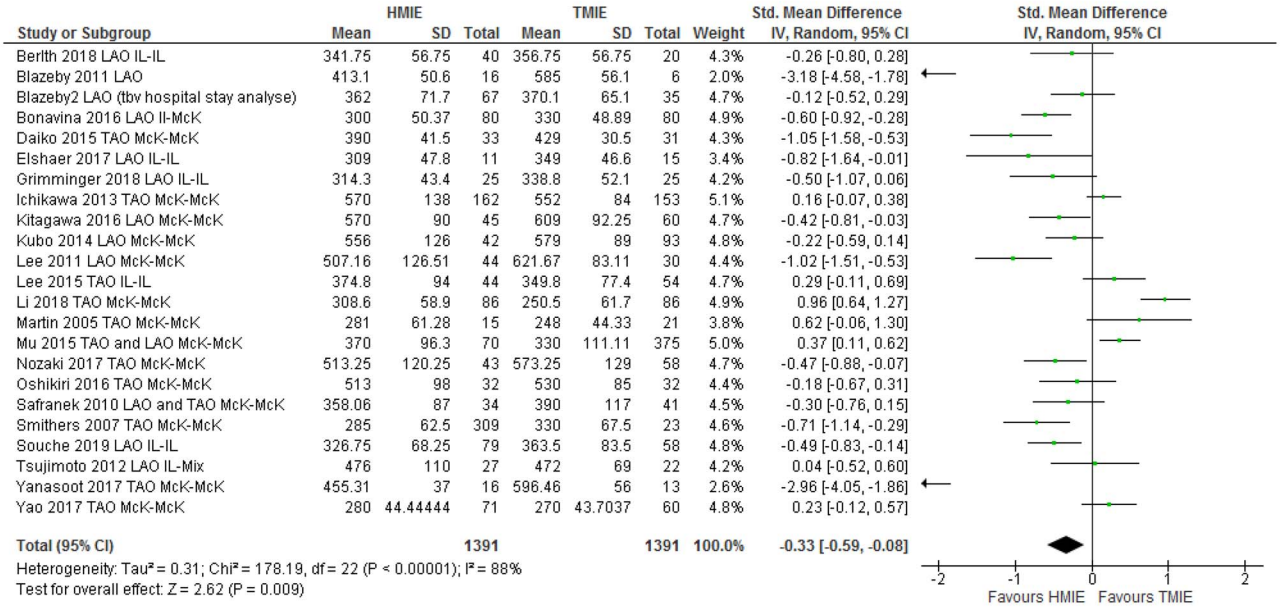
Appendix IV figure 1: Main analysis including all HMIE versus all TMIE.

Appendix IV figure 1A - Wound infection



Relative risk (RR) > 1 favors TMIE and RR<1 favors HMIE.

