Enhanced recovery after thoracic surgery: Systematic review and meta-analysis

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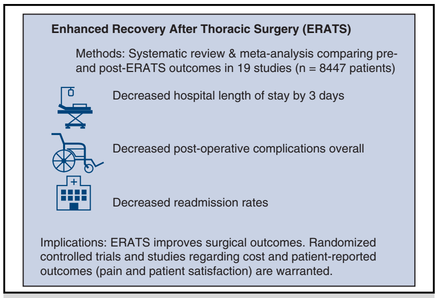
The enhanced recovery after thoracic surgery (ERATS) protocol has been shown to reduce complications and hospital length of stay (LOS).[1-3] In thoracic surgery, the prototypical ERATS pathway involves a preoperative phase, which focuses on patient education and smoking cessation; the intraoperative phase incorporates multimodal anesthesia along with minimally invasive surgery (video-assisted thoracoscopic surgery [VATS]); and the postoperative phase emphasizes the use of incentive spirometry, early mobilization, early chest tube and urinary catheter removal. Goal-directed fluid therapy and minimization of opioids is encouraged.[2-4]

Most of the evidence for ERATS has been published in small, retrospective, single-center studies and case-series reports, all of which are prone to bias.[5-7] In 2016, Fiore and colleagues[8] published a systematic review (SR) of 6 studies on ERATS in lung resections; however, the authors determined their results were inconclusive due to high risk of bias. Li and colleagues[9] also published a SR of 7 randomized-controlled trials (RCTs), but all study participants were from China, Europe, and the Middle East. In 2019, Batchelor and colleagues[3] formulated ERATS guidelines for the Enhanced Recovery After Surgery (ERAS) Society and the European Society of Thoracic Surgeons with an SR. Recently, a few retrospective cohort studies of ERATS in lung resections have been conducted in the United States and Canada, demonstrating that ERATS improves patient outcomes after lung resections and provides more cost-effective care.[10-12] In this updated SR and meta-analysis, we aimed to synthesize the evidence regarding the effect of ERATS, in comparison to conventional care, on surgical outcomes of adult patients undergoing lung resections. We hypothesized that ERATS would improve surgical outcomes by decreasing hospital LOS, postoperative complications, and readmission rates.



ERATS decreased length of stay, postoperative complications, and readmission.

CENTRAL MESSAGE

Enhanced recovery after thoracic surgery decreased hospital length of stay by 3 days, decreased postoperative complications overall, and decreased hospital readmission rates.

PERSPECTIVE

This systematic review/meta-analysis establishes a strong benefit of enhanced recovery after thoracic surgery (ERATS) implementation on postoperative hospital LOS and modest benefit on readmission rates. Future research, including future randomized-controlled trials, should be conducted with larger sample sizes to better determine the association between ERATS and surgical outcomes of lung resections.

See Commentary on page 392.

METHODS

Eligibility Criteria

This SR was conducted in compliance with the preferred reporting items for systematic reviews and meta-analyses statement.[13] We developed inclusion and exclusion criteria with respect to populations, interventions, comparators, outcomes, timing, setting, and study designs (Table E1). Studies

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Abbreviations and Acronyms

ERATS = enhanced recovery after thoracic surgery
LOS = length of stay
RCT = randomized controlled trial
SR = systematic review
VATS = video-assisted thoracoscopic surgery

enrolling adults (age >18 years) who underwent lung resections and compared an ERATS intervention with conventional care were eligible. Of these studies, ones that included at least 3 of the 5 key components of ERATS (ie, preoperative patient education/counseling, minimally invasive surgical technique, opioid-sparing multimodal anesthesia, early chest tube removal, and early feeding/mobilization) were eligible. In terms of outcomes, hospital LOS, 30-day mortality, postoperative complications (as defined by the Society of Thoracic Surgeons[14]) were eligible. Only English-language studies were included. Eligible study designs included the following: RCTs, retrospective cohort studies, prospective cohort studies, case-control studies, and SRs. We did not set a publication time limit. We also included SRs that covered studies published earlier than the past 10 years to assess whether results of recent studies were consistent with studies published in the past. The inclusion criteria for articles included in the meta-analysis is a subset of that for the SR (see details in the Meta-Analysis section). We did not include any SRs in our meta-analysis. However, some of the studies included in the SRs were included in our meta-analysis if they met eligibility criteria.

Data Sources and Searches

We searched PubMed and the Cochrane Library until May 25, 2020, limited to English-language articles. We used medical subject headings as search terms when available and key words when appropriate, focusing on terms to describe adult populations who underwent lung resections and various synonyms of the ERATS intervention (eg, enhanced recovery, fast-track, and multimodal optimization) (Table E2). Similarly, we also searched for unpublished studies using ClinicalTrials.gov.

Study Selection and Data Collection

Two investigators independently reviewed titles, abstracts, and full-text articles using the Covidence online platform (Melbourne, Victoria, Australia) for relevance based on the eligibility criteria described above. Abstracts marked as relevant by both reviewers were reviewed again at the full-text stage. During review of full-text articles and data collection, disagreements between reviewers were resolved by consensus.

Risk-of-Bias Analysis

To assess the risk-of-bias in individual studies, we used Cochrane's risk-of-bias tool[15] to assess RCTs, the Newcastle-Ottawa Scale[16] to assess observational studies (both prospective and retrospective cohort studies), and the A Measurement Tool to Assess systematic Reviews 2[17] tool to assess SRs. Two investigators assigned the risk of bias for each study, and disagreements were resolved by consensus. We did not exclude any studies based on their risk of bias but describe common sources of bias in the results section.

Statistical Analysis

We pooled results for eligible outcomes reported by at least 3 studies that were similar in populations, design, and outcomes. For the binary outcome 30-day readmissions, we conducted a random-effects meta-analysis using the Mantel-Haenszel method and the DerSimonian-Laird estimator was used for τ^2.[18-20] We report the combined risk ratio (RR), 95% confidence interval (CI), and *P* value.

For the LOS outcome, 2 adjustments to the data were made before meta-analysis. First, 2 studies[21,22] reported LOS separately by surgery type within their study population, whereas all of the other studies combined LOS across surgery types. To make these 2 studies comparable to the other studies, we estimated a fixed-effect meta-analysis for each of the 2 studies to yield a single effect estimate for the studies.[23,24] Second, because some studies reported differences in LOS as a median combination of the minimum, quartile 1, quartile 3, and the maximum, we approximated means to include them in our meta-analysis.[25] Wan and colleagues[25] provide methods for approximating the mean and standard error (SE) in 3 cases: when the minimum, median, maximum, and sample size are known, denoted as case C_1; when the 5-number summary and the sample size are known, C_2; and when the first quartile, median, third quartile, and sample size are known, C_3. We encountered 2 of these cases, C_1 and C_3. For the first case, we used Equation 3 and Equation 9 to approximate the mean and SE, respectively. In the third case, we used Equation 14 and Equation 16 to approximate the mean and SE, respectively.[25] We conducted a random-effects meta-analysis for the mean difference in LOS between the ERATS group and the comparison group. The inverse variance method was used for the analysis and the DerSimonian-Laird estimator was used for τ^2.[18] We report the mean difference, 95% CI, and *P* value. Because of the approximation required for studies that reported medians, we also conducted a sensitivity analysis using only the 4 studies that reported means and standard deviations.

For each analysis, we report τ^2 and I^2, a test for heterogeneity. Analyses were conducted using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and the meta package.[26]

RESULTS

Results of Literature Searches

Upon initial search, 927 unique articles were identified. Thirteen additional unpublished studies were found in ClinicalTrials.gov. The 838 articles were screened by title and abstract, and 797 were excluded based on the eligibility criteria. Full-texts of those marked as potentially relevant (41 articles) were screened again using the same eligibility criteria; of these, 19 met full eligibility criteria. Reasons for exclusion at the full-text stage are shown in Figure E1.

Study Characteristics

Of the 19 included studies, 2 were SRs; 1 included 7 RCTs (with a meta-analysis),[9] and the other included 1 RCT, 1 case-control study, 2 prospective cohort studies, and 2 retrospective cohort studies.[8] The SR by Fiore and colleagues[8] included all studies that compared the effect of ERATS versus conventional care on lung resection outcomes, whereas the 1 by Li and colleagues[9] only included RCTs.

