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# Meta-analysis of randomized controlled trials and individual patient data comparing minimally invasive to open oesophagectomy for cancer

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The resources and facilities of the University of Heidelberg were used in conducting this study. There was no additional source of funding.

**Running head: MIS improves outcomes after esophagectomy**

**Background:** Minimally invasive oesophagectomy (MIO) for oesophageal cancer may reduce surgical complications as compared to open oesophagectomy. MIO however is technically challenging and may impair optimal oncological resection. The aim of the present study was to assess if MIO for cancer is beneficial.

**Methods:** A systematic literature search in MEDLINE, Web of Science and CENTRAL was performed and randomized controlled trials (RCTs) comparing MIO to open oesophagectomy were included in a meta-analysis. Survival was analyzed using individual patient data. Random-effects model was used for pooled estimates of perioperative effects.

**Results:** Among 3219 articles, six RCTs were identified including 822 patients. Three-year overall survival (56%, 95% CI 49 – 62 for MIO vs. 52%, 95% CI 44 – 60 for open; p=0.54) and disease-free survival (54%, 47 – 61 vs. 50%, 42 – 58; p = 0.38) were comparable. Overall complication rate was lower for MIO (OR 0.33, 0.20 – 0.53; p < 0.01) mainly due to less pulmonary complications (OR 0.44, 0.27 – 0.72; p < 0.01), including pneumonia (OR 0.41, 0.22 – 0.77; p<0.01).

**Conclusion:** MIO for cancer is associated with a lower risk of postoperative complications compared to open resection. Overall and disease-free survival is comparable for the two techniques.

(PROSPERO2017:CRD42017073147)

Lay Summary

Oesophagectomy for cancer is associated with a high risk of complications. A minimally invasive approach might be less traumatic leading to fewer complications and may also improve oncological outcome. A meta-analysis of randomized controlled trials comparing minimally invasive to open oesophagectomy was performed. The analysis showed that the minimally invasive approach led to fewer postoperative complications,

in particular, fewer pulmonary complications. Survival after surgery was comparable for the two techniques.

TOC summary

Our analysis showed that the minimally invasive approach led to fewer postoperative complications, and in particular, fewer pulmonary complications, while long-term oncological outcome was comparable. The minimally invasive approach should therefore be the preferred method for cancer-related esophagectomy when performed by experienced hands.

## INTRODUCTION

Oesophagectomy is the cornerstone of curative treatment of oesophageal cancer.[1] However, it is associated with major complications and mortality of more than 50% and up to 5%, respectively.[2-7] Furthermore, oesophagectomy has a major impact on patients' quality of life and fitness. This is relevant as patients' prognosis remains poor with a median survival of only 29 months after curative multimodal treatment.[8]

Minimally invasive oesophagectomy (MIO) might be less traumatic and has the potential to reduce pulmonary complications, shorten hospital stay, improve quality of life and improve survival.[9-11] On the other hand, MIO is technically challenging, and this may put the patient at increased risk for serious surgery-related complications.[12-14] Therefore, the application of MIO for cancer has been questioned. For a long time, only single-centre studies[15] and multi-centre retrospective studies such as EsoBenchmark dataset[16] suggested that MIO has the potential to improve postoperative outcome. Recently, also several randomized controlled trials (RCTs) indicated that MIO may be of benefit to the patients compared to an open approach. The MIRO trial suggested a trend towards a better survival after MIO.[17]

Previous meta-analyses comparing MIO to open oesophagectomy included also non-randomized studies, which may have introduced bias.[18, 19] Therefore, the aim of the present study was to analyse the short and long-term outcomes from RCTs comparing MIO with open oesophagectomy.

## METHODS

This meta-analysis was conducted according to the PRISMA guidelines.[20] The resources and facilities of the University of Heidelberg were used to conduct this study. The study was prospectively registered under PROSPERO 2017:CRD42017073147.

### Systematic literature search

The electronic bibliographic databases CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE (via PubMed), and Web of Science were searched.[21] The search strategy for MEDLINE based on a combination of MeSH and free text words were the following:

("esophagectomy"[tiab] OR "oesophagectomy"[tiab] OR „esophageal resection“[tiab] OR „esophagus resection“[tiab] OR „transhiatal resection“[tiab])

AND ("minimally"[ tiab] OR "thoracoscopic"[ tiab] OR "laparoscopic“[tiab] OR "laparoscopical“[tiab] OR "laparoscopically“[tiab])

AND (cancer OR carcinoma OR malignancy OR malignancies)

NOT (comment OR letter OR case report) NOT (animal[tiab] OR rat[tiab] OR rats[tiab] OR mice[tiab])

The full search strategies for the other databases are available online (Supplementary Table 1). Additionally, a hand search of relevant citations was performed. No restriction regarding publication year and language was made. The last search was performed on November 25th 2020.

