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Early outcomes with robot-assisted *vs.* minimally invasive esophagectomy for esophageal cancer: a systematic review and meta-analysis of matched studies

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Abstract. – OBJECTIVE: The current study aimed to compare intraoperative and early postoperative outcomes with robot-assisted esophagectomy (RAE) *vs.* minimally invasive esophagectomy (MIE) for esophageal cancer.

MATERIALS AND METHODS: We searched PubMed, Embase, and Google Scholar for randomized controlled trials (RCTs) or propensity-matched cohort studies comparing RAE with MIE for patients with esophageal cancer.

RESULTS: One RCT and 14 retrospective propensity-matched studies were included. Meta-analysis revealed significantly increased operative time (MD: 32.89 95% CI: 6.42, 59.35 I^2=95% *p*=0.01) and reduced blood loss (MD: -35.15 95% CI: -61.30, -8.99 I^2=82% *p*=0.008) with RAE. Both the results turned statistically non-significant on exclusion of one study. The was no difference between the two techniques for anastomotic leak (RR: 0.98 95% CI: 0.76, 1.24 I^2=0% *p*=0.84), chyle leak (RR: 0.94 95% CI: 0.48, 1.83 I^2=0% *p*=0.86), recurrent laryngeal nerve palsy (RR: 0.92 95% CI: 0.61, 1.39 I^2=70% *p*=0.69), cardiac complication (RR: 1.06 95% CI: 0.64, 1.78 I^2=0% *p*=0.82), infectious complications (RR: 1.06 95% CI: 0.47, 2.42 I^2=0% *p*=0.88), conversion to open surgery (RR: 0.60 95% CI: 0.25, 1.43 I^2=56% *p*=0.25) or early mortality (RR: 1.04 95% CI: 0.74, 1.47 I^2=0% *p*=0.82). However, pulmonary complications were significantly reduced with RAE as compared to MIE (RR: 0.72 95% CI: 0.60, 0.86 I^2=0% *p*=0.003).

CONCLUSIONS: RAE is associated with a tendency of longer operating time and reduced blood loss as compared to MIE. RAE significantly reduces pulmonary complications as compared to MIE but has no impact on the incidence of anastomotic leak, chyle leak, RLN palsy, cardiac complication, infectious complications, conversion to open surgery, or early mortality.

Key Words:
Robotic surgery, Video-assisted surgery, Thoracoscopy, Esophagectomy, Complications, Mortality.

Introduction

Globally, esophageal cancer is the eighth most prevalent cancer and the sixth leading cause of cancer-related deaths[1]. It is frequently metastatic and associated with a low 5-year survival of only 15% to 25%[2]. While the primary management of the disease consists of radical esophagectomy with extended lymphadenectomy, the intervention using open thoracotomy is quite invasive[3]. Since patients with esophageal cancer have poor nutritional status, the morbidity of a major open surgical procedure can make the management of such patients quite challenging[4].

In the past few decades, minimally invasive esophagectomy (MIE) consisting of video-assisted thoracotomy with or without laparoscopically assisted abdominal phase has increasingly replaced open esophagectomy due to its low morbidity and mortality[5]. A meta-analysis[6] has demonstrated that MIE results in significantly lower blood loss, reduced pulmonary complications, and a shorter duration of hospital stay as compared to open surgery. Furthermore, 1-year and 5-year survival rates were also lower with MIE as compared to the open technique[6]. However, a challenge with MIE is the technical complexity of the procedure, especially for the thoracic phase. With further improvements in technology, the technical limitations of MIE were overcome

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with the introduction of robot-assisted esophagectomy (RAE) which provided advantages of better magnification, improved dexterity, tremor filtering, and 3-dimensional visual clarity[7]. However, do these advantages result in better clinical outcomes for esophageal cancer patients is still not clear.

To date, several studies[8-11] have compared outcomes of MIE with RAE but with variable results. A recent systematic review and meta-analysis by Zheng et al[12] have compared short-term outcomes with RAE *vs.* MIE by pooling data from 14 retrospective studies. However, an important limitation of retrospective cohort studies is selection bias which can significantly influence the outcomes. To compare the results of two different surgical techniques, the study groups must be matched for baseline characteristics by methods like propensity-score matching[13]. In the past meta-analysis, only eight of the 14 studies conducted propensity-score matching and no subgroup analysis was conducted by the authors to pool separate data of matched and unmatched studies. Therefore, to overcome these limitations and include data of several new studies published in the past year, we aimed to conduct a systematic review and meta-analysis to compare short-term outcomes of RAE *vs.* MIE by pooling data only from matched studies.

Materials and Methods

The methodological approach of our review was based on the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[14]. We prospectively registered the review protocol on PROSPERO with registration No. CRD42021262784.

Literature Search

We searched for relevant articles electronically on the databases of PubMed and Embase. We also employed Google scholar for searching gray literature. To reduce single reviewer bias, two authors searched the databases independent of each other. The search range was from the time of inception of databases up to 1st July 2021. We selected the following terms to explore for pertinent articles: "esophageal cancer", "esophageal neoplasm", "esophagectomy", "robotic", "minimally invasive", and "video-assisted". Details of the search strategy common to all databases are presented in **Supplementary Table I**. After the initial search, the results were deduplicated and the remaining articles were assessed by their titles and abstracts. We identified studies relevant to the review and extracted their full texts. The two reviewers independently evaluated these studies for final inclusion in the review. Any discrepancies in study selection were resolved by consensus. In the end, manual scoping of the reference list of included studies was carried out for any missed references.