The 17 individual studies (7098 participants in total) identified in our searches included 2 RCTs, 6 prospective cohort studies, and 9 retrospective cohort studies.[10-12,21,22,27-38] Studies represented many countries, including China, Japan, Canada, the United States, Switzerland, Italy, The Netherlands, and the United Kingdom. Individual study sample sizes ranged from 35 to 2886. All studies included a comparison between pre- and post-ERATS groups, and all ERATS participants received at least 3 of the 5 key components of ERATS (Table 1). Whereas most studies enrolled

TABLE 1. Components of enhanced recovery after thoracic surgery included in each study

Study	Preoperative patient education/ counseling	Minimally invasive surgical technique	Opioid-sparing multimodal anesthesia	Early chest tube removal	Early feeding and mobilization
Fiore et al, 2016[8]	x	x	x	x	x
Li et al, 2017[9]	x	x	x		x
Madani et al, 2015[10]	x		x	x	x
Paci et al, 2017[11]	x	x	x	x	x
Van Haren et al, 2018[12]	x	x	x	x	x
Dong et al, 2017[27]	x		x	x	x
Huang et al, 2018[28]	x	x	x	x	x
Brunelli et al, 2017[29]	x	x	x		x
Muehling et al, 2008[30]	x		x		x
Martin et al, 2018[21]	x	x	x	x	x
Numan et al, 2012[31]	x	x	x	x	x
Salati et al, 2012[32]	x		x	x	
Chen and Wang, 2020[33]	x		x	x	x
Razi et al, 2021[22]	x	x	x	x	x
Shiono et al, 2019[34]	x		x	x	x
Haro et al, 2019[35]	x	x	x	x	x
Nelson et al, 2019[36]	x	x	x		x
Rice et al, 2020[37]	x	x	x	x	x
Gonzalez et al, 2018[38]	x	x	x	x	x

patients who underwent various types of lung resections with different surgical approaches (VATS vs thoracotomies), 3 studies only included pulmonary lobectomies,[10,32,33] 1 study only included pneumonectomies,[27] and 2 studies only included VATS.[28,29] All studies reported on LOS and complication rates, whereas 12 studies reported on readmission rates and 9 reported on mortality rates.

Risk-of-Bias Analysis

Most of the studies were determined to have low risk of bias overall. Both SRs were deemed to be low risk of bias because their only missing component on the A Measurement Tool to Assess systematic Reviews 2 checklist[17] was discussion regarding funding and conflicts of interest. Selection bias was low in all studies: pre- and post-ERATS groups in all studies had similar baseline characteristics, and because most of the studies were prospective or retrospective cohort studies that involved electronic health record review, all studies had complete follow-up with all patients accounted for. We rated both RCTs as having a low-medium risk-of-bias due to small sample bias. The RCT published by Dong and colleagues[27] had the potential for confounding bias, although it had low risk of selection bias, performance bias, detection bias, attrition bias, and reporting bias. The RCT published by Muehling and colleagues[30] mentioned utilizing a randomized block design but did not specify details regarding allocation concealment or blinding of participants and personnel. There was low risk of measurement bias in all of the studies given the use of EHR review. Seven studies had a potential for confounding bias because they did not mention which covariates they adjusted for in their statistical analysis.[11,21,22,27,28,33,38] Each individual study was conducted at a single academic medical center; thus, their results would have low applicability to other hospital settings in other nations (Tables E3-E5).

Meta-Analysis

Four studies were not included in any meta-analysis due to heterogeneous study designs and outcomes, including 2 SRs,[8,9] 1 published before 2010,[30] and 1 that only reported results for pneumonectomies[27] (Figure E2).

For 30-day readmission rates, 8 studies were not included in pooled results, including 1 reporting on a 90-day readmission rates,[11] 3 did not report readmission rates,[28,33,36] and 4 reported the number of readmissions but not time period over which the readmissions were counted; that is, the denominator for the readmission rate.[12,21,22,37] Seven studies were included in the meta-analysis for 30-day readmissions: 3 retrospective cohort studies[10,29,34] and 4 prospective studies.[31,32,35,38]

For the analysis of LOS, 3 studies were excluded after further review. The primary reason for exclusion was because the reported measure of LOS was not conducive

TABLE 2. Random-effects meta-analysis for 30-day readmissions in the setting of enhanced recovery after thoracic surgery (ERATS) or not

Study	Readmission rate in non-ERATS group	Readmission rate in ERATS group	Risk ratio (95% confidence interval)
Madani et al, 2015[10]	4.7 (6/127)	6.5 (7/107)	1.38 (0.48-4.00)
Brunelli et al, 2017[29]	7.4 (27/365)	7.2 (17/235)	0.98 (0.55-1.75)
Numan et al, 2012[31]	9.6 (9/94)	2.7 (2/75)	0.28 (0.06-1.25)
Salati et al, 2012[32]	5.2 (12/232)	5.6 (13/232)	1.08 (0.51-2.32)
Shiono et al, 2019[34]	4.8 (6/126)	2.4 (3/126)	0.50 (0.13-1.96)
Haro et al, 2019[35]	6.5 (11/169)	6.3 (8/126)	0.98 (0.40-2.35)
Gonzalez et al, 2018[38]	2.0 (1/50)	2.0 (1/50)	1.0 (0.06-15.55)
Random effects meta-analysis	0.93 (0.65-1.32) ($P = .55$) $\tau^2 = 0$; $I^2 = 0.0\%$ (0.0%-56.6%); $Q = 4.04$ (df = 6; $P = .67$)		

Values are presented as % (n/N) unless otherwise noted.

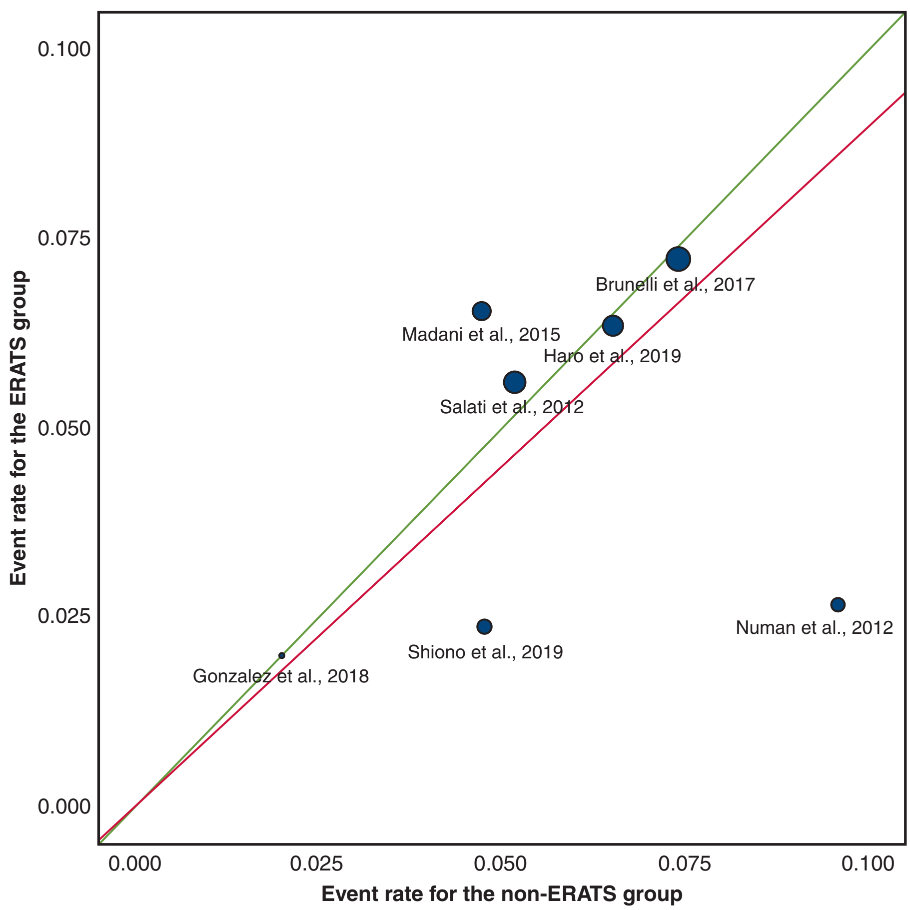

FIGURE 1. L'abbe plot for 30-day readmission. For each study, the 30-day readmission rate for the nonenhanced recovery after thoracic surgery (*non-ERATS*) group (*horizontal axis*) was plotted against the 30-day readmission rate for the ERATS group (*vertical axis*). The studies are plotted as points of varying sizes. The larger points indicate greater precision (1/standard error) in the treatment effect estimate between the 2 groups in the study, smaller points indicate less precision. In the meta-analysis, more precise estimates are given more weight. The *gray 45° line* indicates equal event rates between the 2 groups. The *red line* indicates the random-effects meta-analysis event rate. *Points above the gray line* indicate a higher observed event rate in the ERATS group compared with the non-ERATS group, *points below the gray line* indicate a higher observed event rate in the non-ERATS group, and *points along the gray line* indicate equal observed event rates between the ERATS and non-ERATS group. Similarly, *points above the red line* indicate higher observed event rates in the ERATS group than the estimated meta-analytic effect, *points below the red line* indicate higher observed event rates in the non-ERATS group than the estimated meta-analytic effect, and *point on the red line* indicate observed event rates exactly that of the estimated meta-analytic effect.