### Study selection

RCTs comparing MIO to open oesophagectomy for oesophageal cancer in adults were eligible for inclusion. For the minimally invasive approach the abdominal and/or the thoracic part had to be performed endoscopically. All other studies such as animal

studies, non-randomized studies, meeting abstracts, letters/comments/editorials and publications, for which the full text was irretrievable were excluded. Following the recommendations of the Cochrane Collaboration[22], the screening of titles, abstracts and full texts was independently performed by two reviewers. Any disagreement was resolved by consensus, or by consultation of a third reviewer.

**Data extraction**

Data extraction was performed by two reviewers independently. Discrepancies between the two reviewers were resolved by a third reviewer. Data were extracted from the studies that met the final inclusion criteria using a standardized form. The form was piloted in the first three trials and revised accordingly. The following items were extracted: title, author, year of publication, journal, language, trial duration, trial design, number of treatment groups, total number of patients, evaluable patients, withdrawals, loss to follow-up, and funding source. Further extracted data included age, sex, part of intervention performed minimally invasive or open. Moreover, information to evaluate the outcomes as described below were extracted when available. Authors reporting survival data were contacted for the anonymized individual patient survival data.

**Outcomes**

The comparison of the oncological and perioperative outcomes for open oesophagectomy (open abdomen and open chest) with MIO (chest or abdomen or both performed minimally invasive) for oesophageal cancer was the focus of the present meta-analysis. Oncological outcome included overall and disease-free survival, rate of positive resections margins (R-status) and number of resected lymph nodes as well as cancer recurrence at three years after surgery. Perioperative outcomes included operative time, blood loss, major complications (classified as III to V according to the

Clavien-Dindo classification[23]), anastomotic leakages, overall pulmonary complications, pneumonia, re-operations, length of intensive care unit stay, length of hospital stay and mortality within 90 days.

**Critical appraisal**

The methodological quality of included RCTs was assessed with the Cochrane Collaboration tool for assessing risk of bias 2.0[24]. Five standard domains of bias were assessed: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selecting of the reported result. These domains were rated as "high risk of bias", "low risk of bias" or "some concerns". Finally, an overall risk of bias judgment was made. The blinding of patients, surgeons, data collectors, outcome assessors, and data analysts was assessed as "blinded", "not blinded" or "not reported"[25]. Furthermore, information on funding was recorded as "industry", "independent" or "not reported" [26].

**Statistical analysis**

Analyses were performed as intention-to-treat (ITT) counting conversions in the MIO group using the R environment version 3.4.4 and the "meta" library for meta-analyses.[27]

Individual patient data on survival were censored after three years. The one- and three-year survival rates were estimated separately for the two groups after Freeman-Tukey Double arcsine transformation. The comparison of the Odds ratios (ORs) estimated on the number of events one and three years after surgery was considered the main outcome. This was complemented by the comparison of the one- and three-year restricted mean survival times, which was computed for each study using the

"surv2sample" R library.[28] Additional meta-analysis on individual patient data on overall and disease-free survival were performed after checking for departure from the proportional hazards assumption by plotting the log-cumulative hazard against the log time and by assessing the weighted residuals. The log hazard ratios and their standard errors were pooled using the inverse variance method. Finally, the individual patient data on survival were analysed in a stratified Cox regression with sandwich variance estimation and the adjusted survival curves were plotted for visualization.

For standard meta-analysis on perioperative outcomes, data were pooled using random effects models to account for methodological and clinical heterogeneity between the studies as the primary analysis and complemented by fixed-effect models serving as sensitivity analyses.[29] Statistical heterogeneity was quantified using $I^2$, assessed by visual examination of the forest plot and formally tested with Cochran's Q statistic.[30, 31] $I^2$ less than 25% was considered to indicate low heterogeneity and $I^2$ > 75% to indicate high heterogeneity. Between-study heterogeneity was estimated by the inverse variance method. To compare dichotomous outcomes, ORs and 95% CI were calculated. For continuous outcomes, the mean differences (MD) and 95% CI were calculated. If not reported, means and standard deviations (SD) were substituted as described by *Hozo et al.*[32] No funnel plots were created since the total number of included RCT was less than 10 trials.[24] Sensitivity analyses were performed for total endoscopic vs. laparoscopy only, intrathoracic anastomosis vs. neck anastomosis, conventional endoscopy vs robot-assisted operations and for study quality.

## RESULTS

A total of 3219 articles were screened for eligibility. Of these, 83 trials were assessed by full text analysis, of which 75 articles were excluded for several reasons (Fig. 1). Finally, eight articles from six RCT with 822 patients were included in the

quantitative and qualitative analysis.[9, 17, 33-38] For the individual patient data meta-analysis of overall and disease-free survival, the original data were provided by the investigators of all four European RCTs involving 457 patients.[17, 36-38] Standard meta-analysis of all six RCTs was performed to estimate perioperative outcomes.