Appendix IV figure 1B - Operating time

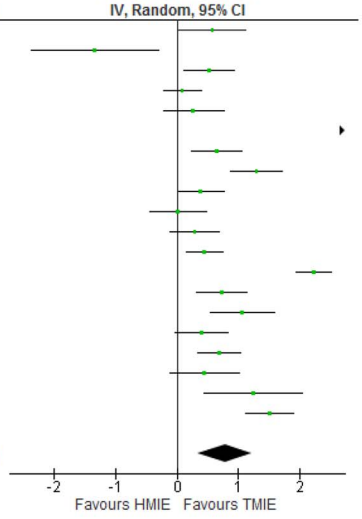


Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

Appendix IV figure 1C – Blood loss

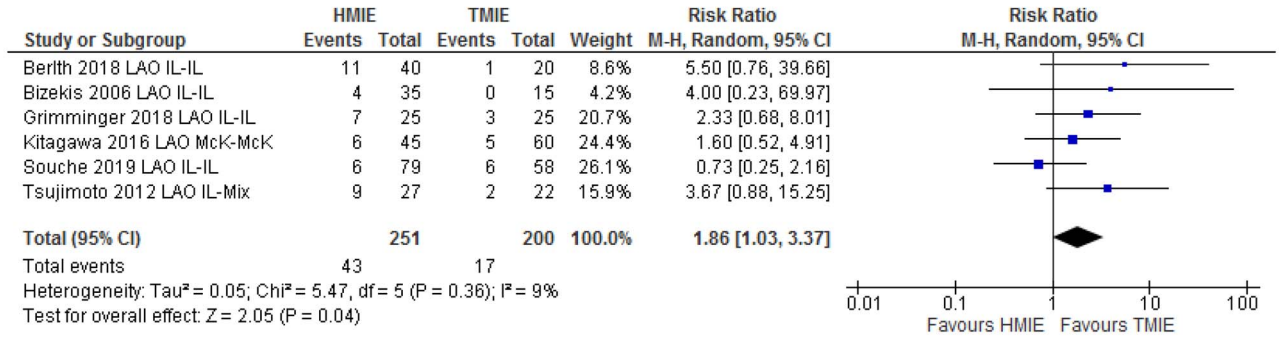
Study or Subgroup	HMIE Mean	HMIE SD	HMIE Total	TMIE Mean	TMIE SD	TMIE Total	Weight	Std. Mean Difference IV, Random, 95% CI
Berlth 2018 LAO IL-IL	450	237.5	40	325	150	20	4.9%	0.58 [0.03, 1.13]
Blazeby 2011 LAO	250.4	142.2	16	445	134.7	6	4.1%	-1.33 [-2.37, -0.30]
Blazeby2 LAO (tbv hospital stay analyse)	330.3	226.4	67	221.5	152.9	35	5.1%	0.53 [0.11, 0.94]
Bonavina 2016 LAO II-McK	300	48.15	80	295	62.96	80	5.2%	0.09 [-0.22, 0.40]
Daiko 2015 TAO McK-McK	498	1,049.25	33	286	283.25	31	5.0%	0.27 [-0.22, 0.76]
Ichikawa 2013 TAO McK-McK	920	183.33	162	410	53.33	153	5.1%	3.72 [3.36, 4.09]
Kinjo 2012 TAO McK-McK	536	363.75	34	320	317.5	72	5.1%	0.64 [0.23, 1.06]
Kitagawa 2016 LAO McK-McK	430	267.5	45	150	164	60	5.1%	1.30 [0.87, 1.72]
Kubo 2014 LAO McK-McK	644	355	42	493	394	93	5.1%	0.39 [0.03, 0.76]
Lee 2011 LAO McK-McK	465	323.3	44	460	355.5	30	5.0%	0.01 [-0.45, 0.48]
Lee 2015 TAO IL-IL	374.8	94	44	349.8	77.4	54	5.1%	0.29 [-0.11, 0.69]
Li 2018 TAO McK-McK	329.8	233.8	86	229.1	210.8	86	5.2%	0.45 [0.15, 0.75]
Mu 2015 TAO and LAO McK-McK	300	148.15	70	100	74.07	375	5.2%	2.23 [1.93, 2.52]
Nozaki 2017 TAO McK-McK	1,231.75	1,056.25	43	649.25	502.5	58	5.1%	0.73 [0.33, 1.14]
Oshikiri 2016 TAO McK-McK	206	102	32	120	49	32	4.9%	1.06 [0.54, 1.59]
Smithers 2007 TAO McK-McK	400	250	309	300	246.25	23	5.1%	0.40 [-0.03, 0.82]
Souche 2019 LAO IL-IL	190	85	79	135.5	70	58	5.2%	0.69 [0.34, 1.03]
Tsujimoto 2012 LAO IL-Mix	544	365	27	373	388	22	4.9%	0.45 [-0.12, 1.02]
Yanasoot 2017 TAO McK-McK	340.63	96.84	16	246.15	24.97	13	4.5%	1.24 [0.43, 2.05]
Yao 2017 TAO McK-McK	150	37.03704	71	100	27.40741	60	5.1%	1.51 [1.12, 1.90]
Total (95% CI)			**1340**			**1361**	**100.0%**	**0.78 [0.34, 1.22]**

Heterogeneity: Tau² = 0.95; Chi² = 424.00, df = 19 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.49 (P = 0.0005)