Eligibility Criteria

The inclusion criteria based on PICOS (population, intervention, comparison, outcomes, and study type) were formulated as follows: 1) Studies on adult patients (>18 years) undergoing esophagectomy for any type of esophageal cancer (*Population*); 2) Studies were to compare patients undergoing RAE (*Intervention*) with MIE (*Comparison*); 3) Studies were to report any of the following short-term *Outcomes*: intra-operative (operating time, blood loss) or early postoperative outcomes (anastomosis leak, chyle leak, recurrent laryngeal nerve (RLN) palsy, pulmonary complications, cardiac complications, infections, early mortality [within 90 days], or conversion rate to open surgery); 4) Studies type eligible for inclusion were either randomized controlled trials (RCTs) or propensity-matched cohort studies.

For this review, we defined RAE and MIE as procedures wherein the thoracic phase of surgery was performed using the robotic platform or video assistance respectively. For the abdominal phase, we included studies using either robotic or laparoscopic aids or using open laparotomy provided the number of patients undergoing open procedures was <10% of the sample size.

We excluded the following studies: 1) Non-propensity matched studies; 2) Studies comparing outcomes of RAE or MIE with open surgery; 3) Studies not reporting any of the relevant outcomes; 4) Non-English language studies, abstracts, case reports, and review articles; 5) Studies reporting duplicate data.

Data Extraction and Quality Assessment

Data from each study was sourced by two authors independently. We extracted details of the first author, publication year, study type, study location, sample size, diagnostic criteria for PTDM, sample size, demographic details, tumor location, tumor grade, histology, the proportion of Ivor-Lewis technique, neoadjuvant therapy, the technique for the abdominal phase of surgery, and study outcomes. Any disagreements were resolved by discussion.

The methodological quality of studies was assessed using the Newcastle-Ottawa scale (NOS)[15]. It was conducted by two authors independent of each other. Any disagreements were solved by a discussion. Studies were assessed for selection of study population, comparability, and outcomes, with each domain being awarded a maximum of four, two, and three points respectively. The maximum score which can be awarded was nine. Studies with nine points were considered to have a low risk of bias, seven to eight points were considered to have a moderate risk of bias and those with scores of six and below were with a high risk of bias.

Statistical Analysis

We conducted the meta-analysis using "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014). Continuous variables were pooled using mean difference (MD) and 95% confidence intervals (CI). Median, range and interquartile range data was converted into mean and standard deviation (SD) when required using the method of Wan et al[16]. Dichotomous outcomes were pooled using risk ratios (RR) with 95% CI.

All data were pooled in a random-effects model. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity. We visually inspected funnel plots to assess publication bias if the outcome included at least ten studies. A sensitivity analysis was carried out to assess the contribution of each study to the pooled estimate by removing one study one at a time and recalculating the pooled RR estimates for the remaining studies.

Results

The results of the search strategy and the number of records at each stage are presented in Figure 1. Of the 3241 unique records identified, 3209 were excluded based on title and abstract information. Thirty-two articles were analyzed by their full texts. Of these, 13 studies were not propensity-matched while four studies reported duplicate data and hence were excluded. Finally, 15 articles were included in our systematic review and meta-analysis[8,9,23-27,10,11,17-22].

Details of included studies are presented in Table I. Only one was an RCT[27] while all were retrospective cohort studies. The minimum sample size was 29 patients per arm while the maximum sample size was 569 patients per arm. A total of 1921 patients undergoing RAE were compared with 1917 patients undergoing MIE in the included studies. Only two studies[21,24] included patients undergoing open laparotomy for the abdominal phase but with no difference between the study groups. All studies recorded a NOS score of 8. One point was deducted from every study as the adequacy of follow-up of the cohorts was not clear. Two studies[18,27] had a small proportion of overlapping data. 61 patients from the RAE group and 57 patients from the MIE group in the RCT of Yang et al[27] were also included in the previous publication[18].

Intra-Operative Outcomes

Meta-analysis indicated significantly increased operative time in minutes with RAE as compared to MIE (MD: 32.89 95% CI: 6.42, 59.35 I^2=95% p=0.01) (Figure 2). Only on the exclusion of the study of Oshikiri et al[24] the results indicated a tendency of reduced operating time with MIE without any statistically significant difference (MD: 25.26 95% CI: -1.01, 51.53 I^2=95% p=0.06). On the sequential exclusion of the remaining studies, there was no change in the significance of the results. There seemed no evidence of publication bias on the funnel plot (**Supplementary Figure 1**).

On pooled analysis, we noted significantly reduced blood loss in milliliters (ml) with RAE as compared to MIE (MD: -35.15 95% CI: -61.30, -8.99 I^2=82% p=0.008) (Figure 3). However, on the exclusion of the study of Oshikiri et al[24], the difference was non-significant with a tendency of reduced blood loss with RAE (MD: -14.39 95% CI: -29.07, 0.29 I^2=42% p=0.05). On sensitivity analysis with the remaining studies, there was no change in the significance of the results. There was no evidence of publication bias on the funnel plot (**Supplementary Figure 2**).

