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 colleagues8 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 colleagues9 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 colleagues3 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.

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
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 Surgeons14) 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 tool13 to assess RCTs, the Newcastle-Ottawa Scale16 to assess observational studies (both prospective and retrospective cohort studies), and the A Measurement Tool to Assess systematic Reviews21 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 $r^2$. 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 studies12,25 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. 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 colleagues25 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 C1; when the 5-number summary and the sample size are known, C2; and when the first quartile, median, third quartile, and sample size are known, C3. We encountered 2 of these cases, C1 and C3. 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. 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 $r^2$. 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 $r^2$ 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),3 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 colleagues8 included all studies that compared the effect of ERATS versus conventional care on lung resection outcomes, whereas the 1 by Li and colleagues5 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
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 checklist17 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 colleagues27 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 colleagues30 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 pneumonectomies27 (Figure E2).

For 30-day readmission rates, 8 studies were not included in pooled results, including 1 reporting on a 90-day readmission rate,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 studies10,29,34 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    | 4.7 (6/127)                         | 6.5 (7/107)                      | 1.38 (0.48-4.00)                     |
| Brunelli et al., 2017  | 7.4 (27/365)                        | 7.2 (17/235)                     | 0.98 (0.55-1.75)                     |
| Numan et al., 2012     | 9.6 (9/94)                          | 2.7 (2/75)                       | 0.28 (0.06-1.25)                     |
| Salati et al., 2012    | 5.2 (12/232)                        | 5.6 (13/232)                     | 1.08 (0.51-2.32)                     |
| Shiono et al., 2019    | 4.8 (6/126)                         | 2.4 (3/126)                      | 0.50 (0.13-1.96)                     |
| Haro et al., 2019      | 6.5 (11/169)                        | 6.3 (8/126)                      | 0.98 (0.40-2.35)                     |
| Gonzalez et al., 2018  | 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)  
\[ \chi^2 = 0; I^2 = 0.0\% (0.0\%-56.6\%); Q = 4.04 (df = 6; P = .67) \]

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.
to meta-analysis. This included 1 study that did not include a measure of variation with the LOS estimate and 2 that reported interquartile ranges that could not be converted into meta-analyzable measures of variation. Additionally, 8 studies reported the median and either the first and third quartiles or the range, and 4 studies 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, the other included a meta-analysis of 486 participants and reported an RR of 0.64 (95% CI, 0.51-0.80); 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.
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 (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. 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 and both societal and medical costs in the ERATS group. 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. Further studies are warranted to study the cost and effect of ERATS on patient-reported outcomes such as pain and patient satisfaction scores.
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, 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 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 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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FIGURE E1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of disposition of articles.\textsuperscript{13}

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

| 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 surgc* 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 surgc* OR operation* OR operativ*)) |
TABLE 3. 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, 2016¹                                                    | 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, 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, standardization of drainage management, and target discharge with written patient goals for each postoperative day | 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, 2017⁷                                                       | 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/monitored 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, 2015⁸                                                  | 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 (13 [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, 2017¹                                                    | Canada (single academic center)                                           | Sample size n = 133 (75 ERATS vs 58 controls). 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 |
| #   | Study                                         | Setting                                      | Source population | Study design and duration                                                                 | ERATS interventions used                                                                                                                                                                                                 | Outcomes reported                                                                                                                                                                                                                                                                                                                                 |
|-----|-----------------------------------------------|----------------------------------------------|-------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5.  | Van Haren et al., 2018                        | 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; \( P \text{ < } .001 \)). 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                             | 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 at POD 7; \( P < .0001 \)), the hospital LOS (18.1 ± 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                            | 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; \( P = .024 \)). |
| #   | Study                          | Setting                                      | Source population | Study design and duration | ERATS interventions used                                                                 | Outcomes reported                                                                                                                                 |
|-----|-------------------------------|----------------------------------------------|-------------------|---------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| 8.  | Brunelli et al, 2017[22]      | 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, 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[23]      | 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[24]        | 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 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 | 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 thoracotomy patients. |

(Continued)
| # | Study | Setting | Source population | Study design and duration | ERATS interventions used | Outcomes reported |
|---|---|---|---|---|---|---|
| 11. | Numan et al, 2012 | 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; \( P < .001 \)). 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 | 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; \( P < .001 \)), with a 3-fold higher proportion of patients discharged before the sixth postoperative day (\( P < .001 \)). 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 | 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 (\( P = .002 \)). |
| #  | Study | Setting | Source population | Study design and duration | ERATS interventions used | Outcomes reported |
|----|-------|---------|-------------------|---------------------------|--------------------------|-------------------|
| 14. | Razi et al, 2021 | 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 \( P = .79 \)), 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\% vs 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 | 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\%); \( P = .306 \)). 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 | 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 (319,500 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 384 JTCVS Open. September 2021 Thoracic: Perioperative: Expert Review Khoury et al