**Selected trials**

The TIME trial was first published in 2012 and the long-term follow-up was later published as separate publications resulting in a total of three articles.[9, 33, 34] Except for the TIME trial and the trial of Guo et al., which was published in 2013[35] all other trials were published in 2018 or 2019.[17, 36-38] The location of the anastomoses and surgical approach (robotic, complete minimally invasive or hybrid) varied between the studies (Table 1). Five of the six RCTs reported conversion rates and the pooled rate was 6% (95% CI 3% to 12%).

**Critical appraisal**

The randomization and allocation procedure of Guo et al. and Ma et al. were questionable and had a high risk of selection bias.[35, 36] Due to the surgical nature of the interventions blinding of the operating surgeons was not possible and at a high risk of bias. For the blinding of other personnel than the operating surgeon remained some concerns. In the RCTs of *Guo et al*. and *Ma et al*. information on incomplete outcome data or selective reporting were insufficient or lacking.[35, 36] All other RCTs were at low risk of attrition and reporting bias.[9, 17, 37, 38] Overall, the study quality of Guo et al. and Ma et al. were inferior to the other trials, mainly due to lack of an adequate randomization process.[35, 36] Details are available online (Supplementary Table 2).

## Quantitative analysis

### Survival

Pooled one-year overall survival was 73% (95% CI 67% to 79%) for MIO vs. 67% (95% CI 61% to 74%) for the open approach (OR 0.85; 95% CI 0.47 to 1.56; p = 0.61). Disease-free survival was 72% (95% CI 66% to 78%) for MIO and 67% (95% CI 60% to 73%) for open oesophagectomy (OR 0.78; 95% CI 0.49 to 1.24; p = 0.30). Pooled three-year overall survival was 56% (95% CI 49% to 62%) for MIO vs. 52% (95% CI 44% to 60%) for open oesophagectomy (OR, 0.88; 95% CI 0.58 to 1.33; p = 0.54). Disease free survival was 54% (95% CI 47% to 61%) vs. 50% (95% CI 42% to 58%) (OR 0.84; 95% CI 0.58 to 1.23; p = 0.38). (Figure 2). When pooling the hazard ratios estimated for each study, heterogeneity was low and no difference was observed for overall (HR 0.89; 95% CI 0.66 to 1.16; p = 0.35) and disease-free survival (HR 0.87; 95% CI 0.66 to 1.14; p = 0.30). Furthermore, both overall and disease-free survival were comparable in both groups in a stratified Cox regression.

### Other oncological outcomes

Positive resection margins (4 RCTs: OR 1.14, 95% CI 0.30 to 4.35, p = 0.84, $I^2$ = 36%) and number of resected lymph nodes (4 RCTs: MD +1.51 lymph nodes, 95% CI -0.86 lymph nodes to +3.88 lymph nodes, p = 0.21, $I^2$ = 44%) as well as local recurrence after at least three years follow-up (2 RCTs: OR 1.24, 95% CI 0.55 to 2.78, p = 0.60, $I^2$ = 13%) were comparable between the two groups.

### Complications

Postoperative complications were statistically significant lower for MIO compared to open oesophagectomy (OR 0.33; 95% CI 0.20 to 0.53; p < 0.01, Figure 3A). Also rate

of pneumonia (OR 0.41; 95% CI 0.22 to 0.77; p < 0.01, Figure 3B), pulmonary complications (OR 0.44; 95% CI 0.27 to 0.72; p < 0.01, Figure 3C) and blood loss (MD -205.44 ml; 95% CI -318.46 ml to -92.42 ml; p < 0.01, Figure 3D) were in favour of MIO. Operation time was shorter in the open group (MD 44.30 min; 95% CI 27.15 min to 61.45 min; p < 0.01, Figure 3E).

There was no statistically significant difference in anastomotic leakage (OR 1.35; 95% CI 0.8 to 2.26; p = 0.26, Figure 3F), re-operation (OR 0.83, 95% CI 0.44 to 1.55; p = 0.56, Figure 3G), the length of ICU stay (MD -0.08, 95% CI -0.56 – 0.4; p = 0.75; Figure 3H), hospital stay (MD -2.32, 95% CI -5.1 – 0.45; p = 0.1; Figure 3I) or 90-day mortality (OR 0.92; 95% CI 0.28 to 3.08; p = 0.9, Figure 3J).

Comparing subgroups of total MIO to hybrid oesophagectomy (thoracotomy) did not show any statistically significant differences between the groups. However, there was a lower although not statistically significant difference in the rate of pneumonia for total MIO ($X^2$ = 3.28; p = 0.07, Figure 3B).

**Sensitivity analyses**

Sensitivity analyses for “laparoscopy only”[17, 38], “neck anastomosis“[35, 37], “robot-assisted oesophagectomy“[37] and for “study quality“[35, 36] did not change the pooled estimates in a relevant way. However, the interpretation of the sensitivity analyses was impaired by the lower number of trials.

