# The effect of the enhanced recovery after surgery program on lung cancer surgery: a systematic review and meta-analysis

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**Background:** Lung cancer is one of the most common causes of cancer-related death worldwide. The enhanced recovery after surgery (ERAS) program is an effective evidence-based multidisciplinary protocol of perioperative care. However, the roles of ERAS in lung cancer surgery remain unclear. This systematic review and meta-analysis aimed to investigate the short-term impact of the ERAS program on lung resection surgery, especially in relation to postoperative complications.

**Methods:** A systematic literature search of PubMed, EMBASE, and the Cochrane Library databases until October 2020 was performed to identify the studies that implemented an ERAS program in lung cancer surgery. The studies were selected and subjected to data extraction by 2 reviewers independently, which was followed by quality assessment. A random effects model was used to calculate overall effect sizes. Risk ratio (RR), risk difference (RD), and standardized mean difference (SMD) with 95% confidence interval (CI) served as the summary statistics for meta-analysis. Subgroup analysis and sensitivity analysis were subsequently performed.

**Results:** A total of 21 studies with 6,480 patients were included. The meta-analysis indicated that patients in the ERAS group had a significantly reduced risk of postoperative complications (RR =0.64; 95% CI: 0.52 to 0.78) and shortened postoperative length of stay (SMD=–1.58; 95% CI: –2.38 to –0.79) with a significant heterogeneity. Subgroup analysis showed that the risks of pulmonary (RR =0.58; 95% CI: 0.45 to 0.75), cardiovascular (RR =0.73; 95% CI: 0.59 to 0.89), urinary (RR =0.53; 95% CI: 0.32 to 0.88), and surgical complications (RR =0.64; 95% CI: 0.42 to 0.97) were significantly lower in the ERAS group. No significant reduction was found in the in-hospital mortality (RD =0.00; 95% CI: –0.01 to 0.00) and readmission rate (RR =1.00; 95% CI: 0.76 to 1.32). In the qualitative review, most of the evidence reported significantly decreased hospitalization costs in the ERAS group.

**Conclusions:** The implementation of an ERAS program for surgery of lung cancer can effectively reduce risks of postoperative complications, length of stay, and costs of patients who have undergone lung cancer surgery without compromising their safety.

**Keywords:** Enhanced recovery after surgery (ERAS); lung cancer surgery; systematic review; meta-analysis

## Introduction

Lung cancer is one of the most common causes of cancer-related death worldwide (1,2), the most common cancer and the leading cause of cancer death in men. Meanwhile, it is the third most common cancer in women (after breast and colorectal cancer) and the second leading cause of cancer death (after breast cancer) (3,4). Surgical resection remains the most preferable treatment for early-stage lung cancer even for those patients with advanced cancer (1). With the implementation of minimally invasive techniques, the preferred surgical method has gradually developed from thoracotomy to video-assisted thoracoscopic surgery (VATS) (5,6). Although VATS is becoming increasingly popular in clinical practice, some important side effects and postoperative complications are still inevitable, such as pneumonia, pleural effusion, pneumothorax, arrhythmia, respiratory failure, and others (7-9). The occurrence of postoperative complications is related to many perioperative factors, such as poor preoperative lung function, improper operation by the surgeon, inadequate expectoration after surgery, sputum accumulation, and long duration of chest tube placement. Therefore, it is urgent to optimize perioperative management in order to reduce the occurrence of complications and improve the quality of life (QoL) of patients.

The Enhanced Recovery After Surgery (ERAS) program, which has become prevalent in recent years, is a multimodal approach encompassing all phases of care: preoperative (including assessment, counselling, nutrition, and smoking cessation), intraoperative (including minimally invasive surgery, standardized anesthetic protocol, and single chest tube placement), and postoperative (including early ambulation, nutrition, and adequate pain relief) (10,11). It is a combination of various procedures spanning patient admission through to discharge and is aimed at minimizing surgical stress, reducing the occurrence of postoperative complications, decreasing length of stay (LOS), increasing QoL during hospitalization, and thus reducing costs related to surgery. The concept of ERAS was first proposed by Dr. Engelman in 1994 (12). In recent years, this multidisciplinary and multimodal perioperative rehabilitation concept has been widely applied in surgeries of various disciplines: colorectal (13), liver (14), gynecological (15), urologic (16), spinal (17), and gastrointestinal surgery (18). Moreover, recent studies have indicated that patients treated with the ERAS program during hepatectomy, laparoscopic colorectal surgery, and spinal surgery have a significant reduction in LOS and risk of postoperative complications (13,14,17). Although ERAS has been used in lung cancer surgery for several years, its effectiveness is still controversial.