Post-Operative Outcomes

Meta-analysis revealed no statistically significant difference in the risk of anastomotic leakage (RR: 0.98 95% CI: 0.76, 1.24 I^2=0% p=0.84) (Figure 4) or chyle leak (RR: 0.94 95% CI: 0.48, 1.83 I^2=0% p=0.86) (Figure 5) between the two surgical techniques. The results were stable on sensitivity analysis. The was no publication bias for studies reporting anastomotic leaks (**Supplementary Figure 3**). Pooled analysis demonstrated no statistically significant difference in RLN palsy with RAE or MIE (RR: 0.92 95% CI: 0.61, 1.39 I^2=70% p=0.69) (Figure 6). No change was noted

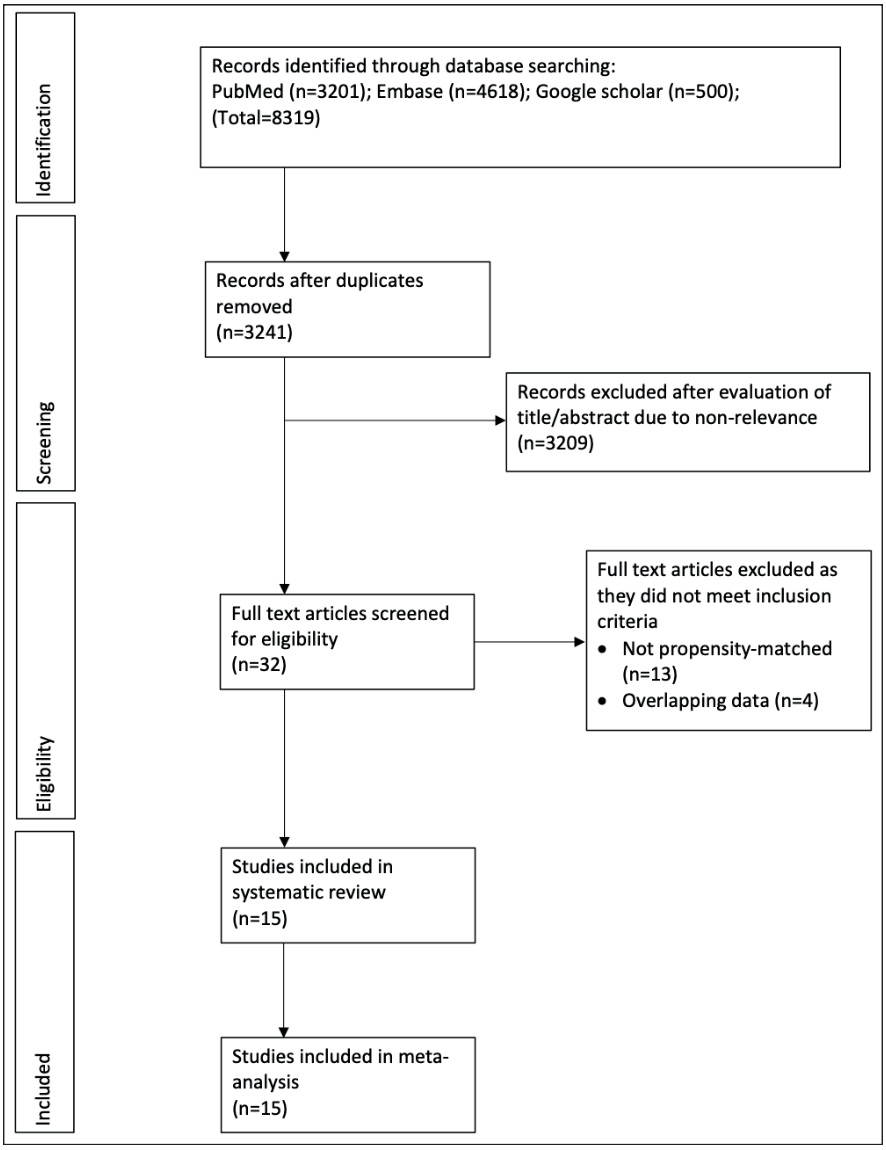

Figure 1. Study flow chart.

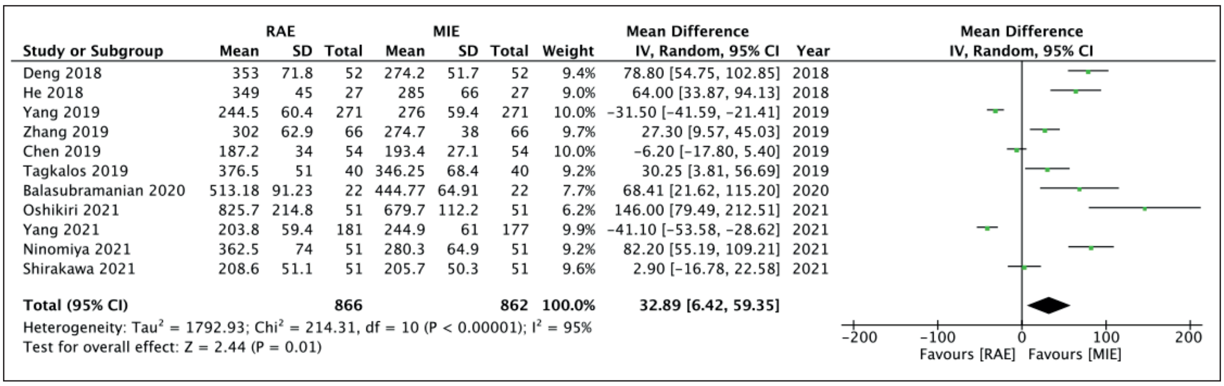

Figure 2. Meta-analysis of operating time between RAE *vs.* MIE.