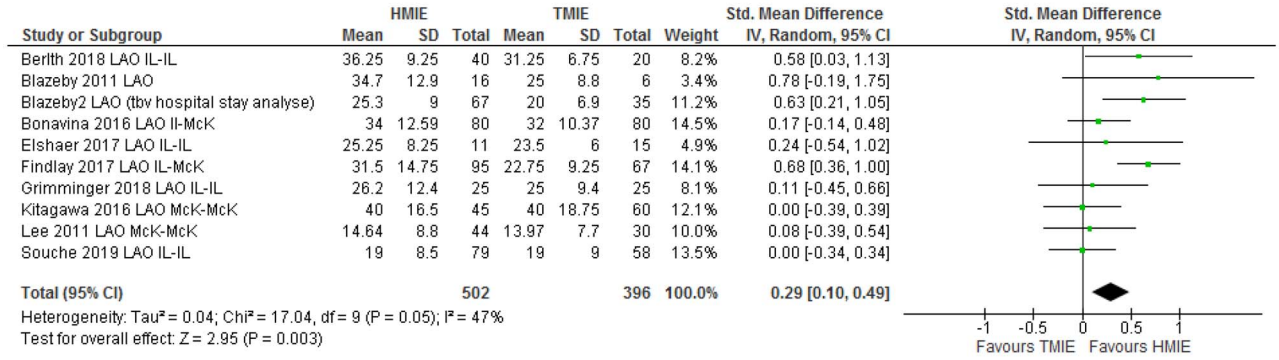
Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

Appendix IV figure 2A – Pneumonia



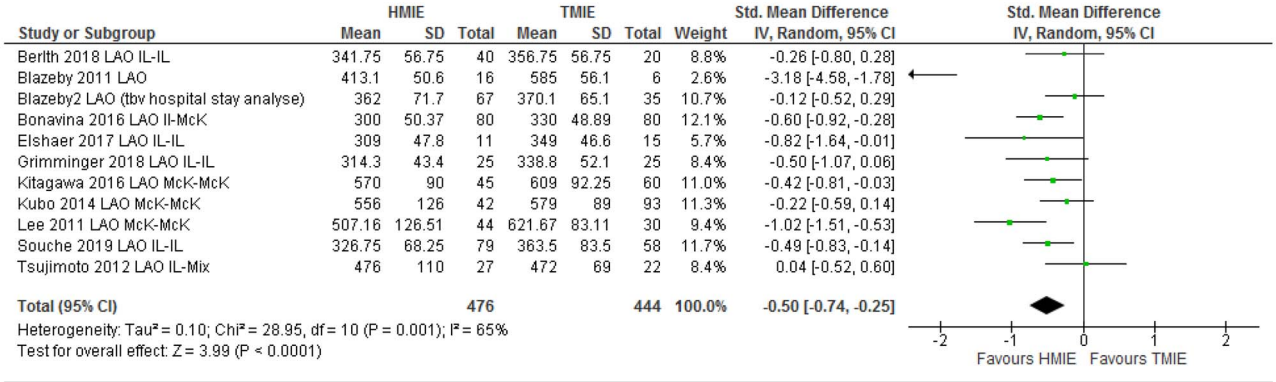
Relative risk (RR) > 1 favors TMIE and RR<1 favors HMIE.

Appendix IV figure 2B – Extracted lymph nodes



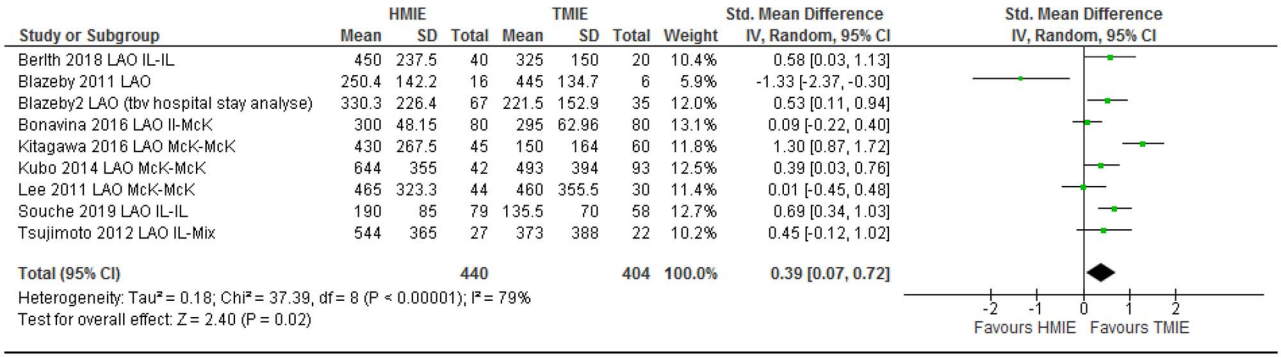
Standardized mean difference (SMD) >0 favors HMIE and SMD <0 favors TMIE.