TABLE 3. Random effects meta-analysis for length of stay (LOS) in the setting of enhanced recovery after thoracic surgery (ERATS) or not

Study	LOS in non-ERATS group	LOS in ERATS group	Mean difference (95% confidence interval)
Madani et al, 2015[10,*]	7.7 ± 3	6 ± 1.5	–1.7 (–2.3 to –1.1)
Paci et al, 2017[11,*]	6.3 ± 3.8	4.3 ± 2.3	–2 (–3.1 to –0.9)
Huang et al, 2018[28]	8.7 ± 4.4	6.6 ± 3.9	–2.1 (–3.9 to –0.3)
Brunelli et al, 2017[29,*]	4.7 ± 3	5 ± 3	0.3 (–0.2 to 0.8)
Salati et al, 2012[32]	8.6 ± 4.7	5.8 ± 3.5	–2.8 (–3.6 to –2)
Chen and Wang, 2020[33]	12 ± 4	8.9 ± 2.4	–3.1 (–3.8 to –2.4)
Shiono et al, 2019[34,*]	24 ± 15.5	7.5 ± 2.7	–16.5 (–19.2 to –13.8)
Haro et al, 2019[35,*]	4.1 ± 1.6	2.9 ± 1.4	–1.2 (–1.5 to –0.9)
Nelson et al, 2019[36,*]	5 ± 1.5	4.3 ± 2.3	–0.7 (–1.2 to –0.2)
Gonzalez et al, 2018[38,*]	9.3 ± 4.2	6.3 ± 3.3	–3 (–4.5 to –1.5)
Martin et al, 2018[21]	4.2 ± 3.7	3.6 ± 3.5	–0.6 (–1.4 to 0.2)
Razi et al, 2021[22,*]	2 ± 0.9	1.8 ± 0.9	–0.3 (–0.5 to –0.1)
Random effects meta-analysis	Mean difference = -2.17 [-2.98, -1.36] ($P < .0001$) $\tau^2 = 1.77$ (2.54 to 19.73); $I^2 = 95.9\%$ (94.3% to 97.1%); $Q = 270.02$ (df = 11; $P < .0001$)		

Values are presented as mean ± standard deviation unless otherwise noted. *Means and standard deviations were approximated.

to meta-analysis. This included 1 study that did not include a measure of variation with the LOS estimate[37] and 2 that reported interquartile ranges that could not be converted into meta-analyzable measures of variation.[12,31] Additionally, 8 studies reported the median and either the first and third quartiles or the range,[10,11,21,29,30,34-36,38] and 4 studies[21,28,32,33] reported estimates of the mean and standard deviation for LOS. We pooled these 12 studies in our analyses.

Readmissions

Seven studies were included in the meta-analysis of 30-day readmission rates; ERATS was associated with lower readmission rates but the difference between groups was not statistically significant: combined RR 0.93 (95% CI, 0.65-1.32) (Table 2). Across the studies, ERATS for thoracic surgeries showed a modest reduction in readmissions on average, but there is not enough evidence for a definitive conclusion.

Results for the effect of ERATS on 30-day readmissions was consistent across studies; we did not find evidence for between study heterogeneity ($\tau^2 = 0$; $I^2 = 0.0\%$ [0.0%-56.6%]; $Q = 4.04$ [$P = .67$]). We illustrate this with a L'abbe plot (Figure 1). The points representing each study lie closely together in the plot, indicating low heterogeneity between the studies.

LOS

Twelve studies were included in the meta-analysis of LOS. ERATS is associated with a significantly lower LOS than conventional care, with a random-effect grand mean difference of –2.17 days (95% CI, –2.98 to –1.36 days) (Table 3). Notable heterogeneity was observed among the studies included in the meta-analysis ($\tau^2 = 1.77$ [2.54-19.73]; $I^2 = 95.9\%$ [94.3%-97.1%]; $Q = 270.02$ [df = 11; $P < .0001$]). We present a forest plot of the analysis for LOS in Figure 2.

Because we approximated the mean and SE for a number of studies, we also conducted a sensitivity analysis for the mean difference between LOS for ERATS and non-ERATS groups that only included the studies for which a mean and SE were reported (Table 3). Our sensitivity analysis included 4 studies and yielded a random-effects grand mean difference of –3.0 (–4.6 to 1.5) ($P = .0001$). This analysis, like our primary LOS analysis, indicated strong evidence that across studies ERATS patients had shorter LOSs by about 3 days, although we caution the reader to interpret the sensitivity analysis with care given the small number of studies included. We also observed notable heterogeneity between the studies in the sensitivity analysis ($\tau^2 = 2.6$ [1.5-50.0]; $I^2 = 91.2\%$ [82.5%-95.6%]; $Q = 45.69$ [df = 4; $P < .0001$]).

Summary of Results

The 2 included SRs both reported a significant decrease in hospital LOS in the ERATS group (1 reported a difference of 1.2-9.1 days), which is consistent with results from 14 of the 17 individual studies. Whereas 1 SR found no difference in postoperative complication rates,[8] the other included a meta-analysis of 486 participants and reported an RR of 0.64 (95% CI, 0.51-0.80)[9]; similarly, 10 of the individual studies also described a significant decrease in postoperative complications, especially pulmonary complications. Only 1 study reported a significant decrease in 30-day readmission

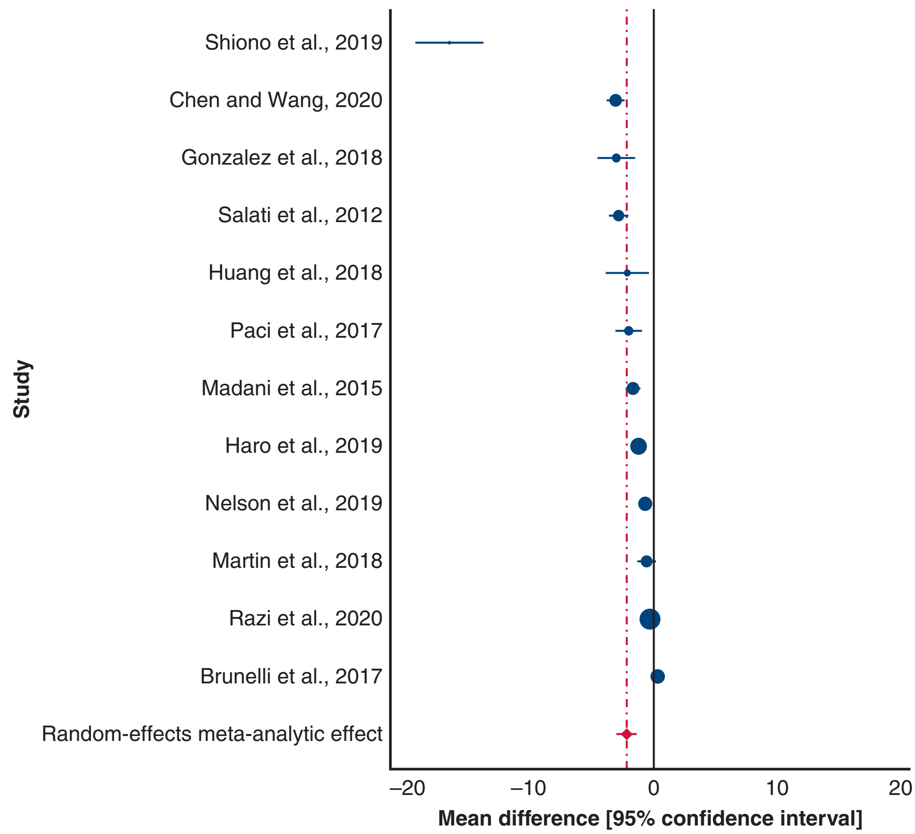

FIGURE 2. Forest plot for length of stay. For each study, a *point along the horizontal axis* denotes the mean difference between the enhanced recovery after thoracic surgery (ERATS) group and the non-ERATS group. The size of the point is proportional to the precision of the estimate with more precise estimates, estimates with smaller standard errors, having larger points and less precise estimates represented with smaller points. The 95% confidence intervals for the mean difference are also plotted. *Points to the left of the gray vertical line* at $x = 0$ indicate that the ERATS group had shorter mean lengths of stays than that of the non-ERATS group; *points to the left of the gray vertical line* indicate that the ERATS group had longer mean lengths of stays than the non-ERATS group; and *points on the gray line* indicate no difference in the mean lengths of stays between the 2 groups. The *dotted red line* indicates the grand mean from the random-effects meta-analysis.

rates.[31] None of the studies reported a significant decrease in 30-day mortality rates. Notably, 1 study found no significant differences in LOS, postoperative complication rates, 30- and 90-day readmission and mortality between the pre- and post-ERATS groups[29] (Table E6).

In our meta-analysis, ERATS pathways was associated with a reduction in readmissions but results were imprecise (not enough evidence for a definitive conclusion). We found strong evidence for reduction in LOS by approximately 3 days for patients receiving ERATS, also pooled results were associated with high statistical heterogeneity.

DISCUSSION

In summary, these studies provide moderate to strong evidence that ERATS improves surgical outcomes in the field of thoracic surgery (Figure 3). Most studies reported a significant decrease in hospital LOS, and our meta-analysis demonstrated a reduction in LOS by 3 days when comparing ERATS patients to controls. Similarly, most studies reported a significant decrease in postoperative complications. Our meta-analysis of readmission rates showed benefit in favor of ERATS but results were imprecise; only 1 of our analyzed studies showed a significant decrease in readmission rates.[31] None of the studies found a significant decrease in 30-day or 90-day mortality rates.