A recent systematic review and meta-analysis of 38 randomized controlled trials (RCTs) found that the ERAS program plays an important role in reducing the rate of complications and shortening the LOS across various surgical specialties (19). However, the findings of this study may not be applicable to pulmonary resection owing to the limited data. Fiore et al. performed a systematic review and meta-analysis in order to evaluate the efficacy of the ERAS program in elective lung resection in 2016 (20), which included 6 studies (1 RCT, 1 case-control, 4 cohort); however, the authors finally failed to reach a convincing conclusion because of the small sample size and high bias risks. A later evidenced-based review and meta-analysis reported by Li et al. in 2017 (21) that included 7 RCTs, demonstrated that the ERAS program in lung cancer surgery could effectively accelerate postoperative recovery and save hospitalization costs without compromising patient safety; however, the inappropriate inclusion criteria and relatively small sample size might have produced considerable biases and reduced the reliability of their results. In order to reach a more substantiated conclusion, we aimed to conduct a systematic review and meta-analysis to determine the short-term impact of the ERAS program on lung resection surgery, especially in relation to postoperative complications.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-433).

## Methods

This systematic review and meta-analysis was conducted and reported in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (22) and the PRISMA statement (23). The review was registered at the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/PROSPERO/) as registration number CRD42020216064.

### Databases and search strategy

The literature review was performed based on 3 online databases: PubMed, EMBASE, and the Cochrane Library

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**Table 1** Details of search strategy for all databases

| Database | Search Strategy |
| --- | --- |
| PubMed | (((((((((Enhanced[All Fields] AND recovery[All Fields]) OR Fast-track[All Fields]) OR ((intensive[All Fields] OR intensity[All Fields]) AND (rehabilitation[Subheading] OR rehabilitation[All Fields] OR rehabilitation[MeSH Terms])) OR (accelerated[All Fields] AND (rehabilitation[Subheading] OR rehabilitation[All Fields] OR rehabilitation[MeSH Terms]))) OR ERAS[All Fields])))) AND ((((((((((((((Pulmonary Neoplasms) OR Neoplasms, Lung) OR Lung Neoplasm) OR Neoplasm, Lung) OR Neoplasms, Pulmonary) OR Neoplasm, Pulmonary) OR Pulmonary Neoplasm) OR Lung Cancer) OR Cancer, Lung) OR Cancers, Lung) OR Lung Cancers) OR Pulmonary Cancer) OR Cancer, Pulmonary) OR Cancers, Pulmonary) OR Pulmonary Cancers) OR Cancer of the Lung) OR Cancer of lung)) OR "Lung Neoplasms"[Mesh]) |
| Embase | ('cancer of lung' OR 'cancer of the lung' OR 'pulmonary cancers' OR 'pulmonary cancer' OR 'lung cancer' OR 'lung cancers' OR 'pulmonary neoplasm' OR 'lung neoplasm' OR 'pulmonary neoplasms' OR 'lung cancer'/exp) AND ('enhanced recovery' OR 'fast track' OR 'intensive rehabilitation' OR 'accelerated rehabilitation' OR eras) |
| Cochrane Library | ((LUNG NEOPLASM[MeSH]) OR ((LUNG OR PULMON*) AND (NEOPLAS* OR CANCER OR CARCINOMA*))) AND ((enhanced recovery) OR (fast track) OR (intensive rehabilitation) OR (accelerated rehabilitation) OR ERAS) |

(from 29 September 2020 to 3 October 2020). The Medical Subject Headings (MeSH) included in the search strategy were "lung neoplasms" and "rehabilitation", and the free terms were searched in PubMed. The key terms and free terms were used in every possible combination by 2 Boolean operators ("AND" and "OR"). The details of search strategies for all databases are displayed in *Table 1*. The articles were independently reviewed and cross-checked by 2 authors (Rongyang Li and Kun Wang). Moreover, we also manually searched the reference lists of excluded publications to identify any further potential nonduplicate studies. Any disagreements among the reviewers were resolved by discussion.

### Study selection and criteria

The inclusion criteria were as follows: (I) involved adult patients undergoing elective pulmonary resection (wedge resection, lobectomy, pneumonectomy, etc.), (II) involved patients who received an ERAS program (we recognized a total of 25 elements in studies encompassing all phases of perioperative care [pre-, intra-, and postoperative] (20,21,24,25), as shown in *Figure 1*), (III) involved an ERAS program with at least 4 elements that covered at least 2 phases of perioperative care, (IV) involved a traditional care control group that had adopted at least 3 elements fewer than the ERAS group, (V) reported at least 1 of the outcome measures of interests (see below), and (VI) written in English.

The exclusion criteria were as follows: (I) ineligible article types, such as case report, reviews, and conference abstracts; (II) no outcomes of interest present; (III) inclusion

of nonhuman participants or written in languages other than English.

### Endpoints and outcome measures

The primary outcome was postoperative complication, which was defined by the presence of any individual complication during the hospitalization or within 30 days after surgery. Other outcomes of interest were in-hospital mortality, LOS, 30-day readmission rate, and total cost of hospitalization.