Appendix IV figure 2C – Operative time



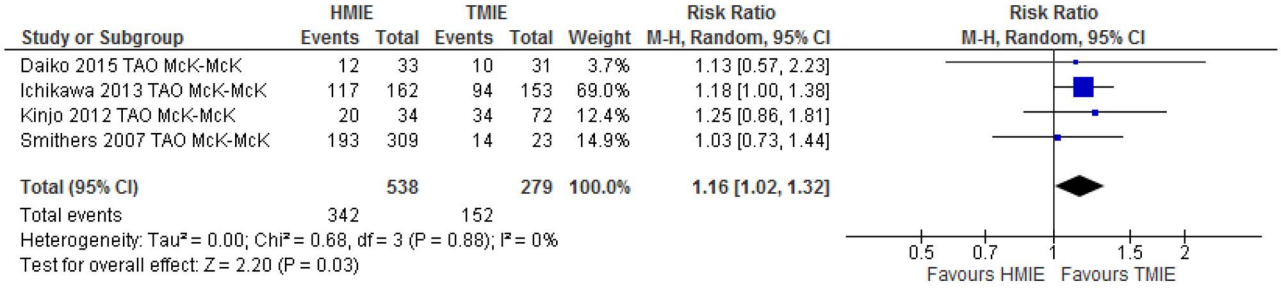
Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

Appendix IV figure 2D – Blood loss



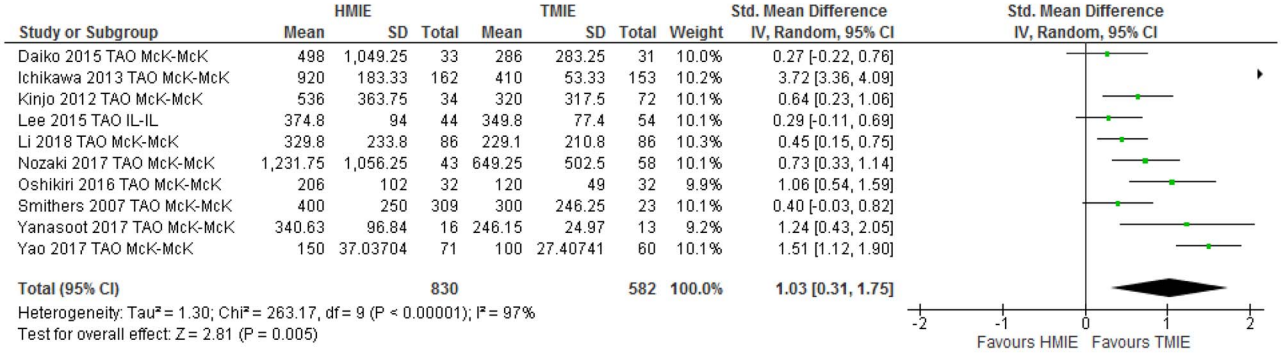
Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

