

Outcomes of thoracoscopy versus thoracotomy for esophageal atresia with tracheoesophageal fistula repair

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: A thoracoscopic approach for repair of esophageal atresia (EA) with tracheoesophageal fistula (TEF) has become a standard procedure in many pediatric surgical centers. However, whether thoracotomy or thoracoscopy offer advantages in terms of surgical outcomes is not known.

Methods: To evaluate the efficacy and safety of thoracoscopic repair (TR) versus conventional open repair (COR) for EA with TEF. PubMed, Cochrane Library, and EMBASE were searched to identify relevant literature until 2016.

Studies comparing surgical outcomes of patients undergoing TR versus COR for EA with TEF were reviewed.

The quality of each included study was assessed using the Newcastle–Ottawa scale score. A fixed or random-effect model was applied depending on heterogeneity tests.

Results: Eight observational clinical studies involving 452 patients were included in this meta-analysis. The meta-analysis of 2 major postoperative complications (leaks and strictures) did not show significant differences between TR and COR. Overall estimates of the odds ratio (OR) of TR versus COR for leaks and strictures were: 1.57 (95% confidence interval [CI], 0.77–3.20; $P=0.22$) and 0.90 (95% CI, 0.27–2.97; $P=0.86$), respectively. However, meta-analysis of operation time (OR = 19.59, 95% CI = 0.77–38.40, $P=0.04$), timing of extubation (OR = –2.50, 95% CI = –3.39 to –1.62, $P < 0.001$), time to 1st oral feeding (OR = –2.58, 95% CI = –3.79 to –1.36, $P < 0.001$), and duration of hospital stay (OR = –10.76, 95% CI = –16.39 to –5.12, $P < 0.001$) showed significant differences.

No randomized controlled trial was included, and most studies had small sample sizes and were based on retrospective analysis.

Conclusion: TR and COR show a similar complication rates of leaks and strictures for EA/TEF repair. Although associated with a longer operative time, TR has the advantages of an earlier time to extubation and 1st oral feeding, and shorter hospital stay.

Abbreviations: CI = confidence interval, COR = conventional open repair, EA = esophageal atresia, MD = mean difference, OR = odds ratio, TEF = tracheoesophageal fistula, TR = thoracoscopic repair.

Keywords: esophageal atresia, short-term outcomes, thoracoscopy, tracheoesophageal fistula

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1. Introduction

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a rare congenital malformation with an incidence of 1 per 5000 newborns.^[1] Since the 1st report by Lobe et al,^[2] a thoracoscopic approach for repair of EA/TEF has become a standard procedure in many pediatric surgical centers. Several reports have shown the effectiveness and safety of thoracoscopic repair (TR).^[3–5] Compared with conventional open repair (COR), the main advantages of TR are the superior visualization provided by thoracoscopy and avoidance of the thoracotomy incision.

However, the potential benefits of TR of EA/TEF with regard to surgical outcomes remain unclear. Some reports have made the comparison between TR and COR of neonatal EA/TEF,^[6–8] but the efficacy and safety of these 2 procedures are controversial.

The aim of the present study was to evaluate the efficacy and safety of TR and COR by a systematic review and meta-analysis. This strategy was based on evaluation of surgical outcomes of patients who underwent TR versus COR for EA with TEF.

2. Methods

This study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Ethical approval and written informed

consent from patients were not necessary because our study was based on summaries and analyses of results of published studies.

2.1. Search strategy

Studies comparing the outcomes of TR and COR were identified through a systematic search in PubMed, Cochrane Library, and EMBASE. “Esophageal atresia,” “tracheoesophageal fistula,” “thoracoscopy,” and “thoracotomy” were the core terms. The search strategy for PubMed was (esophageal atresia odds ratio [OR] EA) AND (tracheoesophageal fistula OR TEF) AND (minimally invasive OR thoracoscopy OR thoracoscopic) AND (open repair OR thoracotomy). Reference lists of each article were scrutinized for information on additional studies. Two reviewers (YFY and RD) screened all studies and selected articles that satisfied the eligibility criteria independently.