A few studies noticed a significant decrease in postoperative pain[28,31,33] and both societal and medical costs in the ERATS group (mean difference in societal cost –$4396 Canadian per patient,[11] difference in medical costs of 7300 Chinese Yuan[27] and €4415 Euros[38]). Costs were measured differently in various studies and thus were only described qualitatively instead of being included in the meta-analysis. Some studies also noted a significant reduction in the amount of opioid administration after ERATS.[21,22,37] Further studies are warranted to study the cost and effect of ERATS on patient-reported outcomes such as pain and patient satisfaction scores.

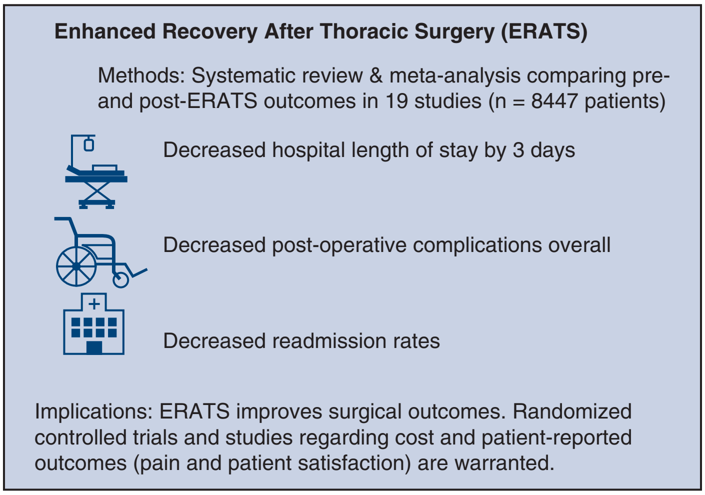

FIGURE 3. In this systematic review and meta-analysis of enhanced recovery after thoracic surgery (ERATS), we analyzed 19 studies comparing pre-ERATS and post-ERATS outcomes (N = 8447 patients overall) per the preferred reporting items for systematic reviews and meta-analyses guidelines. ERATS decreased length of stay, postoperative complications, and readmission. Randomized controlled trials and studies regarding cost and patient-reported outcomes (pain and patient satisfaction) are warranted.

Although these studies have a low risk of bias overall, this body of literature is not without its limitations. In the SR by Fiore and colleagues[8] the authors highlight the potential for confounding bias in observational studies and thus the need for well-designed RCTs to provide conclusive evidence about the effect of ERATS in lung resection outcomes. Some of these studies only included patients who underwent VATS lung resections; because the utilization of VATS is among the key elements of ERATS in thoracic surgery, Brunelli and colleagues[29] discuss that operating with VATS in both pre- and post-ERATS patients could potentially mask the effect of other ERATS elements on surgical outcomes. In addition, van Haren and colleagues[12] highlighted that ERATS was independently associated with decreased pulmonary and cardiac complications after thoracotomy, but not after minimally invasive surgery. The different surgical populations (including different types of lung resections and surgical approaches such as VATS or thoracotomies) and ERATS intervention components in these studies, together with varying statistical methods and outcome measures across the studies, renders it difficult to perform a meta-analysis on multiple outcome measures. Another limitation of this study was the inability to analyze postoperative pulmonary complications in our meta-analysis as only 5 articles included certain pulmonary complications (such as pneumonia, atelectasis, respiratory failure, and prolonged air leaks) as an outcome.

CONCLUSIONS

The reviewed studies establish a strong benefit of ERATS implementation on postoperative hospital LOS and modest benefit on readmission rates. Future research, including future RCTs, should be conducted with larger sample sizes to better determine the association between ERATS and surgical outcomes of lung resections. Studies regarding the effect of ERATS on specific postoperative pulmonary complications, cost, and patient-reported outcomes such as pain scores and patient satisfaction scores are also warranted.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: enhanced recovery after surgery, lung resection, systematic review, meta-analysis

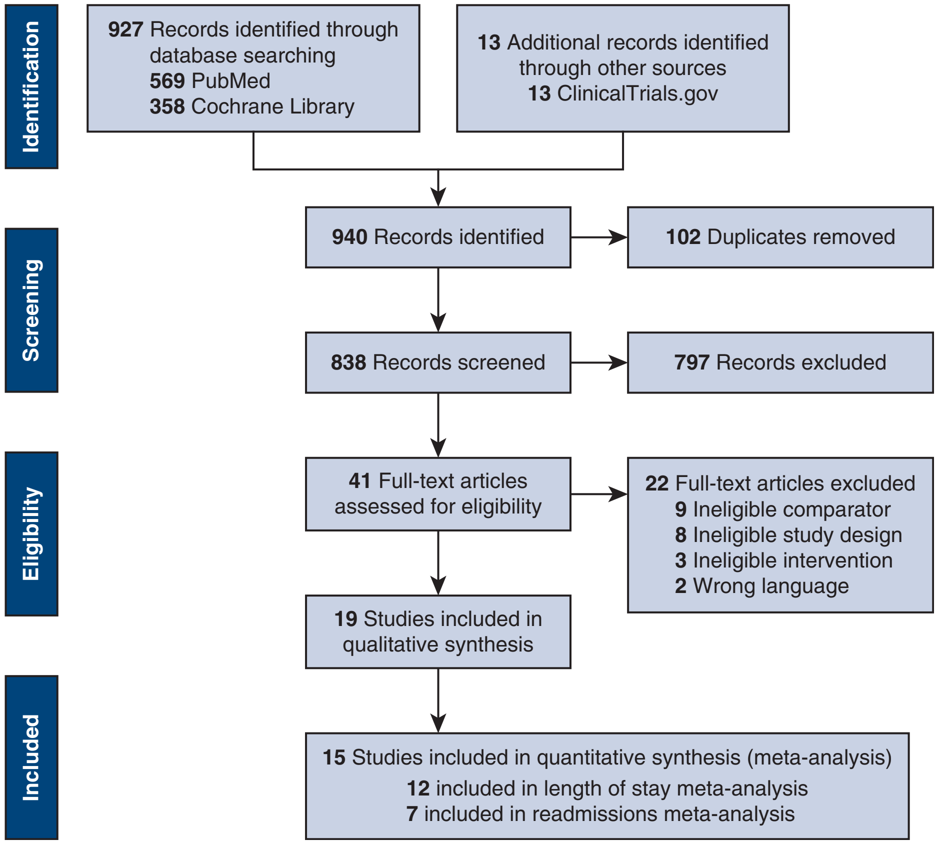

FIGURE E1. Preferred reporting items for systematic reviews and meta-analyses (*PRISMA*) flow diagram of disposition of articles.[13]

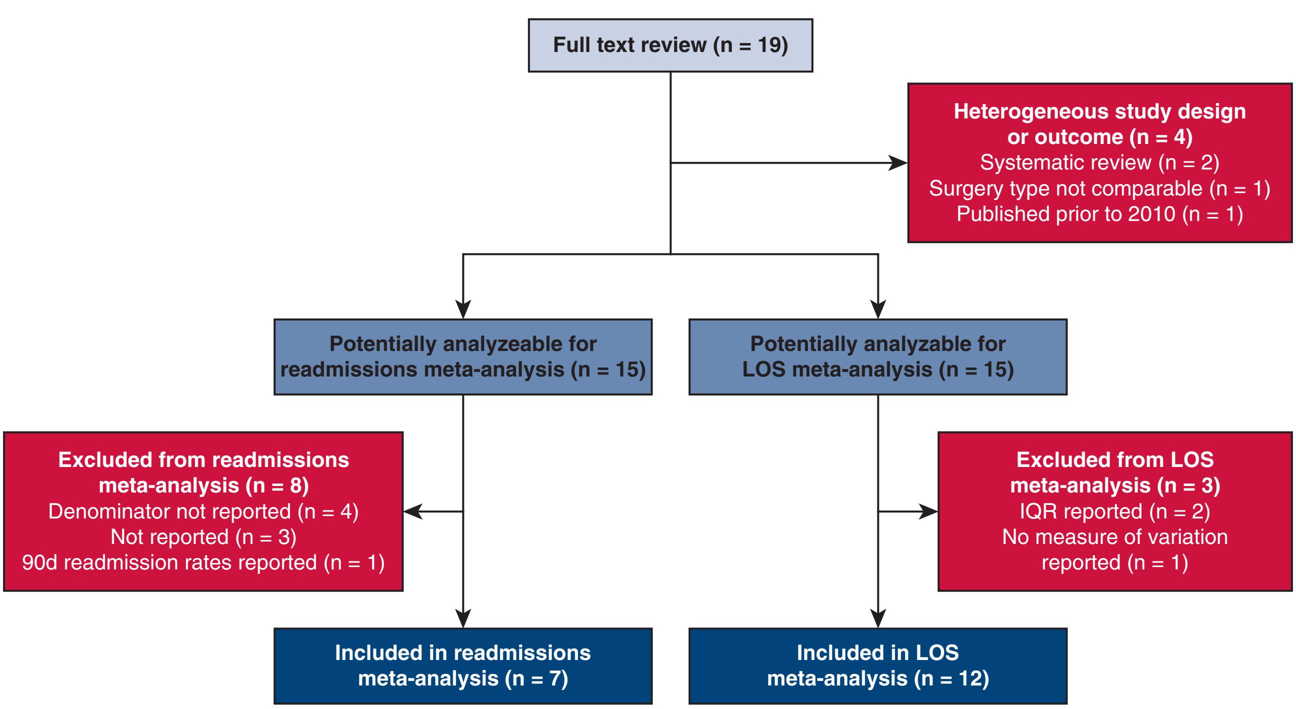

FIGURE E2. Study attrition for meta-analysis. *LOS*, Length of stay; *IQR*, interquartile range.