## DISCUSSION

This is the first individual patient data meta-analysis of RCTs showing that oncological outcomes of MIO are comparable to open oesophagectomy. Furthermore, MIO is associated with a lower risk of overall complications.

Previous studies showed that for resection margin status and number of resected lymph nodes comparable results can be achieved for minimally invasive and open oesophagectomy,[39-41] which was confirmed in the present study. Furthermore, it was hypothesized that MIO is associated with improved overall and disease-free survival as the MIRO trial showed a difference between hybrid MIO and open, albeit the difference was not statistically significant.[17] A recent meta-analysis by Gottlieb-Vedi et al. including also non-randomized studies showed better survival after MIO.[18] However, the present meta-analysis including 457 patients from four European RCTs representing the currently highest level of evidence could not confirm better survival after MIO. This discrepancy might be explained by the minimization of bias due to the inclusion of only RCTs. Alternatively, the present study may still have insufficient statistical power to detect a small difference in survival, if one exists at all.

The present meta-analysis showed that the benefit of MIO may lie in reducing postoperative complications without having an adverse effect on oncological outcomes. If robotic platforms have the potential to further improve oncological outcomes is unclear yet.[37, 42] The overall complication rate was lower after MIO mainly due to a reduction of pulmonary complications. Major complications, such as anastomotic leakages and 90-day mortality were not affected. This may be of importance as pulmonary complications, in particular pneumonia, were identified as risk factors for a decreased overall survival.[43, 44] Additionally, other major complications may negatively affect long-term survival of oesophageal cancer patients, especially

anastomotic leakage.[14, 45-47]. The learning curve for MIO is estimated at more than 100 procedures per surgeon[48] compared to approximately 70 procedures for open esophagectomy.[49] At present, due to centralization of complex oncological surgical procedures including oesophagectomy, most surgeons may have passed the learning curve for MIO. This was likely not the case in the RCTs included in this meta-analysis. If more experience in MIO also leads to even better outcomes in the future remains to be determined. Self-evidently, a careful and stepwise implementation of MIO into the routine surgical practice is essential.[5]

The strength of the present meta-analysis is on the inclusion of only RCTs. This minimizes the risk of selection and reporting bias. Furthermore, the risk of type II error is small and therefore the findings are likely relevant even for small differences between the groups. This is particularly true for clearly defined data, such as, oncological outcome, especially, when assessed as overall and disease-free survival in an individual patient data meta-analysis. Thus, it was for this reason why the present study's main outcome of interest was changed from the perioperative outcome (as published under PROSPERO) to the oncological outcome (as highlighted in the present analysis).

There are several limitations to be addressed. First, blinding of patients was not done in the included studies. A potentially resulting assessor bias may play a role in particular for outcomes that may be influenced by the patient itself or the surgical team when deciding on the duration of intensive care or hospital stay. Regrettably, this drawback remains a challenge of many surgical RCTs although it has been shown that it is evitable. The ROMIO trial, which was a feasibility study on the comparison of different access techniques for esophagectomy, demonstrated that blinding of patients is possible at least during the first week after surgery.[50, 51]

Furthermore, it remains unclear whether the proficiency of the surgeons for the two surgical approaches was comparable, which may have introduced performance bias and the problem of the poor control arm. This means that less experienced surgeons might have operated in the control arm with inferior surgical quality, and thereby making results of the intervention arm appear superior.[52] However, as this meta-analysis included only RCTs and individual patient data, this bias may be less prominent when compared to non-randomized trials. In RCTs the allocation of surgical expertise should also be allocated at random and distributed uniformly to the groups compared. Accordingly, the outcome of the control groups in the RCT included in the present meta-analysis are within the normal range of published data.[17, 37] However, as shown by Markar et al., there is evidence that for a further minimization of the performance bias and the variation of surgical outcome credentialing of surgeons and standardization of surgical technique, as well as, institutional quality improvement programmes should be implemented before enrolment in the study.[53]

Another limitation of the present study is the heterogeneity of minimally invasive techniques. Superiority of one minimally invasive technique over another could not be demonstrated as shown in the subgroup analyses. Sensitivity analyses did also not reveal an impact of potential bias on quantitative results, although some of the included trials had a considerable risk of bias.

Finally, important outcome parameters, such as, the influence on the duration of intensive care unit stay and hospital stay within a structured perioperative fast recovery program, return to normal daily activity and quality of life were not addressed in the present study as the included studies did not provide sufficient data for meta-analyses.

**Author contributions:**

Study design and coordination: BM, PP, MD, and TS

Data contribution and analysis: BM, PP, HN, SF, JS, EK, PH, RW, FN, AB, PG, CG, TDY, GP, MP, SS, DvdP, MC, PvdS, RvH, AH, MD, TS

Writing of the manuscript: BM, PP, HN, and TS

BM, PP, RW and TS all have independently verified the underlying data.