2.2. Study selection

There is limited evidence on comparisons between TR and COR for patients with EA with TEF. Most studies are retrospective reviews from 1 institution. Multiinstitutional studies were also included in the meta-analysis. In addition, surgical outcomes of patients undergoing TR versus COR for EA and TEF should be reported. If outcomes were not provided for all patients, at least one of the outcome measures was required. We excluded the following studies from the meta-analysis: conference abstracts; unpublished studies; different definitions of several outcomes (e.g., stricture, leak); insufficient outcome data to extrapolate the OR, or mean difference (MD).

2.3. Data extraction and quality assessment

Data were extracted onto a standardized data-extraction sheet by 2 reviewers (YFY and RD) independently. Disagreements were solved by checking the articles and contacting authors if required. Extracted information comprised: first author, publication year, country, study design, numbers of cases and controls, characteristics of the study population, and endpoint data. The quality of each included study was assessed using Newcastle–Ottawa scale (NOS) scores with a maximum score of 9.^[9] Studies with a score of ≥ 6 were classified as “high quality.”

2.4. Outcome variables

Primary outcome variables were the incidence of postoperative strictures and leaks. Operative time, time to extubation, time to 1st oral feeding, and duration of hospital stay were also evaluated.

2.5. Statistical methods

Pooled results were expressed as the OR of leaks and strictures with 95% confidence intervals (CIs), MD of operative time, and time to extubation with 95% CIs. If the MD value was missing, mean values and ranges were employed to estimate the MD.^[10] Analyses were undertaken if at least 3 studies comparing the same outcome for TR and COR could be combined. Each meta-analysis was done using all available studies. Dichotomous and continuous outcomes were presented by the OR and MD, respectively. Data were pooled using the Mantel–Haenszel method for dichotomous outcomes and the inverse variance method for continuous outcomes. Heterogeneity among studies was assessed using the I^2 statistic: 0% to 24% denoted “good”

homogeneity; 25% to 50% denoted “low” heterogeneity; 51% to 74% denoted “moderate” heterogeneity; and 75% to 100% denoted “high” heterogeneity. If the I^2 statistic indicated heterogeneity, a random-effects model of analysis was used. Otherwise, a fixed-effects model of analysis was used. Pooled ORs were calculated and $P < 0.05$ (2-sided) was considered significant. Sensitivity analysis was done for all outcomes. All statistical analyses were undertaken using Reviewer Manager 5.3 (RevMan, Copenhagen, Denmark).

3. Results

3.1. Literature search and characteristics of studies

A total of 113 studies were identified through database searching and “reference mining” of review articles and relevant publications (Fig. 1). Full text of 14 studies was assessed for eligibility, and 5 articles were excluded based on the inclusion criteria. Thus, the remaining 9 studies evaluating TR versus COR (1 randomized controlled trial and 8 observational clinical studies) published between 2008 and 2014 were assessed. Eight observational clinical studies were considered suitable for the meta-analysis, the characteristics of which are listed in Table 1.

Outcomes of TR versus COR using leaks, strictures, operative time, time to extubation, time to 1st oral feeding, and duration of hospital stay as primary parameters were evaluated. Main data for surgical outcomes are summarized below and in Table 2.

3.2. Results of meta-analysis

3.2.1. Leaks. Seven studies investigated the postoperative occurrence of leaks. After pooling of data, there was no significant heterogeneity among studies ($I^2 = 0\%$). Pooled estimates (OR, 1.57; 95% CI, 0.77–3.20; $P = 0.22$) showed no significant differences for leaks in TR and COR groups (Fig. 2).

3.2.2. Strictures. Six studies investigated the postoperative occurrence of strictures. Two studies were excluded for using different definitions of “stricture.”^[7,16] Therefore, 5 studies were included in the meta-analysis of strictures. After pooling of data, there was moderate heterogeneity among studies ($I^2 = 53\%$). Pooled estimates (OR, 0.90; 95% CI, 0.27–2.97; $P = 0.86$) showed no significant differences for strictures in TR and COR groups (Fig. 3).

3.2.3. Operative time. Six studies investigated the outcome of operative time. One study showed a longer operative time in the COR group,^[11] whereas the other 5 studies suggested that the operative time of TR was longer. After pooling of data, there was moderate heterogeneity among studies ($I^2 = 56\%$). Pooled estimates (MD, 19.59; 95% CI, 0.77–38.40; $P = 0.04$) showed a significant difference for operative time in TR and COR groups (Fig. 4A).