TABLE E1. Systematic review eligibility criteria

Criterion	Inclusion criteria	Exclusion criteria
Population(s)	Patients age >18 y who undergo lung resections (with or without VATS)	Children age <18 y, pregnant women, adults who undergo other types of thoracic surgery (such as esophagectomies)
Interventions	ERATS protocol	Conventional care (no ERATS intervention); just single components of ERATS (not all key elements of ERATS protocol)
Comparators	ERATS vs pre-ERATS protocol for thoracic surgery	No comparison (all patients had ERATS intervention); nonconcordant historical controls
Outcomes	Hospital LOS, 30-day mortality, post-operative complications (as defined by the STS*)	All other outcomes
Timing	No criteria set	None excluded
Settings	Inpatient hospital settings	Other nonhospital settings
Study designs	RCTs, retrospective cohort studies, prospective cohort studies, case-control studies, systematic reviews	Nonsystematic reviews, case reports, case series, cross-sectional studies, and modeling studies (such as cost-effectiveness analyses)

VATS, Video-assisted thoracoscopic surgery; *ERATS*, enhanced recovery after thoracic surgery; *LOS*, length of stay; *STS*, Society of Thoracic Surgeons; *RCT*, randomized controlled trial. *General Thoracic Surgery Database training manual.[14]

TABLE E2. Systematic review detailed search strategy

Database	Search terms
PubMed	(("enhanced recovery" OR "fast-track" OR fasttrack OR "accelerated rehabilitation" OR ERAS OR FTS OR "rapid recovery" OR "early recovery" OR "multimodal optimization" OR "early mobilization") AND (lung OR lungs OR pulmon*) AND (resect* OR surger* OR surgic* OR operation* OR operativ*)) AND English[lang]
Cochrane Library	("enhanced recovery" OR "fast-track" OR fasttrack OR "accelerated rehabilitation" OR ERAS OR FTS OR "rapid recovery" OR "early recovery" OR "multimodal optimization" OR "early mobilization") AND (lung OR lungs OR pulmon*) AND (resect* OR surger* OR surgic* OR operation* OR operativ*)

TABLE E3. Summary characteristics of studies included in the systematic review and meta-analysis

#	Study	Setting	Source population	Study design and duration	ERATS interventions used	Outcomes reported
1.	Fiore et al, 2016[8]	Systematic review that included 2 studies from the United States (1997 and 1998), 3 studies from Europe (2008-2012), and 1 study from Japan (2006)	Total sample size was 1612 participants (821 ERATS vs 791 control). Sample size of included studies ranged from 58-464 (most studies had half of sample exposed to ERATS). 2 studies involved only patients undergoing lobectomy, and 4 studies involves a variety of lung resection procedures (ranging from wedge resection to pneumonectomy). One study included only VATS procedures, and 1 study only included thoracotomies	Systematic review (included 1 RCT, 2 retrospective cohort studies, 2 prospective cohort studies, and 1 case-control study)	Most included studies had the following ERATS components: preoperative patient education/ counseling and prophylactic antibiotics, intraoperative epidural anesthesia/analgesia, and postoperative standardized chest tube management, early removal of epidural catheter, early removal of oxygen support, early feeding, and early mobilization	The 1 RCT reported no differences in hospital LOS, but all the nonrandomized studies reported decreased LOS (difference, 1.2-9.1 d). There were no significant differences in readmissions, overall complications, and mortality rates. Two nonrandomized studies also reported decreased hospital costs in the ERATS group
2.	Li et al, 2017[9]	Systematic review that included 4 studies from China (2010-2017), 2 studies from Europe (2008 and 2017), and 1 study from the Middle East (2011)	Total sample size was 486 (243 ERATS vs 243 control). Majority of patients were diagnosed with primary non–small cell lung cancers (n = 472). 326 patients (67%) underwent lobectomy, 78 (16%) underwent pneumonectomy, and 82 (17%) underwent sublobar resections. Most patients had standard posterolateral thoracotomy (n = 392; 81%), and only 94 (19%) had VATS procedures	Systematic review (included 7 RCTs); study duration ranged from 1-3 y	Most included studies had the following ERATS components: preoperative patient education/ counseling and intensive pulmonary physiologic therapy, postoperative epidural analgesia/nonsteroidal analgesic painkillers, intravenous fluid restriction, early oral feeding, and early ambulation	Meta-analysis demonstrated that ERATS group had significantly lower morbidity rates (RR, 0.64; $P < .001$), especially the rates of pulmonary (RR, 0.43; $P < .001$) and surgical complications (RR, 0.46; $P = .010$). There was no significant difference in inpatient mortality or cardiovascular complications. Qualitatively, most studies reported significantly shorter hospital LOS, ICU stay, and decreased hospitalization costs in the ERATS group
3.	Madani et al, 2015[10]	Canada (single academic center)	Sample size n = 234 (107 ERATS vs 127 control). Only open pulmonary lobectomies	Retrospective cohort study (August 2011-October 2013)	ERATS intervention included preoperative patient education/ counseling, opioid-sparing pain control, preferred extubation in the operating room or postanesthesia care unit, early and structured mobilization, early feeding and optimization of nutritional status, standardized drain management, and target discharge with written patient goals for each postoperative day	The ERATS group had decreased LOS (median, 6 d; IQR, 5-7 d vs 7 d; 6-10 d; $P < .05$), total complications (40 [37%] vs 64 [50%]; $P < .05$), urinary tract infections (3 [3%] vs 15 [12%]; $P < .05$), and chest tube duration (median, 4 d; IQR, 3-6 d vs 5 d; 4-7 d; $P < .05$), with no difference in readmissions (7 [7%] vs 6 [5%]; $P < .05$) or chest tube reinsertion (4 [4%] vs 6 [5%]; $P < .05$). Decreased LOS was driven by patients without complications (median, 5 d; IQR, 4-6 d vs 6 d; 5-7 d; $P < .05$)
4.	Paci et al, 2017[11]	Canada (single academic center)	Sample size n = 133 (75 ERATS vs 58 control). All elective lung resections (except pneumonectomies and extended resections)	Prospective before/after cohort study (August 2011-August 2013)	ERATS intervention included preoperative patient education/ counseling, opioid-sparing pain control, preferred extubation in the operating room or	The ERATS group had shorter median LOS (4 d; IQR, 3-6 d vs 6 d; IQR, 4-9 d; $P < .01$), decreased total complications (32% vs 52%; $P = .02$), and decreased pulmonary complications (16% vs 34%; $P = .01$), with no

(Continued)