Appendix IV figure 3A – All complications



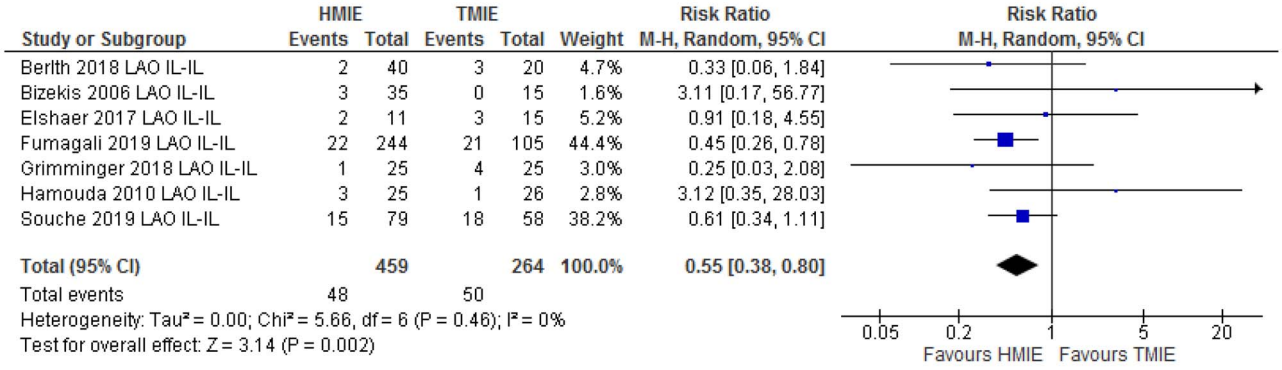
Relative risk (RR) > 1 favors TMIE and RR<1 favors HMIE.

Appendix IV figure 3B – Blood loss



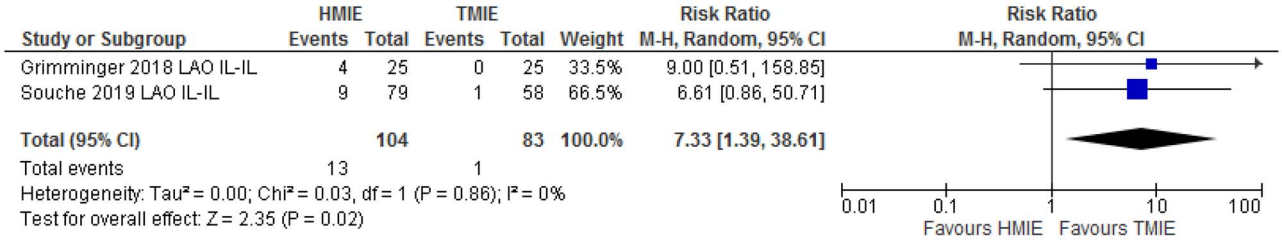
Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

Appendix IV figure 4A – Anastomotic leakage



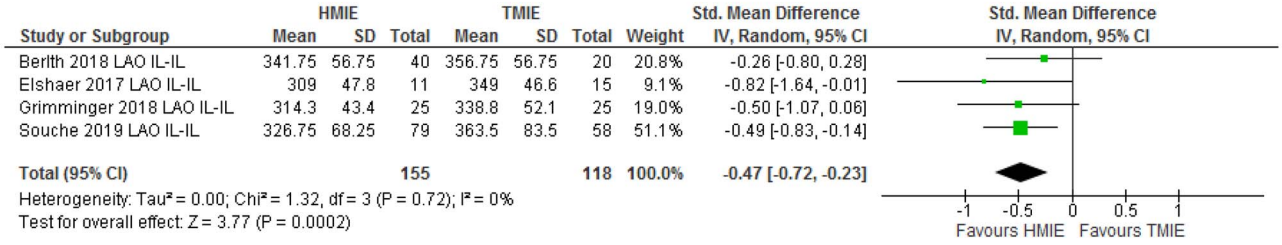
Relative risk (RR) > 1 favors TMIE and RR<1 favors HMIE.

Appendix IV figure 4B – Wound infection



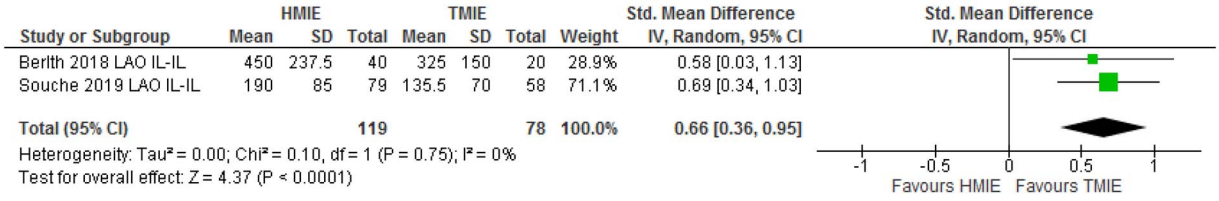
Relative risk (RR) > 1 favors TMIE and RR<1 favors HMIE.