3.2.4. Time to extubation. Three studies showed data on postoperative time to extubation. All studies showed a longer time to extubation in the COR group than in the TR. After pooling of data, there was no significant heterogeneity among studies ($I^2 = 8\%$). Pooled estimates (MD, -2.50; 95% CI, -3.39 to -1.62; $P < 0.001$) showed a significant difference for time to extubation in TR and COR groups (Fig. 5A).

3.2.5. Time to 1st oral feeding. Four studies investigated the postoperative time to 1st oral feeding. All 4 studies showed a longer postoperative time to 1st oral feeding in the COR group than in the TR group. However, the data of only 2 studies^[6,7]

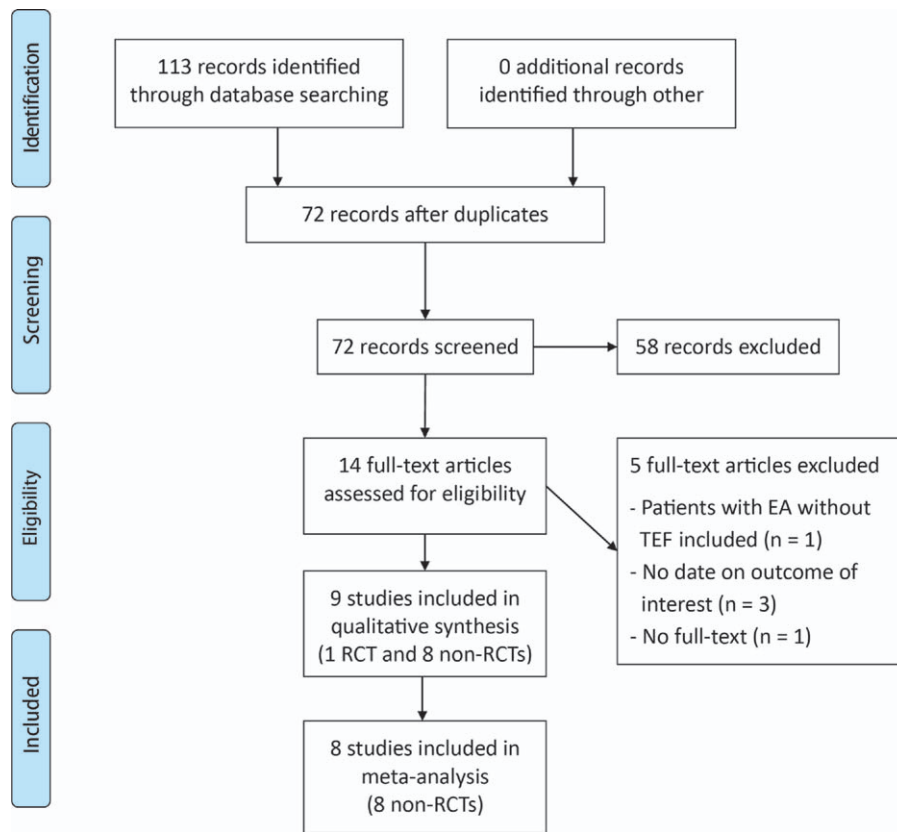


Figure 1. Flow diagram of this meta-analysis.

were available for our meta-analysis. After pooling of data, there was no significant heterogeneity among studies ($I^2=0\%$). Pooled estimates (MD, -2.58 ; 95% CI, -3.79 to -1.36 ; $P<0.001$) showed a significantly longer postoperative time to 1st oral feeding in TR and COR groups (Fig. 5B).

3.2.6. Hospital stay. Five studies investigated the duration of hospital stay. All studies showed longer hospitalization in the COR group than in the TR group. However, the data of only 2 studies^[6,15] were available for our meta-analysis. After pooling of data, there was low heterogeneity among studies ($I^2=35\%$).

Table 1
Characteristics of studies in the meta-analysis.