TABLE E3. Continued

#	Study	Setting	Source population	Study design and duration	ERATS interventions used	Outcomes reported
					postanesthesia care unit, early and structured mobilization, early feeding and optimization of nutritional status, standardized drain management, and target discharge with written patient goals for each postoperative day	difference in readmissions. There was a trend toward less postdischarge caregiver burden for the ERATS group (53 ± 90 h vs 101 ± 252 h; $P = .17$). Overall societal costs were lower in the ERATS group (mean difference per patient: –$4396 Canadian; 95% confidence interval –$8674 to $618 Canadian)
5.	Van Haren et al, 2018[12]	United States (single academic medical center)	Sample size N = 2886 (324 ERATS vs 929 transitional period vs 1615 control). Included patients undergoing pulmonary resection for primary lung cancer (both VATS and open thoracotomy)	Retrospective cohort study (January 2006-December 2016)	ERATS intervention included preoperative patient education, preventive analgesia, perioperative steroids, opioid-sparing analgesia, total intravenous anesthesia, goal-directed fluid therapy, regional analgesia with preincisional posterior intercostal nerve block and local wound infiltration with long-acting liposomal bupivacaine, early ambulation, early oral intake, and early chest tube removal	For all patients, LOS decreased in both ERATS and transitional periods compared to pre-ERATS (4 [3] vs 4 [3] vs 5 [3] days; $P < .001$). Pulmonary complications were decreased with ERATS compared with transitional and pre-ERATS (19.9% vs 28.2% vs 28.7%; $P = .004$). Cardiac complications decreased with ERATS (12.3% vs 13.1% vs 18.1%; $P = .001$). There was less thoracic epidural use (2.9% vs 44.5% vs 75.5%; $P < .001$). There were no differences in hospital readmission or mortality rates. Following thoracotomy, ERATS was associated with decreased LOS, less ICU readmission, and decreased frequency of pneumonia, atrial arrhythmias, and need for home oxygen (all $P < .05$). ERATS was independently associated with decreased pulmonary ($P = .046$) and cardiac complications ($P = .001$) on logistic regression after thoracotomy, but not minimally invasive surgery
6.	Dong et al, 2017[27]	China (single academic medical center)	Sample size n = 35 (17 ERATS vs 18 control). All patients with non–small cell lung cancer and only pneumonectomies	RCT (June 2012-March 2014)	ERATS intervention included preoperative patient education, preoperative carbohydrate diet, intraoperative warming, postoperative analgesia with patient-controlled epidural analgesia and oral nonsteroidal analgesic painkillers, early postoperative feeding, chewing gum to promote bowel movements, early removal of urinary catheter, and early postoperative ambulation	In the ERATS group, latency to the first postoperative flatus (1.5 ± 0.6 vs 3.1 ± 0.8 s in controls; $P < .0001$), C-reactive protein (71.36 ± 5.48 vs 80.71 ± 8.32 mg/L in at POD 7; $P < .0001$), the hospital LOS (18.1 ± 1.4 vs 27.4 ± 6.6 d; $P < .0001$), and the medical costs (29.9 ± 2.7 vs 37.2 ± 3.6 thousand Chinese Yuan, $P < .0001$) were significantly reduced. The ERATS group also had a relatively lower postoperative complication rate (23.5% of 17 vs 33.3% of 18 in control group) although it was statistically insignificant
7.	Huang et al, 2018[28]	China (single academic medical center)	Sample size n = 83 (38 ERATS vs 45 control). All patients with non–small cell lung cancer and only uniportal VATS procedures	Retrospective cohort study (January 2016-February 2017).	ERATS intervention included preoperative patient education, alcohol and tobacco cessation 2-4 wk preoperatively, preoperative respiratory	The ERATS group had better VAS, to estimate wound pain on the third post-operative day (3.11 vs 3.69; $P = .003$), shorter chest tube duration (5.26 vs 7.02; $P = .021$), and shorter length of hospital stay (6.58 vs 8.69; $P = .024$).

(Continued)

TABLE E3. Continued

#	Study	Setting	Source population	Study design and duration	ERATS interventions used	Outcomes reported
					function exercises, preoperative carbohydrate loading, prophylactic antibiotics, intraoperative warming, intraoperative anesthesia (with general anesthesia, local anesthesia, and intercostal nerve block), goal-directed fluid therapy, postoperative analgesia (opioid-sparing and oral nonsteroidal anti-inflammatory analgesics), postoperative aerosol inhalation with respiratory function training, early ambulation, and early removal of urinary catheter and chest tubes	There were no significant differences between the groups in terms of operative duration, number of lymph nodes retrieved, blood loss, VAS on POD 1, or complication rate
8.	Brunelli et al, 2017[29]	United Kingdom (single academic medical center)	Sample size n = 600 (235 ERATS vs 365 control). 561 VATS lobectomies and 39 VATS segmentectomies	Retrospective cohort study (April 2014-January 2017)	ERATS intervention included preoperative patient education, preoperative carbohydrate loading, preoperative and intraoperative warming, no prolonged fasting, postoperative discharge when criteria met, early mobilization, early oral feeding, nausea and vomiting prevention, goal-directed fluid therapy, and opioid-sparing analgesia	Between the pre- and post-ERATS groups, there were no significant differences in LOS (ERATS median 5 d vs pre-ERATS 4; $P = .44$), cardiopulmonary complication rates (22.6% vs 22.4%; $P = .98$), 30-d mortality rates (3.8% vs 2.2%; $P = .31$), and 90-d mortality rates (4.7% vs 3.0%; $P = .37$). No significant differences were noted in terms of 30-d (7.2% vs 7.4%; $P = .94$) or 90-d readmission rates (9.8% vs 12.3%; $P = .34$). The risk-adjusted cardiopulmonary morbidity rates were similar in the 2 periods ($P = .76$), whereas the risk-adjusted 30-d mortality was significantly higher in the ERATS period compared with the pre-ERATS mortality ($P = .0004$)
9.	Muehling et al, 2008[30]	Germany (single academic medical center)	Sample size n = 58 (30 ERATS vs 28 control). Only thoracotomy procedures	Randomized controlled trial (timing not specified)	ERATS intervention included preoperative patient education, minimizing preoperative fasting to 2 h instead of 6 h, preoperative and intraoperative warming, early mobilization, early oral feeding, and opioid-sparing analgesia	Between the pre- and post-ERATS groups, there was no differences in LOS (media LOS for both groups were 11 d) or mortality rates (3% vs 4%). ERATS group had decreased postoperative pulmonary complications (6.6% vs 35%; $P = .009$). Subgroup of patients with reduced preoperative FEV1 (<75% of predicted value) experienced less pulmonary complications in the ERATS group (7% vs 55%; $P = .023$). Overall morbidity was not significantly different (26% vs 46%; $P = .172$)
10.	Martin et al, 2018[21]	United States (single academic medical center)	Sample size n = 363 (139 ERATS vs 224 control). 162 VATS lung resections vs 81 ERATS VATS lung	Prospective before/after cohort study (January 2015-May 2017)	ERATS intervention included preoperative patient education, preoperative carbohydrate loading, postoperative	When comparing ERATS thoracotomy and control thoracotomy patients, length of stay (4.0 vs 6.0 days; $P = .009$) decreased significantly. No difference between ERATS VATS and control

(Continued)

TABLE E3. Continued

#	Study	Setting	Source population	Study design and duration	ERATS interventions used	Outcomes reported
			resections. 62 thoracotomies vs 58 ERATS thoracotomies		discharge when criteria met, early mobilization, early oral feeding, goal-directed fluid therapy, opioid-sparing analgesia, and early removal of chest tubes	VATS (median 2 vs 3 d). There were no differences in postoperatively complications. There was no difference in readmissions for ERATS VATS and control VATS (2% vs 7%) or ERATS thoracotomy vs control thoracotomy (17% vs 10%). There was no difference in mortality between ERATS VATS and control VATS (1% vs 1%) or between ERATS thoracotomy and control thoracotomy (0% vs 2%). When comparing control VATS to ERATS-VATS, median postoperative morphine equivalents (86 vs 22 mg; $P < .0001$), total fluid balance (1279 vs 227 mL; $P < .0001$), and mean inflation adjusted hospital costs ($20,169 vs $14,870; $P = .0003$) all decreased significantly. When comparing control thoracotomy with ERATS thoractomy patients, median postoperative morphine equivalents (130 vs 54 mg; $P < .0001$), total fluid balance (788 vs L489 mL; $P = .012$), and mean inflation adjusted hospital costs ($41,950 vs $26,089; $P < .00001$) all decreased significantly
11.	Numan et al, 2012[31]	Netherlands (single academic medical center)	Sample size n = 169 (75 ERATS vs 94 control)	Prospective before/after cohort study (April 2006-December 2008)	ERATS intervention included preoperative patient education, physiotherapy, early ambulation, opioid-sparing analgesia, and early removal of chest tubes	ERATS had reduced length of hospital stay (6.3 vs 7.5 d; $P = .014$). There was no difference in complications (13 patients vs 13 patients; $P = .555$). ERATS had less readmissions (2 patients vs 9 patients; $P = .015$). ERATS had less postoperative pain (pain score 2.7 vs 3.6; $P = .026$). In addition, a trend toward improvement in physical quality of life was observed 1 mo ($P = .03$) and 6 mo ($P = .07$) postoperatively
12.	Salati et al, 2012[32]	Italy (single academic medical center)	Sample size n = 464 (232 ERATS vs 232 control). Only lobectomies	Prospective before/after cohort study with propensity score matching (2000-2007 vs 2008-October 2010)	ERATS intervention included preoperative patient education, postoperative atrial fibrillation prophylaxis, opioid-sparing analgesia, and early removal of chest tubes	ERATS had postoperative stay reduction of 2.8 d (5.8 d vs 8.6 d, $P < .0001$), with a 3-fold higher proportion of patients discharged before the sixth postoperative day ($P < .0001$). There was no difference in cardiopulmonary complications (42 [18.1%] vs 38 [16.4%]; $P = .6$). There was no difference in readmissions (13 [5.6%] vs 12 [5.2%]; $P = .8$)
13.	Chen and Wang, 2020[33]	China (single academic medical center)	Sample size n = 337 (169 ERATS vs 168 control). Only lobectomies	Retrospective cohort study (July 2015-June 2017)	ERATS intervention included preoperative patient education, respiratory function training, early ambulation, opioid-sparing analgesia, and early removal of chest tubes	ERATS group had shorter length of hospital stay (8.9 vs 12.0 d; $P < .001$). ERATS group had lower incidence of postoperative lung complication (11 [6.5%] vs 32 [19.0%]; $P = .008$). ERATS group had shorter enterokinesia recovery times ($P < .001$), lower pain scores ($P < .001$), higher nursing satisfaction ($P < .001$), FVC ($P = .002$), and FEV1 ($P = .002$).