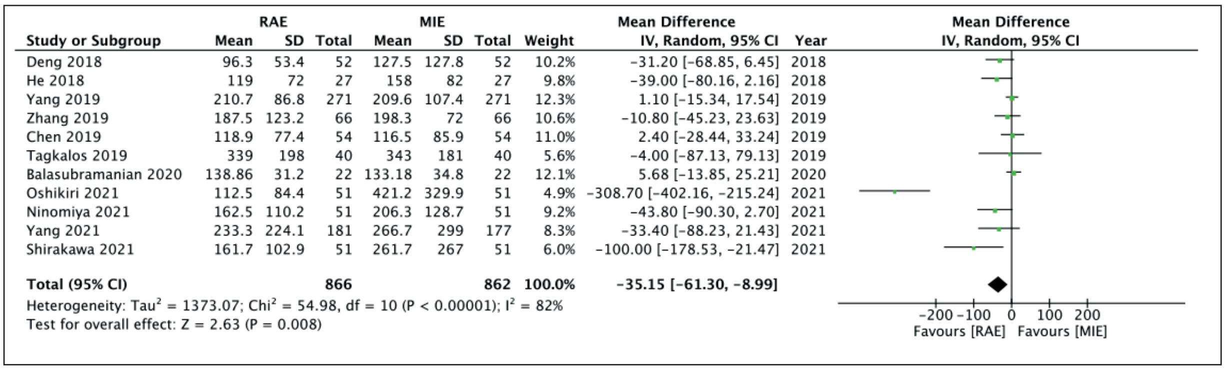

Figure 3. Meta-analysis of blood loss between RAE *vs.* MIE.

on sensitivity analysis and there was no evidence of publication bias (**Supplementary Figure 4**).

Our meta-analysis revealed significantly reduced risk of pulmonary complications with RAE as compared to MIE (RR: 0.72 95% CI: 0.60, 0.86 I^2=0% p=0.003) (Figure 7) but no difference in cardiac (RR: 1.06 95% CI: 0.64, 1.78 I^2=0% p=0.82) (Figure 8) or infectious complications (6 studies) (RR: 1.06 95% CI: 0.47, 2.42 I^2=0% p=0.88) (Figure 9). None of these results changed on sensitivity analysis. The was no publication bias for studies reporting pulmonary complications (**Supplementary Figure 5**).

Meta-analysis revealed no difference in the risk of conversion to open surgery between the two groups (RR: 0.60 95% CI: 0.25, 1.43 I^2=56% p=0.25) (Figure 10). The results were stable on sensitivity analysis. On pooled analysis of early mortality (inclusive of in-hospital, 30-day, and 90-day mortality), we noted no statistically significant difference between the two surgical techniques (RR: 1.04 95% CI: 0.74, 1.47 I^2=0% p=0.82) (Figure 11). The results were stable on sensitivity analysis with no evidence of publication bias (**Supplementary Figure 6**).

Discussion

Our systematic review and meta-analysis indicate that the use of the robotic technique is associated with significantly increased operative time but with reduced blood loss as compared to MIE. Pooled analysis of early postoperative complications indicated that pulmonary complications are significantly reduced with RAE, but there is no difference between the two surgical techniques for anastomotic leak, chyle leak, RLN palsy, cardiac complication, infectious complications, conversion to open surgery, or early mortality.