Appendix IV figure 4C – Operating time



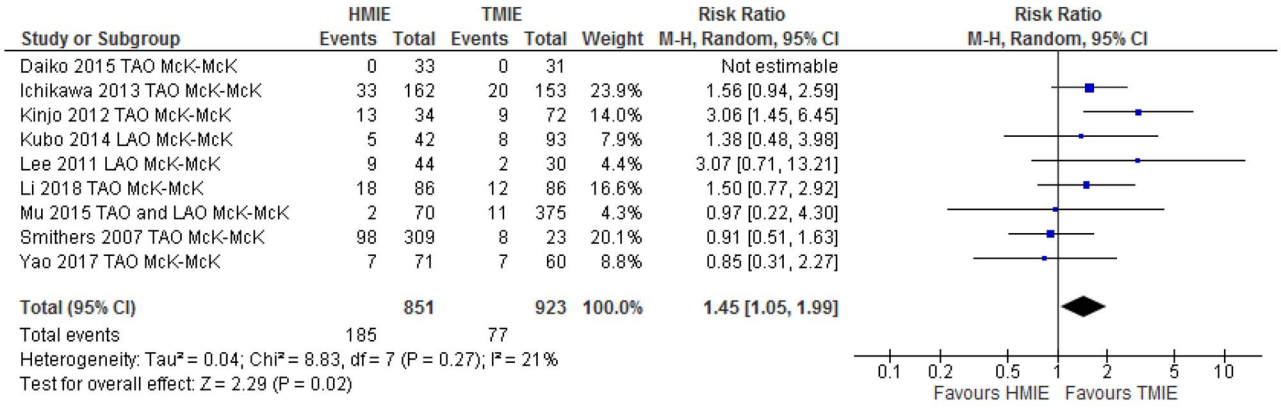
Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

Appendix IV figure 4D – Blood loss



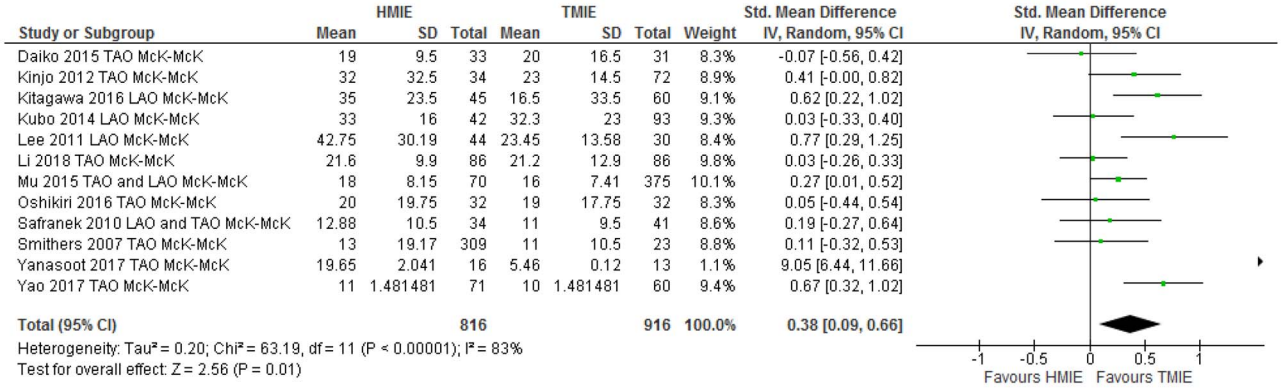
Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