Study	Region	Study type	Sample size	Age at surgery, day	Gestational age, week	Sex (m/f)	Weight, kg	Anomalies, %*	Conversion n, %†	NOS
Al Tokhais [2008] ^[11]	USA	OCS (retrospective)	TR:23 COR:22	NA	36.3 36.3	NA	2.7 ± 0.7 2.4 ± 0.7	39.1 59.1	3 (13)	7
Lugo [2008] ^[12]	USA	OCS (retrospective)	TR:8 COR: 25	NA	36.9 (28–40) 36.7 (30–41)	6/2 10/15	2.7 (1.7–3.4) 2.4 (1.2–3.3)	87.5 72	1 (12.5)	7
Kawahara [2009] ^[13]	Japan	OCS (retrospective)	TR:7 COR: 10	1 (1–3) 2 (0–12)	39.4 (37–41) 37.6 (33–41)	NA	2.8 (2.5–3.7) 2.5 (1.5–2.9)	71.4 70	NA	6
Burford [2011] ^[14]	USA	OCS (retrospective)	TR:104 COR:72	1.2 ± 1.1 3.7 (1–64)	NA 37.3 (28–42)	NA	2.6 ± 0.5 2.7 (0.98–4.62)	NA 61	5 (4.8)	6
Szavay [2011] ^[8]	Germany	OCS (retrospective)	TR:25 COR:32	NA	NA	NA	2.7 (1.5–3.5) 2.1 (0.8–3.3)	40 31	8 (32)	6
Ma [2012] ^[15]	China	OCS (prospective)	TR:18 COR:15	NA	39.0 ± 2.7 39.7 ± 2.9	15/3 7/8	2.6 ± 0.8 2.3 ± 0.6	61.1 60	2 (11.1)	6
Bishay [2013] ^[16]	UK	RCT	TR:5 COR: 5	1 (1–5) 1 (1–2)	40 (39–41) 40 (38–41)	3/2 4/1	3.3 (2.9–3.7) 3.3 (2.6–3.5)	NA	1 (20)	/
Koga [2014] ^[6]	Japan	OCS (retrospective)	TR:25 COR: 40	3.1 ± 2.3 3.8 ± 2.9	38.1 ± 1.7 38.6 ± 1.3	NA	2.6 ± 0.4 2.6 ± 0.4	48 30	0	8
Yamoto [2014] ^[7]	Japan	OCS (retrospective)	TR:11 COR:15	1.9 (0–7) 3.7 (0–10)	38.6 (36–40) 38.5 (37–40)	7/4 11/4	2.6 (2.1–3.1) 2.7 (2.2–3.1)	54.5 46.7	0	7

COR=conventional open repair, NA=not available, NOS=Newcastle–Ottawa scale, OCS=observational clinical study, RCT=randomized controlled trial, TR=thoracoscopic repair.

* At least 1 major associated anomaly.

† Conversion to open thoracotomy.

Table 2

Main outcomes of TR and COR in this meta-analysis.

Study	Sample size	Leak n, %	Stricture n, %*	Operation time (mean, minute)	Time to extubation (mean, day)	Time to 1st oral feeding, day	Hospital stay, day
Al Tokhais [2008] ^[11]	TR: 23 COR: 22	4 (17.4) 3 (13.6)	2 (8.7) 4 (18.8)	149.4±47 179±65.6	NA NA	10 (7–17) 16.3	NA 21.8 (11–38)
Lugo [2008] ^[12]	TR: 8 COR: 25	1 (14) 5 (20)	1 (14) 13 (52)	156±47.6 123±30.8	NA NA	9.8 (7–17) 37 (7–360)	66 (8–280) NA
Kawahara [2009] ^[13]	TR: 7 COR: 10	2 (28.6) 3 (30)	2 (28.6) 0	NA NA	NA NA	NA NA	NA NA
Burford [2011] ^[14]	TR:104 COR: 72	8 (7.6) 2 (2.7)	4 (31.7) 4 (40)	NA NA	NA NA	NA NA	18.1 (6–120) 29.1 (5–159)
Szavay [2011] ^[8]	TR: 25 COR: 32	1 (4) 1 (3.1)	NA NA	140±31 106±54	NA NA	NA NA	NA NA
Ma [2012] ^[15]	TR: 18 COR: 15	NA NA	NA NA	185±54 148±43	5.1±4.6 10.6±8.3	NA NA	42.5±22.1 43.8±24.3
Bishay [2013] ^[16]	TR:5 COR: 5	1 (20) 0	3 (60) 1 (20) [†]	180±23.8 150±34.1	NA NA	NA NA	NA NA
Koga [2014] ^[6]	TR: 25 COR: 40	3 (12) 1 (2.5)	7 (28) 5 (12.5)	228±63 209±98	2.8±1.3 5.6±4.2	7.7±2.6 10.5±4.9	33.4±5.6 45.5±18.1
Yamato [2014] ^[7]	TR: 11 COR: 15	2 (18.2) 3 (20)	3 (27.3) 5 (33.3) [†]	174.5±38.5 155.3±20.2	3.5±0.9 5.6±2.1	8.9±1.9 11.3±3.0	56.9 (24–210) 67.7 (39–271)

COR = conventional open repair, NA = not available, TR = thoracoscopic repair.