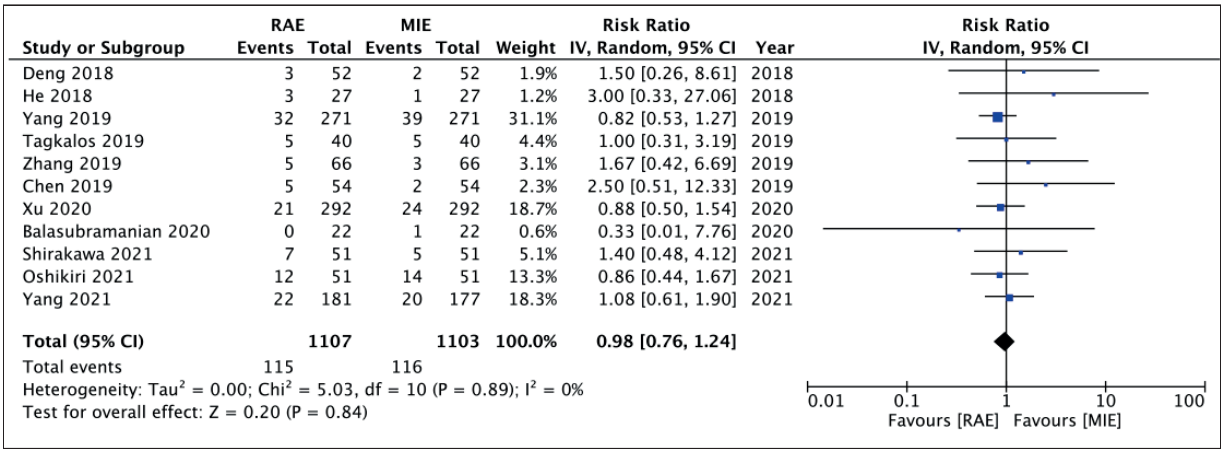

Figure 4. Meta-analysis of anastomotic leak between RAE *vs.* MIE.

Study or Subgroup	RAE Events	RAE Total	MIE Events	MIE Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Deng 2018	0	52	1	52	4.4%	0.33 [0.01, 8.00]	2018
He 2018	0	27	1	27	4.4%	0.33 [0.01, 7.84]	2018
Yang 2019	4	271	2	271	15.4%	2.00 [0.37, 10.83]	2019
Zhang 2019	0	66	1	66	4.3%	0.33 [0.01, 8.04]	2019
Chen 2019	1	54	2	54	7.8%	0.50 [0.05, 5.35]	2019
Balasubramanian 2020	1	22	1	22	6.0%	1.00 [0.07, 15.00]	2020
Xu 2020	3	292	4	292	19.9%	0.75 [0.17, 3.32]	2020
Yang 2021	5	181	2	177	16.6%	2.44 [0.48, 12.44]	2021
Ninomiya 2021	3	51	4	51	21.1%	0.75 [0.18, 3.18]	2021
Total (95% CI)		**1016**		**1012**	**100.0%**	**0.94 [0.48, 1.83]**	
Total events	17		18				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.78$, df = 8 (P = 0.88); $I^2 = 0\%$
Test for overall effect: Z = 0.18 (P = 0.86)

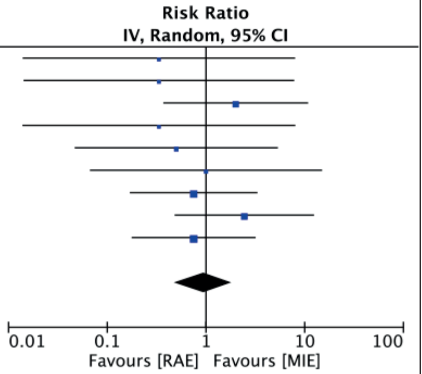

Figure 5. Meta-analysis of chyle leak between RAE *vs.* MIE.

Study or Subgroup	RAE Events	RAE Total	MIE Events	MIE Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Deng 2018	7	52	4	52	7.0%	1.75 [0.54, 5.62]	2018
He 2018	4	27	3	27	5.6%	1.33 [0.33, 5.40]	2018
Zhang 2019	4	66	3	66	5.3%	1.33 [0.31, 5.73]	2019
Chen 2019	7	54	17	54	10.1%	0.41 [0.19, 0.91]	2019
Yang 2019	79	271	41	271	14.6%	1.93 [1.37, 2.70]	2019
Balasubramanian 2020	3	22	1	22	2.9%	3.00 [0.34, 26.66]	2020
Tsunoda 2020	3	45	9	45	6.5%	0.33 [0.10, 1.15]	2020
Xu 2020	24	292	27	292	12.8%	0.89 [0.53, 1.50]	2020
Shirakawa 2021	8	51	9	51	9.4%	0.89 [0.37, 2.12]	2021
Oshikiri 2021	8	51	24	51	11.0%	0.33 [0.17, 0.67]	2021
Yang 2021	59	181	48	177	14.8%	1.20 [0.87, 1.65]	2021
Total (95% CI)		**1112**		**1108**	**100.0%**	**0.92 [0.61, 1.39]**	
Total events	206		186				

Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 33.86$, df = 10 (P = 0.0002); $I^2 = 70\%$
Test for overall effect: Z = 0.40 (P = 0.69)

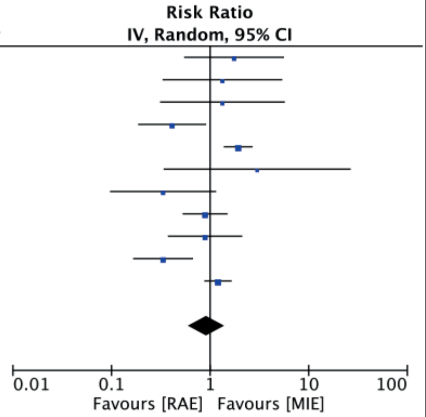

Figure 6. Meta-analysis of RLN palsy between RAE *vs.* MIE.