(Continued)
| # | Study | Setting | Source population | Study design and duration | ERATS interventions used | Outcomes reported |
|---|---|---|---|---|---|---|
| 17. | Nelson et al, 2019 | 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 vs 5 control; P = 0.06). ERATS had decreased cardiopulmonary complications (23 [25%] ERATS vs 51 [34%] transition vs 94 [41%] control; P = 0.025). ERATS was associated with facilitated delivery of adjuvant chemotherapy (62% ERATS vs 50% transition vs 40% control; P < 0.001), with a shortened interval to receive adjuvant chemotherapy (P = 0.04), and a higher rate of receiving 4 or more cycles. ERATS era (OR, 3.6; P < 0.001), the transitional era (OR, 2.01; P = 0.007), 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 | 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 = 0.038). ERATS had less pulmonary complications (13 [11%] vs 28 [23%]; P = 0.015). No significant differences in cardiac morbidity (P = 1), gastrointestinal morbidity (P = 0.688), neurologic morbidity (P = 0.625), 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/hospital mortality (1 [1%] vs 0 [0%]; P = 1), 30-d mortality (1 [1%] vs 0 [0%]; P = 1), or 90-d mortality (3 [2%] vs 1 [1%]; P = 0.625). 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 < 0.001), reduced morphine milligram equivalents (whether tramadol was included [median 14.2 vs 57.8; P = 0.001] or excluded [median 2.7 vs 57.8; P < 0.001] and regardless of surgical approach); lower average daily pain scores (median 1.3 vs 1.8; P = 0.004) (this difference was present only among patients |
| #  | Study                      | Setting                              | Source population                      | Study design and duration                                                                 | ERATS interventions used                                                                 | Outcomes reported                                                                 |
|----|----------------------------|--------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| 19 | Gonzalez et al, 2018       | 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.
| # | Reference | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Incomplete outcome assessment | Selective reporting | Other bias |
|---|-----------|-----------------------------|------------------------|---------------------------------------|-----------------------------|-------------------|-----------|
| 6. Dong et al, 2017 | 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 | Low risk: Randomized block design | N/A (did not specify) | N/A (did not specify) | Low risk: Complete follow-up | Low risk: All prespecified 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

| #  | Reference                           | Representativeness of exposed cohort | Selection of non-exposed cohort | Ascertainment of exposure | Demonstration of outcome 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 |
|----|-------------------------------------|-------------------------------------|--------------------------------|---------------------------|-----------------------------------------------------------|-------------------------------------------------------|-----------------------|------------------------------------------|---------------------------------|------------------------|
| 1  | Madani et al., 2015                  | 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-post-operative outcomes | Complete follow-up: All subjects accounted for (retrospective chart review) | Selection: 4/4; Outcome: 2/2 |
| 2  | Paci et al., 2017                    | 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 (VAES vs open thoracotomy), resection (anatomic 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; Outcome: 1/2; Outcome: 3/3 |
| 3  | Van Haren et al., 2018               | 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 predicting 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; Outcome: 2/2; Outcome: 3/3 |
| 4  | Huang et al., 2018                   | 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 (or retrospective chart review) | Selection: 4/4; Outcome: 1/2; Outcome: 2/3 |
| 5  | Brunelli et al., 2017               | 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 | Data collected from a prospectively maintained quality | Yes: 30-d and 90-d postoperative outcomes | Complete follow-up: All subjects accounted for | Selection: 4/4; Outcome: 2/2; Outcome: 3/3 |

(Continued)
| #  | Reference                          | Representativeness of exposed cohort | Selection of non-exposed cohort | Ascertainment of exposure | Demonstration of outcome 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 |
|----|------------------------------------|---------------------------------------|---------------------------------|---------------------------|---------------------------------------------------------------|------------------------------------------------------|----------------------|---------------------------------------------|---------------------------------|---------------------------- |
| 10 | Martin et al., 2018<sup>1</sup>    | 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: 2/2, Outcome: 3/3 |
| 11 | Numan et al., 2012<sup>1</sup>     | 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<sup>1</sup>    | 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<sup>2</sup>    | 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<sup>1</sup>      | 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                              | Demonstration of outcome  | Assessment of outcome  | Follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | Total category scores | (Continued) |

(Continued)
| #  | Reference                  | Representativeness of exposed cohort | Selection of non-exposed cohort | Ascertainment of exposure | Demonstration of 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 |
|----|----------------------------|-------------------------------------|---------------------------------|---------------------------|------------------------------------------------------------------------|----------------------------------------------------------|-----------------------|-------------------------------------------|--------------------------------|------------------------|
| 16. | Haro et al, 2019**         | 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, gender, Charlson comorbidity index, sex, race, diagnosis, and procedure | Data collected from EHR | Yes: 30-d postoperative outcomes         | Selection: 4/4; Comparability: 2/2; Outcome: 3/3 |
| 17. | Nilsson et al, 2019**      | 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**         | 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- and 90-d postoperative outcomes | Complete follow-up | Selection: 4/4; Comparability: 2/2; Outcome: 3/3 |
| 19. | Gonzalez et al, 2018**     | 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.
| Analysis question                                                                 | Fiore et al, 2016 | Li et al, 2017 |
|----------------------------------------------------------------------------------|-------------------|----------------|
| 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.