**Conflicts of Interest**

The authors declare no competing interests according to the ICMJE guidelines that could have inappropriately influenced their work on this article.

**Figure Legends**

**Figure 1:** PRISMA flow diagram

**Figure 2:** Kaplan-Meier curve of survival data (**Individual patient data meta-analysis**). **A)** Overall survival; **B)** Disease-free survival: Red line, open oesophagectomy; green line, minimally invasive oesophgectomy.

**Figure 3:** Forest plots of perioperative outcome data (**Standard meta-analysis**) **A)** Overall complications; **B)** Pneumonia; **C)** Pulmonary complications; **D)** Blood loss; **E)** Operating time; **F)** Anastomotic leakage; **G)** Re-operation; **H)** ICU stay; **I)** Hospital stay; **J)** 90-day mortality. ICU, intensive care unit; MIS, minimally invasive surgery.

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| Study /Year | Procedures | Anastomosis | n | Tumor types | | |
|---|---|---|---|---|---|---|
| | | | | AEG | SCC | Other |
| TIME trial 2012 [9, 33, 34] | totally minimally invasive | cervical (64%), thoracic (29%) | 59 | 35 | 24 | 0 |
| | open | cervical (66%), thoracic (27%) | 56 | 36 | 19 | 1 |
| Guo 2013 [35] | totally minimally invasive | cervical | 111 | n/r | n/r | n/r |
| | open | cervical | 110 | n/r | n/r | n/r |
| Ma 2018 [36] | totally minimally invasive | thoracic | 47 | 43 | 0 | 4 |
| | open | thoracic | 97 | 91 | 2 | 4 |
| van der Sluis 2019 [37] | totally minimally invasive (robot-assisted) | cervical | 54 | 41 | 13 | 0 |
| | open | cervical | 55 | 43 | 12 | 0 |
| Paireder 2018 [38] | hybrid (abdominal part laparoscopic) | thoracic | 14 | 10 | 4 | 0 |
| | open | thoracic | 12 | 11 | 1 | 0 |
| Mariette 2019 [17] | hybrid (abdominal part laparoscopic) | thoracic | 103 | 57 | 46 | 0 |
| | open | thoracic | 104 | 66 | 38 | 0 |

AEG; adenocarcinoma of esophagogastric junction; SSC, squamous cell carcinoma.