Study or Subgroup	RAE Events	RAE Total	MIE Events	MIE Total	Weight	Risk Ratio IV, Random, 95% CI	Year
He 2018	5	27	2	27	1.3%	2.50 [0.53, 11.79]	2018
Deng 2018	5	52	4	52	2.0%	1.25 [0.36, 4.40]	2018
Tagkalos 2019	6	40	7	40	3.1%	0.86 [0.32, 2.33]	2019
Zhang 2019	4	66	7	66	2.2%	0.57 [0.18, 1.86]	2019
Chen 2019	8	54	13	54	4.9%	0.62 [0.28, 1.36]	2019
Yang 2019	71	271	99	271	47.9%	0.72 [0.56, 0.92]	2019
Balasubramanian 2020	3	22	4	22	1.6%	0.75 [0.19, 2.97]	2020
Tsunoda 2020	8	45	20	45	6.2%	0.40 [0.20, 0.81]	2020
Xu 2020	25	292	29	292	11.9%	0.86 [0.52, 1.44]	2020
Oshikiri 2021	9	51	11	51	4.9%	0.82 [0.37, 1.80]	2021
Ninomiya 2021	10	30	19	30	9.4%	0.53 [0.30, 0.94]	2021
Shirakawa 2021	10	51	9	51	4.7%	1.11 [0.49, 2.50]	2021
Total (95% CI)		**1001**		**1001**	**100.0%**	**0.72 [0.60, 0.86]**	
Total events	164		224				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.10$, df = 11 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 3.65 (P = 0.0003)

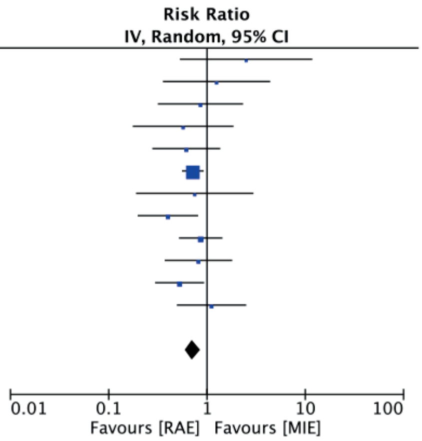

Figure 7. Meta-analysis of pulmonary complications between RAE *vs.* MIE.

Study or Subgroup	RAE Events	RAE Total	MIE Events	MIE Total	Weight	Risk Ratio IV, Random, 95% CI	Year
He 2018	1	27	0	27	2.6%	3.00 [0.13, 70.53]	2018
Yang 2019	9	271	11	271	35.3%	0.82 [0.34, 1.94]	2019
Zhang 2019	5	66	2	66	10.3%	2.50 [0.50, 12.43]	2019
Chen 2019	2	54	0	54	2.9%	5.00 [0.25, 101.77]	2019
Tsunoda 2020	6	45	6	45	23.8%	1.00 [0.35, 2.87]	2020
Xu 2020	5	292	7	292	20.5%	0.71 [0.23, 2.22]	2020
Yang 2021	2	181	1	177	4.6%	1.96 [0.18, 21.38]	2021
Total (95% CI)		**936**		**932**	**100.0%**	**1.06 [0.64, 1.78]**	
Total events	30		27				

Heterogeneity: Tau² = 0.00; Chi² = 3.61, df = 6 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

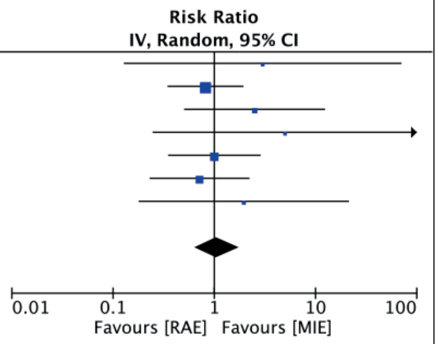

Figure 8. Meta-analysis of cardiac complications between RAE *vs.* MIE.

To the best of our knowledge, three prior systematic reviews and meta-analyses[6,12,28] have compared outcomes of RAE with MIE, albeit with several limitations. While two of these reviews[6,28] could compare data only from a limited number of studies, the meta-analysis of Zheng et al[12] did not pool data of matched and unmatched studies separately. The importance of baseline matching of patients can be gauged by the fact that several early outcomes after esophagectomy are influenced by different confounding factors[29-32]. Indeed, comparing outcomes of cohorts with uneven baseline characteristics can lead to a skewed interpretation of the results with significant bias in the quality of evidence. Thus, in this review, we identified only RCTs or propensity-matched retrospective studies to present the best available evidence to practicing surgeons.

Comparing intra-operative outcomes, we noted a significantly increased operative time of around 32 minutes with RAE as compared to MIE. Similarly, Zheng et al[12] in their review have also reported an increased operative time of 30 minutes with RAE. One reason for the longer duration of surgery with RAE could be the need for repositioning of the robotic carts for different phases of the procedure (thoracic and abdominal). Moreover, the learning curve with the recent RAE technique as compared to the widely adopted MIE method could have also led to the differences in outcomes. Zhang et al[33] demonstrated that for a surgeon experienced in open and MIE at least 26 cases are needed to gain surgical proficiency and reduce operating time with RAE. On examination of our forest plot, it can be noted that in only two studies[18,27] the operating time with RAE was shorter as compared to MIE and both were predominantly from the same setup. In the RCT of Yang et al[27] only those surgeons who had overcome the learning experience with RAE were involved and this could have resulted in shorter operating times.