* Necessitating at least 1 esophageal dilatation.

† Necessitating at least 2 dilatations.

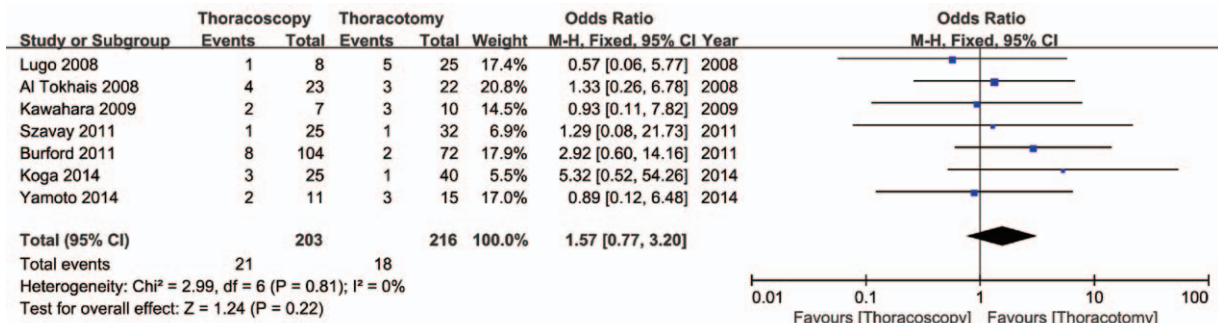


Figure 2. Forest plot for a meta-analysis of leaks.

Pooled estimates (MD, -10.76; 95% CI, -16.39 to -5.12; $P < 0.001$) showed a significant difference for duration of hospital stay (Fig. 5C).

3.3. Sensitivity analysis

We undertook successive exclusion of each study individually to recalculate ORs (95% CI) and MDs (95% CI). Heterogeneity of operative time between TR and COR was moderate ($I^2 = 56\%$). When the study by Al Tokhais et al (2008)^[11] was excluded, no

heterogeneity was observed and a greater significant difference for operative time ($I^2 = 0\%$, $P < 0.001$, Fig. 4B) noted. There was no substantial change in pooled ORs (95% CI) or MDs (95% CI) during other analyses.

4. Discussion

Thoracoscopic repair of congenital esophageal anomalies remains a novel concept for many surgeons. It is considered to be one of the most technically challenging minimally invasive

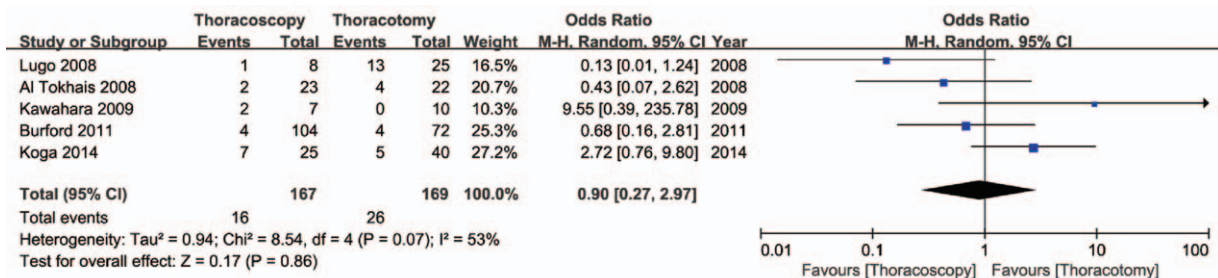


Figure 3. Forest plot for a meta-analysis of strictures.