Appendix IV figure 5A – Pulmonary complications



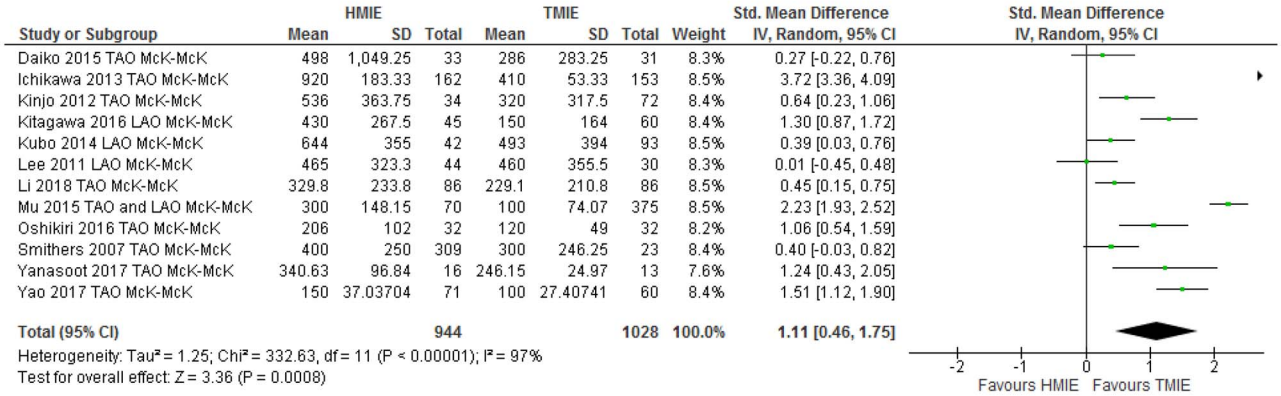
Relative risk (RR) > 1 favors TMIE and RR<1 favors HMIE.

Appendix IV figure 5B – Hospital length of stay



Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

Appendix IV figure 5C – Blood loss



Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

APPENDIX IV-A: MAIN ANALYSIS INCLUDING ALL HMIE VERSUS ALL TMIE

1. *Wound infection*

Relative risk (RR) > 1 favors TMIE and RR < 1 favors HMIE.

2. *Operating time*

Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

3. *Blood loss*

Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE.

APPENDIX IV-B: SUBGROUP ANALYSIS INCLUDING LAPAROSCOPY-ASSISTED HYBRID MINIMALLY INVASIVE ESOPHAGECTOMY VERSUS TOTALLY MINIMALLY INVASIVE ESOPHAGECTOMY

1. *Pneumonia*

Relative risk (RR) > 1 favors TMIE and RR < 1 favors HMIE.

2. *Extracted lymph nodes*

Standardized mean difference (SMD) >0 favors HMIE and SMD <0 favors TMIE.

3. Operative time

Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

4. Blood loss

Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE.

APPENDIX IV-C: SUBGROUP ANALYSIS INCLUDING THORACOSCOPY-ASSISTED HYBRID MINIMALLY INVASIVE ESOPHAGECTOMY VERSUS TOTALLY MINIMALLY INVASIVE ESOPHAGECTOMY

1. All complications

Relative risk (RR) > 1 favors TMIE and RR < 1 favors HMIE.

2. Blood loss

Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE.

APPENDIX IV-D: SUBGROUP ANALYSIS INCLUDING LAPAROSCOPY-ASSISTED HYBRID MINIMALLY INVASIVE IVOR LEWIS ESOPHAGECTOMY VERSUS TOTALLY MINIMALLY INVASIVE IVOR LEWIS ESOPHAGECTOMY

1. Anastomotic leakage

Relative risk (RR) > 1 favors TMIE and RR < 1 favors HMIE.

2. Wound infection

Relative risk (RR) > 1 favors TMIE and RR < 1 favors HMIE.

3. Operating time

Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

4. Blood loss

Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE.

APPENDIX IV-E: SUBGROUP ANALYSIS INCLUDING HYBRID MINIMALLY INVASIVE MCKEOWN ESOPHAGECTOMY VERSUS TOTALLY MINIMALLY INVASIVE MCKEOWN ESOPHAGECTOMY

1. Pulmonary complications

Relative risk (RR) > 1 favors TMIE and RR < 1 favors HMIE.

2. Hospital length of stay

Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE

3. Blood loss

Standardized mean difference (SMD) >0 favors TMIE and SMD <0 favors HMIE.