Our analysis also suggests significantly reduced blood loss with RAE as compared to MIE. Our results are in contrast to the pooled analysis of Siaw-Acheampong et al[6] who reported no difference in blood loss between the two surgical techniques. However, even with data from 11

Study or Subgroup	RAE Events	RAE Total	MIE Events	MIE Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Tagkalos 2019	0	40	1	40	6.7%	0.33 [0.01, 7.95]	2019
Zhang 2019	1	66	0	66	6.7%	3.00 [0.12, 72.33]	2019
Yang 2019	2	271	2	271	17.7%	1.00 [0.14, 7.05]	2019
Tsunoda 2020	3	45	2	45	22.3%	1.50 [0.26, 8.55]	2020
Xu 2020	3	292	5	292	33.4%	0.60 [0.14, 2.49]	2020
Yang 2021	3	181	1	177	13.3%	2.93 [0.31, 27.94]	2021
Total (95% CI)		**895**		**891**	**100.0%**	**1.06 [0.47, 2.42]**	
Total events	12		11				

Heterogeneity: Tau² = 0.00; Chi² = 2.48, df = 5 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

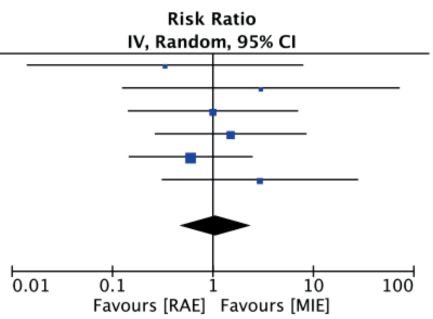

Figure 9. Meta-analysis of infectious complications between RAE *vs.* MIE.

Study or Subgroup	RAE Events	RAE Total	MIE Events	MIE Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Weksler 2017	38	569	58	569	44.7%	0.66 [0.44, 0.97]	2017
Zhang 2019	1	66	0	66	6.5%	3.00 [0.12, 72.33]	2019
Yang 2019	2	271	16	271	20.6%	0.13 [0.03, 0.54]	2019
Tsunoda 2020	0	45	0	45		Not estimable	2020
Yang 2021	7	181	6	177	28.2%	1.14 [0.39, 3.33]	2021
Ninomiya 2021	0	30	0	30		Not estimable	2021
Shirakawa 2021	0	51	0	51		Not estimable	2021
Total (95% CI)		**1213**		**1209**	**100.0%**	**0.60 [0.25, 1.43]**	
Total events	48		80				

Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 6.84$, df = 3 (P = 0.08); $I^2 = 56\%$
Test for overall effect: Z = 1.15 (P = 0.25)

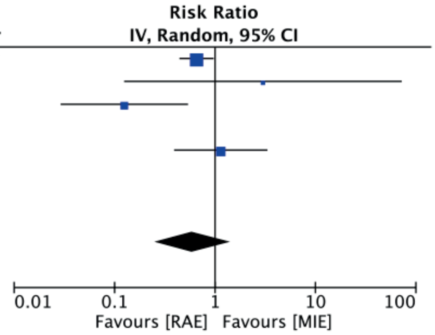

Figure 10. Meta-analysis of conversion to open surgery between RAE *vs.* MIE.

studies, the difference in blood loss with RAE was just 35.15 ml and such a small volume may not be clinically significant. Furthermore, on examination of the forest plot, it can be noted that the majority of the studies found no difference in blood loss with the two surgical techniques. On the exclusion of the outliner study of Oshikiri et al[24], the results were no longer statistically significant, and the MD was just 14 ml.

Anastomotic leakage is a fearful complication of esophagectomy which can result in significant postoperative morbidity[31]. Several variables affecting the strength of the anastomosis like obesity, use of neoadjuvant therapy, and location can influence the rates of postoperative leakage[34]. In the previous review, Zheng et al[12] have noted an increased tendency of anastomotic leakage in RAE patients as compared to MIE. However, our analysis of matched studies demonstrated no difference between the two groups. Similar results were noted for chyle leak as well. Another important complication of interest with esophagectomy is RLN palsy which can result due to thermal injury, stretching, compression, or vascular compromise of the nerve[35]. The pooled incidence of RLN palsy in our analysis was 18.5% in the RAE group and 16.7% in the MIE group. These figures concur with the RLN incidence of 0-59% reported in the literature[35]. In our meta-analysis, we noted no significant impact of the surgical technique on RLN palsy, and these results contrast with the previous two meta-analyses[12,28] which have noted significantly reduced incidence of RLN palsy with RAE as compared to MIE. We believe the addition of new studies and selective inclusion of matched data could have led to these reliable but contrasting results. However, important to note is that our analysis did not differentiate in the grade of nerve injury in the two groups due to limited data. Oshikiri et al[24] have suggested