**Table 1:** Summary and characteristics of included trials

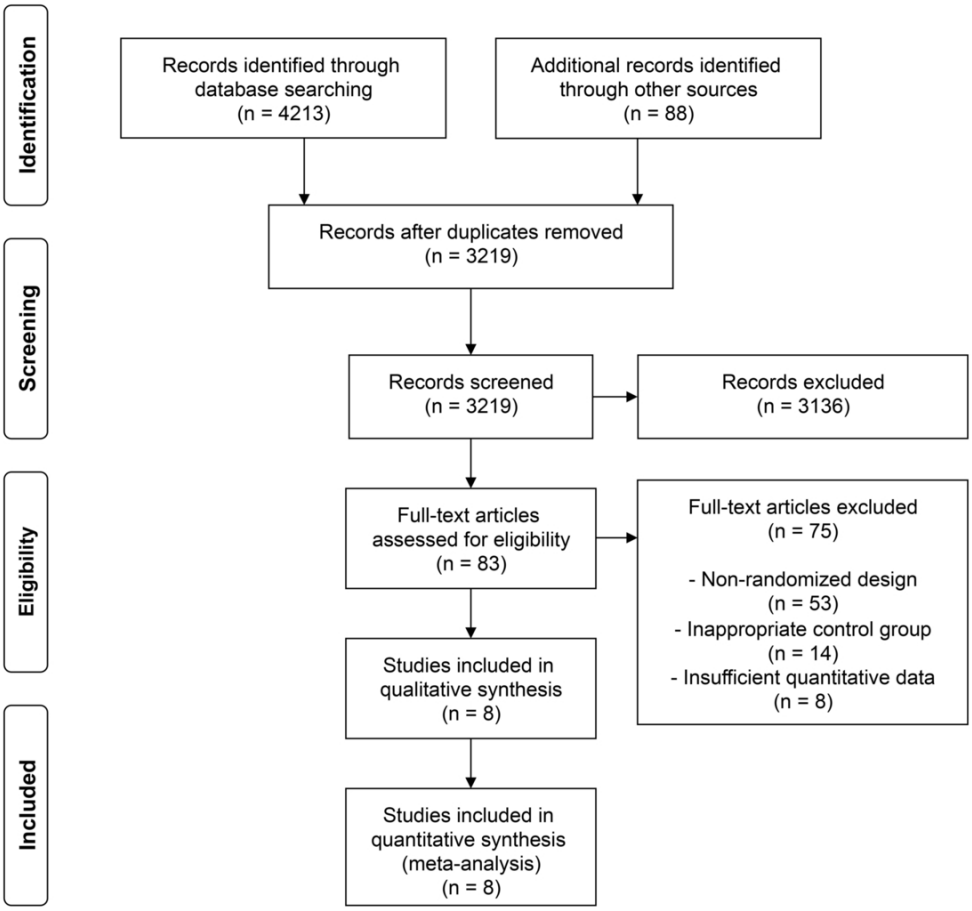


Figure 1: PRISMA flow diagram for the included studies

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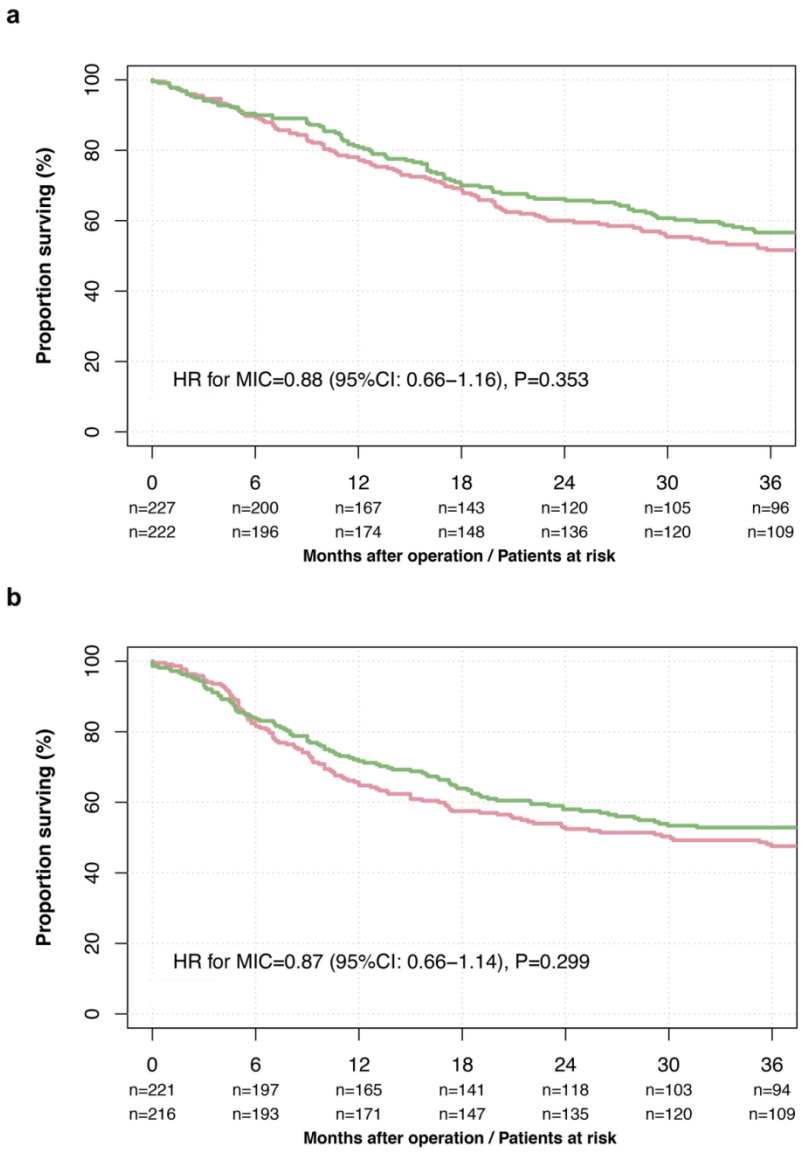



Figure 2: Survival data

209x297mm (150 x 150 DPI)