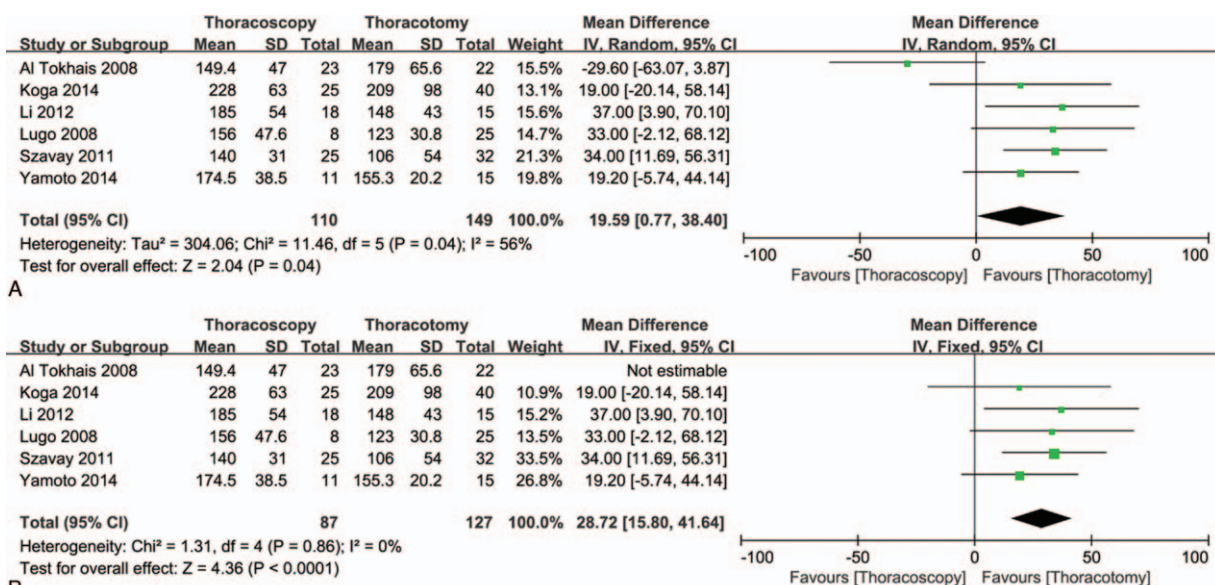


Figure 4. Forest plot for a meta-analysis of operative time (A), and operative time with exclusion of the study by Al Tokhais et al (2008) (B).

procedures for neonates. An increasing number of endoscopic surgeons are becoming familiar with this procedure.

A few studies^[7-8,11,12,17] have described a superior or comparative outcome for patients undergoing a thoracoscopic approach for correction of EA with TEF. Lugo et al^[12] showed comparable outcomes between the thoracoscopic method and the open method. Al Tokhais et al^[12] concluded that TR is safe and comparable with conventional thoracotomy. Allal et al^[17] confirmed the reliability of TR, and affirmed a reduced requirement for analgesia with comparable outcomes. Szavay et al^[18] justified TR for its comparable complication rates.

Yamato et al^[17] demonstrated that the thoracoscopic approach was favorable and safe for EA/TEF repair in carefully selected patients. Koga et al^[6] confirmed that TR is less traumatic than OR: direct retraction of the lung is unnecessary, which results in lower impact to the respiratory tract and a smoother recovery. Moreover, a meta-analysis carried out in 2012 concluded that there were no significant differences between TR and COR with respect to leaks and strictures.^[18]

Compared with COR, TR has superior visualization and avoids the thoracotomy incision. We investigated further the surgical differences of these 2 procedures through a meta-