Study or Subgroup	RAE Events	RAE Total	MIE Events	MIE Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Yerokun 2016	3	170	3	170	4.8%	1.00 [0.20, 4.88]	2016
Weksler 2017	46	569	39	569	71.0%	1.18 [0.78, 1.78]	2017
Deng 2018	2	52	2	52	3.2%	1.00 [0.15, 6.83]	2018
He 2018	0	27	1	27	1.2%	0.33 [0.01, 7.84]	2018
Yang 2019	0	271	2	271	1.3%	0.20 [0.01, 4.15]	2019
Tagkalos 2019	2	40	1	40	2.1%	2.00 [0.19, 21.18]	2019
Zhang 2019	1	66	1	66	1.6%	1.00 [0.06, 15.65]	2019
Chen 2019	0	54	0	54		Not estimable	2019
Balasubramanian 2020	0	22	1	22	1.2%	0.33 [0.01, 7.76]	2020
Xu 2020	6	292	7	292	10.3%	0.86 [0.29, 2.52]	2020
Yang 2021	1	181	2	177	2.1%	0.49 [0.04, 5.34]	2021
Shirakawa 2021	0	51	0	51		Not estimable	2021
Ninomiya 2021	0	30	1	30	1.2%	0.33 [0.01, 7.87]	2021
Total (95% CI)		**1825**		**1821**	**100.0%**	**1.04 [0.74, 1.47]**	
Total events	61		60				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.80$, df = 10 (P = 0.96); $I^2 = 0\%$
Test for overall effect: Z = 0.23 (P = 0.82)

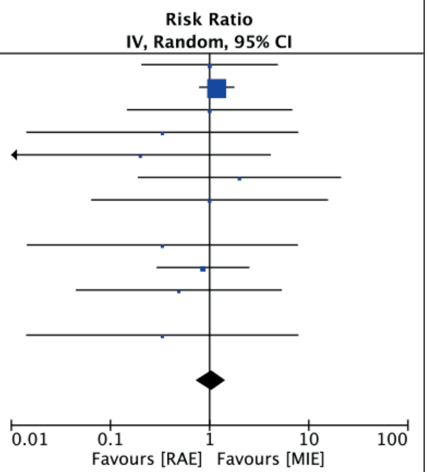

Figure 11. Meta-analysis of early mortality between RAE *vs.* MIE.

that Clavien-Dindo grade 2 nerve injury can be significantly reduced with RAE due to magnified 3-dimensional imaging and dexterity offered by the robotic arm. However, there is a need for further studies differentiating the different grades of nerve injury with RAE *vs.* MIE.

It has been demonstrated[6] that the use of MIE has significantly reduced the incidence of pulmonary complications as compared to open thoracotomy. Pulmonary complications, like pneumonia, pleural effusion, etc. can significantly reduce 5-year overall survival and cancer-specific survival in patients with esophagectomy[36]. Thus, minimally invasive surgical techniques like RAE and MIE, which can reduce the incidence of pulmonary adverse events can significantly impact the long-term prognosis of these patients. Prior reviews have produced contrasting results on the impact of surgical technique (RAE or MIE) on pulmonary complications with one reporting no statistically significant difference[6] while another indicated significantly reduced risk with RAE[12]. In our analysis, we noted that the use of RAE was associated with a statistically significant 38% reduced risk of pulmonary complications as compared to MIE. Since pulmonary complications can be influenced by several baseline factors, like age, tumor location and neoadjuvant therapy[37], our analysis of matched studies provides superior evidence on the benefits of RAE.

Theoretically, the improved visualization, mobility, and precision offered by the robotic platform should lead to overall better outcomes and a reduced rate of short-term complication as compared to minimally invasive surgeries. However, except for pulmonary complications, we noted no difference between RAE and MIE for other adverse outcomes like cardiac complications, infections, conversion rate to open surgery, and early mortality. Similar results have also been reported by Harbison et al[38] in an analysis of the American cancer database. The authors in a multivariable-adjusted analysis demonstrated no statistically significant difference in the risk of overall mortality, infections, conversion surgery, anastomotic leak, bleeding, and readmission rates between RAE and MIE groups.

Our results should be interpreted with the following limitations. Firstly, our review is not a comprehensive analysis of all data available in literature due to the selective inclusion of matched studies. Secondly, most of the studies in our review were from Asian countries, and hence, may not be generalizable to the global population. Thirdly, outcomes of RAE can be significantly influenced by surgeon experience. Several different surgeons with widely different experiences and surgical skills were involved in the included studies. It is unclear how this variable could have influenced our results. Fourthly, the included studies used different techniques of esophagectomy (Ivor-Lewis, McKeown, transhiatal) in their respective cohorts. A subgroup analysis was not possible due to the lack of data and the impact of these technique variations on clinical outcomes were not accounted for. Lastly, there was a small proportion of overlapping data in our meta-analysis from two studies[18,27].

Conclusions

RAE is associated with a tendency for longer operating time and reduced blood loss as compared to MIE. The use of robot assistance significantly reduces pulmonary complications as compared to conventional minimally invasive surgical techniques but has no impact on the incidence of anastomotic leak, chyle leak, RLN palsy, cardiac complication, infectious complications, conversion to open surgery, or early mortality.

Our results assume clinical significance since robotic surgery is associated with high healthcare costs and recommendations for the use of RAE cannot be sustained if the increased expenditure does not translate into significantly improved patient outcomes. While technological advancements in medical science are always welcomed, especially for an organ like the esophagus due to its unique anatomical features, the benefits of the technological advancement should also be equally shared by the patient without an excessive monetary burden. Since the current analysis could include only one RCT, there is a need for further trials comparing RAE with MIE to better delineate outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

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