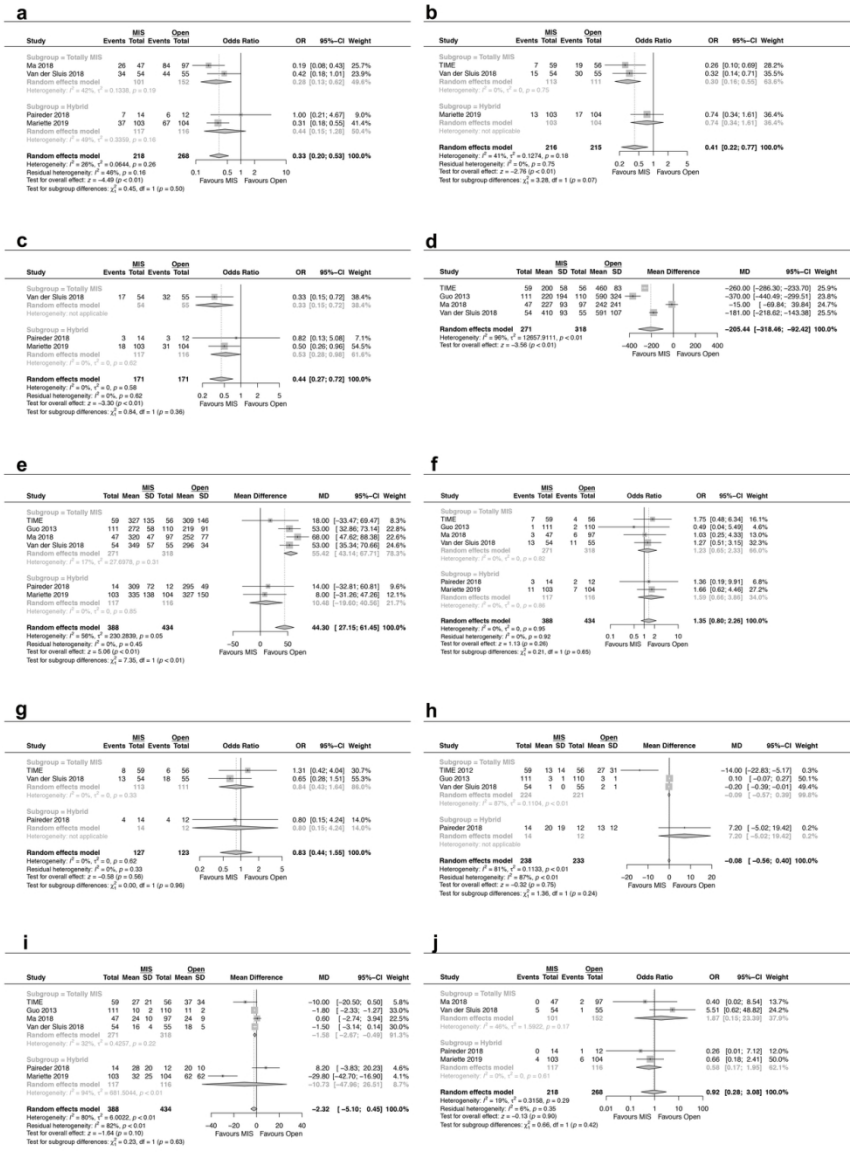



Figure 3: Perioperative outcome

209x297mm (150 x 150 DPI)

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | 5 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 7 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 8 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 9 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 8 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 8 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 9 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 9 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 9 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 9 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 10 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 10 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | 11 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 11 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 11 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 11 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | 11 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 11 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 10 |
| Certainty | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 10 |

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| assessment | | | |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 12 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | 12 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | 12 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | 12 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | 12 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 29 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 29 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 29 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | 29 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 12 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 12 |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 15 |
| | 23b | Discuss any limitations of the evidence included in the review. | 16 |
| | 23c | Discuss any limitations of the review processes used. | 16 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | 18 |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | 10 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 10 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | 11 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 2 |
| Competing interests | 26 | Declare any competing interests of review authors. | 2 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | 29 |