(Continued)

TABLE E3. Continued

#	Study	Setting	Source population	Study design and duration	ERATS interventions used	Outcomes reported
14.	Razi et al, 2021[22]	United States (single academic medical center)	Sample size n = 372 (310 robotic [184 ERATS vs 126 control] vs 62 thoracotomy [32 ERATS vs 30 control])	Retrospective cohort study (January 2017-January 2019)	ERATS intervention included preoperative patient education, preoperative carbohydrate loading, postoperative discharge when criteria met, postoperative atrial fibrillation prophylaxis, early oral feeding, goal-directed fluid therapy, opioid-sparing analgesia, and early removal of urinary catheter and chest tubes	There were no significant differences in LOS for robotic anatomic resections (both median 3; $P = .33$), robotic wedge resections (both median 1; $P = .79$), or thoracotomy (3 vs 4; $P = .10$). There were no significant differences in complications for robotic anatomic resections ($P = .18$), robotic wedge resections ($P = .86$), or thoracotomy ($P = .38$). There were no significant differences in readmission rates for robotic anatomic resections (3.4% vs 3%; $P = .29$), robotic wedge resections (1 [1%] vs 0 [0%]; $P = .62$), or thoracotomy (4 [12.5%] vs 3 [10%]; $P = .88$). Both groups had significant reduction of postoperative pain with an overall reduction of postoperative opioids requirement. Median in-hospital opioids use (morphine milligram equivalent per day) was reduced from 30 to 18.36 ($P = .009$) for the robotic thoracoscopy group and slightly increased from 15.48 to 21.0 ($P = .27$) in the thoracotomy group. Median postdischarge opioids prescribed (total morphine milligram equivalent) was significantly reduced from 480.0 to 150.0 ($P < .001$) and 887.5 to 150.0 ($P < .001$) for both robotic and thoracotomy groups, respectively
15.	Shiono et al, 2019[34]	Japan (single academic medical center)	Sample size n = 252 (126 ERATS vs 126 control). Only lobectomies and segmentectomies via thoracotomy	Retrospective cohort study with propensity score matching (April 2013-March 2018)	ERATS intervention included preoperative patient education, postoperative discharge when criteria met, early oral feeding, opioid-sparing analgesia, and early removal of chest tubes	ERATS group had decreased LOS (median 4 vs 5 d; $P < .001$). There were no significant differences in complications (16 [12.7%] vs 24 [19.1%]; $P = .167$). There were no significant differences in readmission rates (3 [2.4%] vs 6 [4.8%]; $P = .304$). There were no differences in 30-d (both 0, $P = .999$) or 90-d mortality (0 vs 1 [0.8%]; $P = .999$). ERATS had shorter median duration of chest tube drainage (1 [range 1-9] vs 1 [range, 1-18]; $P = .029$)
16.	Haro et al, 2019[35]	United States (single academic medical center)	Sample size n = 295 (126 ERATS vs 169 control). 79 ERATS patients had minimally invasive surgery (9 VATS vs 70 robotic), and 67 control patients had minimally invasive surgery (23 VATS vs 44 robotic).	Prospective before/after cohort study with propensity score matching (October 2015-March 2019)	ERATS intervention included preoperative patient education, postoperative discharge when criteria met, early mobilization, early oral feeding, goal-directed fluid therapy, opioid-sparing analgesia, and early removal of urinary catheter and chest tubes	ERATS group reduced LOS by 1.2 d (3.2 vs 4.4 d; $P < .01$). ERATS group had decreased overall morbidity (20% vs 32%; $P = .02$). There were no significant differences in readmission rates (6.6% vs 6.3%; $P = .94$). There were no significant differences in 30-d mortality (0 in both). ERATS had less direct costs of surgery and hospitalization ($19,500 vs $23,000; $P < .01$), increased minimally invasive surgery (62.7% vs 39.6%), reduced ICU use (21.4% vs 70.4%), improved chest tube (54.8% vs

(Continued)

TABLE E3. Continued

#	Study	Setting	Source population	Study design and duration	ERATS interventions used	Outcomes reported
						24.3%), and urinary catheter (65.1% vs 20.1%) removal by POD 1, increased ambulation (>3 times) on POD 1 (54.8% vs 46.8%), and reduced opioid use by 19 oral morphine equivalents daily (82 vs 101; $P = .04$)
17.	Nelson et al, 2019[36]	United States (single academic medical center)	Sample size n = 471 (92 ERATS [71 open vs 21 VATS/robotic] vs 149 transition [106 open vs 43 VATS/robotic] vs 230 control [168 open vs 62 VATS/robotic])	Retrospective cohort study (January 2006-December 2017)	ERATS intervention included preoperative patient education, minimizing preoperative fasting to 2 h vs 8 h, early mobilization, early oral feeding, goal-directed fluid therapy, and opioid-sparing analgesia	ERATS had shorter LOS (4 d ERATS vs 4 transition vs 5 control; $P = .006$). ERATS had decreased cardiopulmonary complications (23 [25%] ERATS vs 51 [34%] transition vs 94 [41%] control; $P = .025$). ERATS was associated with facilitated delivery of adjuvant chemotherapy (62% ERATS vs 50% transition vs 40% control; $P < .001$), with a shortened interval to receive adjuvant chemotherapy ($P = .041$), and a higher rate of receiving 4 or more cycles. ERATS era (OR, 3.6; $P < .001$), the transitional era (OR, 2.01; $P = .007$), pN status, tumor grade and histology, age, and preoperative performance status were associated with completing adjuvant therapy. The surgical approach (open or thoracoscopic) was not associated with completing adjuvant chemotherapy
18.	Rice et al, 2020[37]	United States (single academic medical center)	Sample size n = 246 (123 ERATS vs 123 control). 50 minimally invasive vs 73 open in each group	Retrospective cohort study with propensity score matching	ERATS intervention included preoperative patient education, minimizing preoperative fasting to 2 h vs 8 h, early mobilization, early oral feeding, goal-directed fluid therapy, opioid-sparing analgesia, and early removal of chest tubes	ERATS had shorter LOS (3 vs 4 d; $P = .038$). ERATS had less pulmonary complications (13 [11%] vs 28 [23%], $P = .015$). No significant differences in cardiac morbidity ($P = 1$), gastrointestinal morbidity ($P = .688$), neurologic morbidity ($P = .625$), and miscellaneous complications. There were no significant differences in readmission rates (5 [4%] vs 4 [3%]; $P = 1$). There were no significant differences in 30-d/in-hospital mortality (1 [1%] vs 1 [1%]; $P = 1$), 30-d mortality (1 [1%] vs 0 [0%]; $P = 1$), or 90-d mortality (3 [2%] vs 1 [1%]; $P = .625$). There were no significant differences in reoperation (3 [3%] vs 3 [3%]; $P = 1$) or ICU readmission (2 [2%] vs 2 [2%]; $P = 1$). ERATS had greater number of adjunct analgesics used postoperatively (median 3 vs 2; $P < .001$), reduced morphine milligram equivalents (whether tramadol was included [median 14.2 vs 57.8; $P < .001$] or excluded [median 2.7 vs 57.8; $P < .001$] and regardless of surgical approach), lower average daily pain scores (median 1.3 vs 1.8; $P = .004$) (this difference was present only among patients

(Continued)

TABLE E3. Continued

#	Study	Setting	Source population	Study design and duration	ERATS interventions used	Outcomes reported
						undergoing thoracotomy). The proportion of patients who were prescribed discharge opioids varied whether tramadol was included (96% each group; $P = 1.00$) or excluded (39% vs 80%; $P < .001$) in the analysis
19.	Gonzalez et al, 2018[38]	Switzerland (single academic medical center)	Sample size n = 100 (50 ERATS vs 50 control). VATS only	Prospective ERATS patient enrollment with retrospective control cohort (June 2016-November 2017)	ERATS intervention included preoperative patient education, preoperative carbohydrate loading, intraoperative warming, early mobilization, early oral feeding, nausea and vomiting prevention, goal-directed fluid therapy, opioid-sparing analgesia, and early removal of urinary catheter and chest tubes	ERATS had significantly shorter LOS (median 4 vs 7 d; $P < .0001$). ERATS had decreased pulmonary complications (16% vs 38%; $P = .01$) and decreased overall postoperative complications (24% vs 48%; $P = .03$). There were no significant differences in readmission (1 patient in each group was readmitted). There were no significant differences in mortality (no 30-d mortality). ERATS had significantly lower average total hospitalization costs (€15,945 vs €20,360; $P < .0001$), mainly due to lower costs during the postoperative period (€7449 vs €11,454; $P < .0001$) in comparison with the intraoperative period (€8496 vs €8906; $P = .303$). Cost-minimization analysis showed a mean saving in the ERATS group of €3686 per patient

ERATS, Enhanced recovery after thoracic surgery; *VATS*, video-assisted thoracoscopic surgery; *RCT*, randomized controlled trials; *LOS*, length of stay; *RR*, risk ratio; *ICU*, intensive care unit; *IQR*, interquartile range; *POD*, postoperative day; *VAS*, visual analogue scale; *FEV1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *OR*, odds ratio.