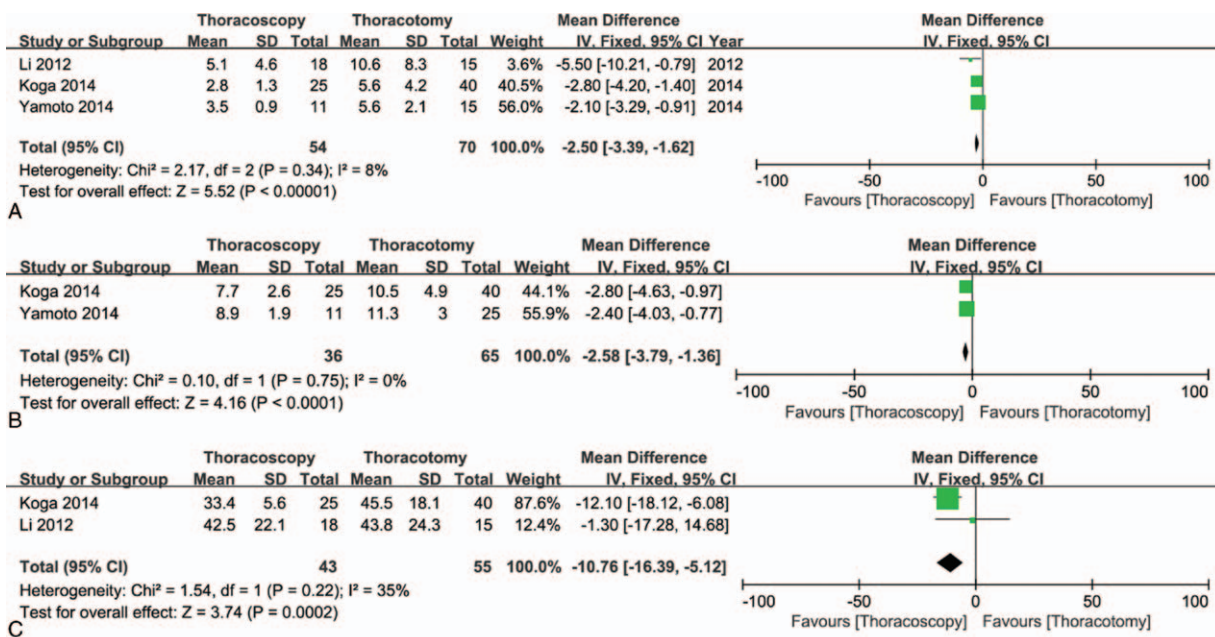


Figure 5. Forest plot for timing of extubation (A), time to 1st oral feeding (B), and duration of hospital stay (C).

analysis. We found no significant difference in TR versus COR with regard to short-term complications such as leaks and strictures. However, TR showed an earlier time to extubation and 1st oral feeding, and shorter hospital stay, but a longer operative time. In 4 studies that included data on intraoperative blood loss, the heterogeneity test suggested that the MD of blood loss carried significant heterogeneity ($I^2=95\%$). Therefore, we stopped the pooled analysis for intraoperative blood loss. Due to the limited number of studies available, we did not investigate other outcomes (e.g., postoperative pain, mean duration of morphine analgesia).

Our study is the 2nd meta-analysis focusing on this topic.^[18] In our meta-analysis, studies after 2012 and several new results were added. Before pooling data, we limited the selection criteria to primary outcomes. For example, we pooled only studies that had an identical definition of stricture (requiring at least 1 esophageal dilatation), and excluded 2 studies^[7,16] with different definition of stricture. In addition, the selection criterion for the surgical procedure in all studies was EA with TEF (type C). Reports on EAs that had excessively long gap defects were excluded from our meta-analysis. There were no significant differences in mean gestational age and weight at the time of surgery between TR and COR, and the primary procedures of TR and COR were approximately similar. These findings showed that we tried to minimize clinical heterogeneity. Sensitivity analysis of operative time showed that heterogeneity changed when 1 study^[11] was excluded. There may be 2 reasons for this observation: a larger number of surgeons or training house staff; steep learning curve to achieve expertise in TR.

On the other hand, we are fully aware of the limitations. There was no randomized controlled trial and only 1 prospective study in our meta-analysis. Most other studies had small sample sizes and were based on a retrospective analysis. In the study with the largest population, 104 TR versus 72 COR, a contemporary thoracotomy series was compared with a multiinstitutional thoracoscopic series.^[14] Most patients were not allocated randomly to “thoracoscopic” or “open” groups, which were determined by multiple factors instead (mainly by birthweight, associated anomalies, general condition of the patient, and the surgeon’s expertise). Also, due to the small number of selected studies, assessment of publication bias was not appropriate. Thus, interpretation of the overall results should be considered with caution.

In conclusion, this meta-analysis suggests that, compared with COR, TR is associated with a similar complication rates of leaks and strictures, and longer operative time. However, the considerable advantages of TR cannot be ignored: concerning time to extubation and 1st oral feeding, and duration of hospital stay. Multicenter, prospective, randomized trials are warranted to confirm the differences between the TR and COR for EA with TEF repair. At the same time, long-time experience regarding

functional results and other complications still need to be investigated in the future.

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