# PRISMA 2020 Checklist

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

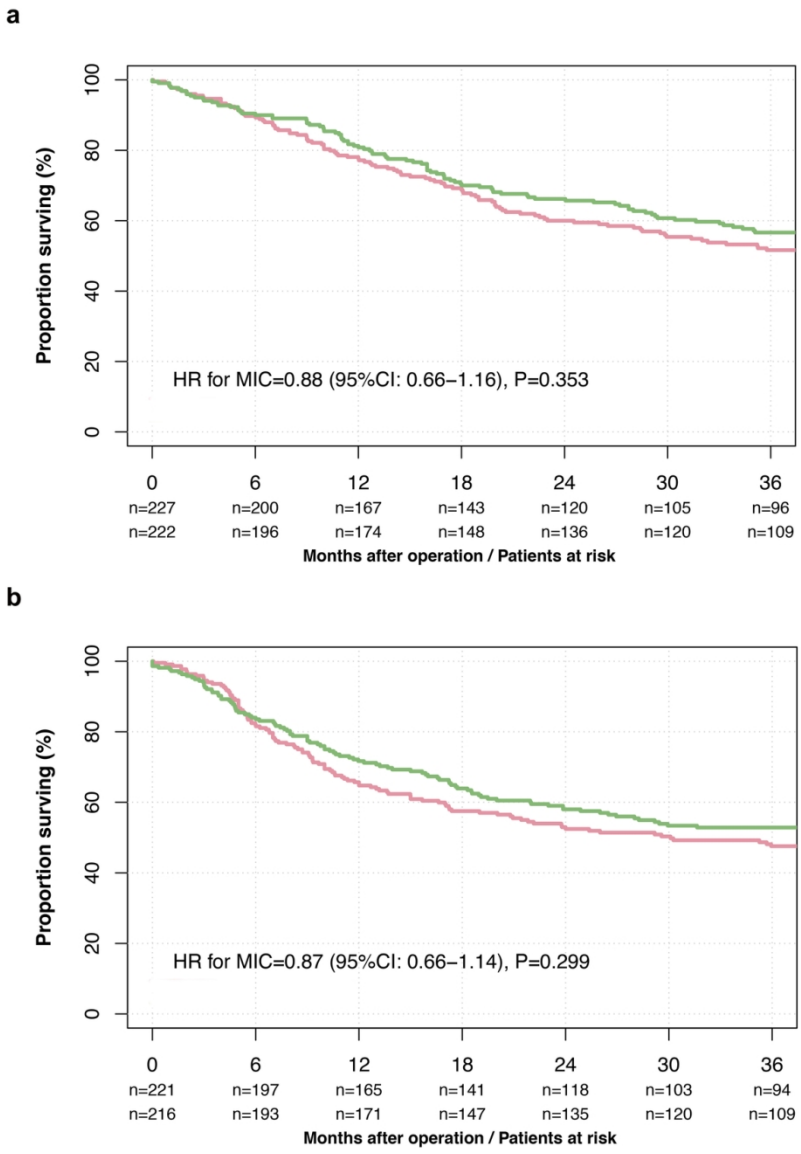
| Pubmed |
| --- |
| ((((esophagectom*[tiab] OR oesophagectom*[tiab] OR "Esophagectomy"[Mesh] OR ((esophageal[tiab] OR oesophageal[tiab] OR esophagus[tiab] OR oesophagus[tiab] OR transhiatal[tiab]) AND (resection[tiab] OR excision[tiab] OR remov*[tiab] OR ablation[tiab] OR ectomy[tiab])))) AND (minimally[tiab] OR minimal[tiab] OR thoracoscop*[tiab] OR laparoscop*[tiab] OR "Laparoscopy"[Mesh] OR "Minimally Invasive Surgical Procedures"[Mesh] OR "Thoracoscopy"[Mesh]) AND (cancer[tiab] OR cancerous[tiab] OR carcinoma*[tiab] OR malignanc*[tiab] OR tumor[tiab] OR tumour[tiab])) NOT (comment[pt] OR letter[pt] OR "case reports"[pt] OR "case reports"[ti] OR "case report"[ti])) NOT (animal[ti] OR rat[ti] OR rats[ti] OR mice[ti] OR mouse[ti] OR pig[ti] OR piglet[ti])) NOT (animals[mh] NOT humans[mh]) |
| **Web of Science** |
| TS = (esophagectom* OR oesophagectom* OR ((esophageal OR oesophageal OR esophagus OR oesophagus OR transhiatal) AND (resection OR excision OR removal OR ablation)))<br>AND TS = (minimally OR thoracoscopic OR laparoscopic* OR laparoscop* OR thoracoscop*)<br>AND TS = (cancer OR carcinoma OR malignanc* OR tumor OR tumour)<br>NOT (TI = (comment OR letter OR "case reports" OR "case report"))<br>NOT (TI = (animal OR rat OR rats OR mice OR mouse OR pig OR piglet)) |
| **CENTRAL (Cochrane Library)** |
| ((esophagectom* or oesophagectom*) OR ((esophageal OR oesophageal OR esophagus OR oesophagus OR transhiatal) AND (resection OR excision OR removal OR ablation))):ti,ab,kw<br>OR MeSH descriptor: [Esophagectomy] explode all trees<br>AND<br>(minimally OR laparoscopic OR laparoscopic* OR laparoscop* OR thoracoscop*):ti,ab,kw OR<br>MeSH descriptor: [Thoracoscopy] explode all trees<br>MeSH descriptor: [Laparoscopy] explode all trees<br>MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees<br>AND<br>(cancer OR carcinoma OR malignanc* OR tumor OR tumour):ti,ab,kw<br>NOT (comment or letter or "case reports" or "case report"):ti<br>NOT (animal or rat or rats or mice or mouse or pig or piglet):ti |

**Table S1:** Details of Search Strategy

| Study /Year | Risk of Bias | | | | | |
|---|---|---|---|---|---|---|
| | R | D | O | M | S | Overall |
| TIME trial 2012 [9, 33, 34] | ⊕ | ⊖ | ⊕ | s/c | ⊕ | s/c |
| Guo 2013 [35] | ⊖ | ⊖ | s/c | s/c | s/c | ⊖ |
| Ma 2018 [36] | ⊖ | ⊖ | s/c | s/c | s/c | ⊖ |
| van der Sluis 2019 [37] | ⊕ | ⊖ | ⊕ | s/c | ⊕ | s/c |
| Paireder 2018 [38] | ⊕ | ⊖ | ⊕ | s/c | ⊕ | s/c |
| Mariette 2019 [17] | ⊕ | ⊖ | ⊕ | s/c | ⊕ | s/c |

R, bias arising from the randomization process; D, bias due to deviations from intended interventions; O, bias due to missing outcome data; M, bias in measurement of the outcome; S, bias in the selection of the reported results; s/c: some concerns; n/r: not reported.
⊕, low risk of bias; ⊖, high risk of bias.

**Table S2:** Critical Appraisal and Risk of Bias Assessment

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