TABLE E4. Risk of bias analysis for randomized controlled trials[15]

#	Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome assessment	Selective reporting	Other bias
6.	Dong et al, 2017[27]	Low risk: Computer-generated block randomization initiated by a data manager in the respiratory research group	Low risk: Sequential opaque envelopes	Low risk: Both the surgeon and the thoracic research assistant interviewing potential candidates for the study were blind to the randomization code. When evaluating outcomes, a thoracic research assistant blinded to intervention was assigned to ensure double blind and minimize potential bias	Low risk: Complete follow-up with all patients accounted for (chart review)	Low risk: All prespecified outcomes were reported	Low-medium risk: Small sample size bias (n = 35). Also potential for confounding bias because they did not mention which covariates were adjusted for
9.	Muehling et al, 2008[30]	Low risk: Randomized block design	N/A (did not specify)	N/A (did not specify)	Low risk: Complete follow-up	Low risk: All pre-specified outcomes were reported	Low-medium risk: Small sample size bias (n = 58)

N/A, Not available.

TABLE E5. Risk of bias analysis for observational studies[16]

#	Reference	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration outcome of interest was not present at start of study	Comparability of cohorts on basis of design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total category scores
3.	Madani et al, 2015[10]	Truly representative of the average	Drawn from same community as the exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Adjusted for age, gender, BMI, and ASA score	Data collected from both paper and electronic hospital charts	Yes: 30-d post-operative outcomes	Complete follow-up: All subjects accounted for (retrospective chart review)	Selection: 4/4; Comparability: 2/2; Outcome: 3/3
4.	Paci et al, 2017[11]	Truly representative of the average	Drawn from same community as the exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Did not mention which covariates were adjusted for. Subgroup analyses were performed to investigate economic effect of ERATS based on employment status, operative approach (VATS vs open thoracotomy), resection (anatomy and nonanatomic), and postoperative complications	Data collected from electronic hospital charts and patient questionnaires. Unit costs were obtained from hospital finance department or from provincial health ministry records. Physician billing fees were ascertained using the fee schedule from the province of Quebec in 2013	Yes: 30-d and 90-d postoperative outcomes	Complete follow-up: All subjects accounted for (chart review)	Selection: 4/4; Comparability: 1/2; Outcome: 3/3
5.	Van Haren et al, 2018[12]	Truly representative of the average	Drawn from same community as the exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Adjusted for age, gender, time period (pre-ERATS, transition, and ERATS), performance status, readmission to ICU, extent of surgical resection, surgical approach, utilization of epidural catheter, extent of surgical resection, pathologic stage, ASA score, and preexisting COPD	Data collected from thoracic surgery database (prospectively maintained by thoracic surgery team members and reviewed monthly by departmental data analyst to ensure accuracy; data is also submitted to STS database and subject to independent review for accuracy)	Yes: 30-d postoperative outcomes	Complete follow-up: All subjects accounted for (retrospective chart review)	Selection: 4/4; Comparability: 2/2; Outcome: 3/3
7.	Huang et al, 2018[28]	Truly representative of the average	Drawn from the same community as the exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Did not mention which covariates were adjusted for	Data collected from electronic hospital charts	Unclear how long patients were followed for post-operative complications – authors stated short follow-up time	Complete follow-up: All subjects accounted for (retrospective chart review)	Selection: 4/4; Comparability: 1/2; Outcome: 2/3
8.	Brunelli et al, 2017[29]	Truly representative of the average	Drawn from same community as	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics.	Data collected from a prospectively maintained quality-	Yes: 30-d and 90-d postoperative outcomes	Complete follow-up: All subjects accounted	Selection: 4/4; Comparability: 2/2; Outcome: 3/3

(Continued)

TABLE E5. Continued

#	Reference	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration outcome of interest was not present at start of study	Comparability of cohorts on basis of design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total category scores
			the exposed cohort			Adjusted for age, sex, BMI, FEV1, DLCO, presence of underlying coronary artery disease, cerebrovascular disease, diabetes, performance score, and duration of surgery	improvement institutional database		for (retrospective chart review)	
10.	Martin et al, 2018[21]	Truly representative of average	Drawn from same community as exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Did not mention which covariates were adjusted for	Data collected from EHR. Readmissions captured through the Virginia Hospital and Healthcare Association database. Financial data obtained from the University of Virginia Clinical Data Repository	Yes: 30-d postoperative outcomes	Complete follow-up	Selection: 4/4; Comparability: 1/2; Outcome: 3/3
11.	Numan et al, 2012[31]	Truly representative of average	Drawn from same community as exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Adjusted for age, surgical approach, BMI, adjuvant treatment, and baseline quality of life	Data collected from EHR	Yes: Followed for 6 mo	Complete follow-up	Selection: 4/4; Comparability: 2/2; Outcome: 3/3
12.	Salati et al, 2012[32]	Truly representative of average	Drawn from same community as exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Adjusted for age, gender, BMI, smoking history, ASA score, Zubrod score, and FEV1	Data collected from EHR	Yes: 30-d postoperative outcomes	Complete follow-up	Selection: 4/4; Comparability: 2/2; Outcome: 3/3
13.	Chen and Wang, 2020[33]	Truly representative of average	Drawn from same community as exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Did not mention which covariates were adjusted for	Data collected from EHR	Unclear how long patients were followed for postoperative complications	Complete follow-up	Selection: 4/4; Comparability: 1/2; Outcome: 2/3
14.	Razi et al, 2021[22]	Truly representative of average	Drawn from same community as exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Did not mention which covariates were adjusted for	Data collected from EHR	Yes: 30-d postoperative outcomes	Complete follow-up	Selection: 4/4; Comparability: 1/2; Outcome: 3/3
15.		Truly representative of average		Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in	Data collected from EHR		Complete follow-up	

(Continued)

TABLE E5. Continued

#	Reference	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration outcome of interest was not present at start of study	Comparability of cohorts on basis of design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total category scores
	Shiono et al, 2019[34]		Drawn from same community as exposed cohort			baseline characteristics. Propensity scores were calculated by a logistic model and included the following variables: age, gender, comorbidities, smoking status, neoadjuvant treatment, pulmonary function, BMI, operative time, and blood loss during surgery		Yes: 30-d and 90-d postoperative outcomes		Selection: 4/4; Comparability: 2/2; Outcome: 3/3
16.	Haro et al, 2019[35]	Truly representative of average	Drawn from same community as exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Propensity scores were based on the following covariates: age-adjusted Charlson comorbidity index, sex, race, diagnosis, and procedure	Data collected from EHR	Yes: 30-d postoperative outcomes	Complete follow-up	Selection: 4/4; Comparability: 2/2; Outcome: 3/3
17.	Nelson et al, 2019[36]	Truly representative of average	Drawn from same community as exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Adjusted for age, surgical approach, extent of resection, FEV1, preoperative performance status, gender, and the postoperative month	Data collected from EHR	Yes: Followed for 12 mo	Complete follow-up for postoperative outcomes. Chemotherapy data available for 175 patients who received chemotherapy	Selection: 4/4; Comparability: 2/2; Outcome: 3/3
18.	Rice et al, 2020[37]	Truly representative of average	Drawn from same community as exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Covariates used for propensity score matching included sex, age, surgical approach, extent of resection, and performance status	Data collected from EHR	Yes: Followed for 30-d and 90-d postoperative outcomes	Complete follow-up	Selection: 4/4; Comparability: 2/2; Outcome: 3/3
19.	Gonzalez et al, 2018[38]	Truly representative of average	Drawn from same community as exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERATS groups were very similar in baseline characteristics. Did not mention which covariates were adjusted for	Data collected from EHR	Yes: 30-d postoperative outcomes	Complete follow-up	Selection: 4/4; Comparability: 1/2; Outcome: 3/3

EHR, Electronic health record; *ERATS*, enhanced recovery after thoracic surgery; *BMI*, body mass index; *ASA*, American Society of Anesthesiologists; *VATS*, video-assisted thoracoscopic surgery; *ICU*, intensive care unit; *STS*, Society of Thoracic Surgeons; *COPD*, chronic obstructive pulmonary disease; *FEV1*, forced expiratory volume in 1 second; *DLCO*, diffusing capacity of carbon monoxide.

TABLE E6. Risk of bias analysis for systematic reviews[17]

Analysis question	Fiore et al, 2016[8]	Li et al, 2017[9]
Did the research questions and inclusion criteria for the review include components of PICO?	Yes	Yes
Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
Did the review authors use a comprehensive literature search strategy?	Yes	Yes
Did the review authors perform study selection in duplicate?	Yes	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes
Did the review authors provide a list of excluded studies and justify the conclusions?	Yes	Yes
Did the review authors describe the included studies in adequate detail?	Yes	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	Yes: Cochrane ROB tool	Yes: Jadad score
Did the review authors report on the sources of funding for the studies included in the review?	No	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A	Yes
If meta-analysis was performed, did the review authors assess the potential influence of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	Yes
Did the review authors account for risk of bias in individual studies when interpreting/discussing the results of the review?	Yes	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely influence on the results of the review?	N/A	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No

PICO, Population, intervention, comparator group, outcome; *ROB*, risk of bias; *N/A*, not available.