### Data collection

The 2 reviewers (Rongyang Li and Kun Wang) independently browsed the eligible studies and extracted the corresponding data to fill in a predefined table. Any discrepancies were resolved by consensus. The following data were extracted from each study: (I) publication data: authors, year, and country; (II) experimental data: study design, study period, ERAS elements, surgical procedures, and extent of resection; (III) demographic data: sample size, age, gender, body mass index (BMI), and predicted forced expiratory volume in 1 second (FEV1%); (IV) outcome data: postoperative complications, in-hospital mortality, LOS, 30-day readmission, and total cost of hospitalization. We did not contact authors to obtain any unpublished data.

### Quality assessment

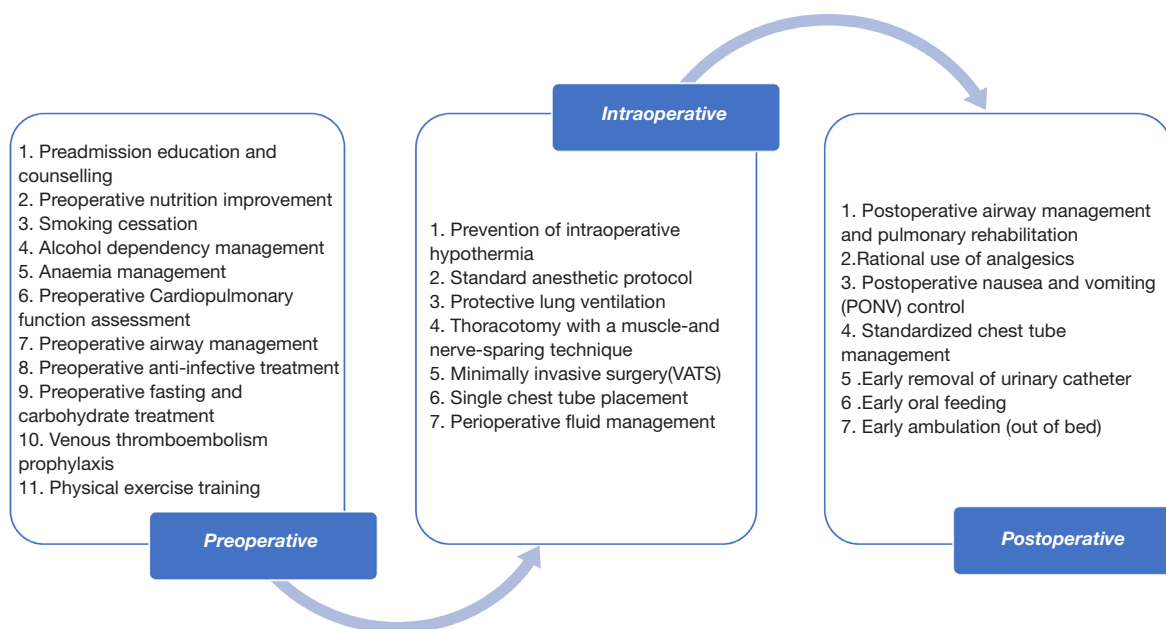Quality of included cohort studies was evaluated using the

**Figure 1** Care elements implemented in the ERAS program for lung cancer surgery. ERAS, enhanced recovery after surgery; VATS, video-assisted thoracoscopic surgery; PONV, postoperative nausea and vomiting.

Newcastle-Ottawa Quality Assessment Scale (NOS) (26). We identified studies with a score equal to or higher than 6 as eligible for our meta-analysis. We used the Cochrane risk of bias tool to assess the quality of RCTs (27). Due to the nature of the interventions involved in ERAS, it is often unfeasible to blind patients and staff; therefore, high risk of performance bias was assumed if a study did not mention blinding of staff or patients.

The quality of each study was independently appraised by 2 investigators (Rongyang Li and Kun Wang). Any disagreements regarding the quality assessment were resolved by consulting a third investigator (Chenghao Qu).

### Statistical analysis

We calculated the risk ratio (RR) with 95% confidence interval (CI) to summarize the effects of ERAS programs on dichotomous data. If no events occurred in both the experimental and control group, the pooled risk difference (RD) estimates and 95% CIs were applied. The standardized mean difference (SMD) with 95% CI served as the appropriate statistics to summarize the mean values with standard deviations (SDs) for continuous variables. If the SDs were not provided, we did not incorporate the data in

the quantitative synthesis because the extrapolation of SDs was only applicable for studies with a large sample size and normal distribution of outcomes according to the guidelines of the Cochrane Collaboration (27). Meta-analysis was not performed when the number of studies was very small (n<5), because the results might have been misleading; instead, a qualitative summary of evidence was performed.

Cochrane Q test and $I^2$ statistics were used to quantify the heterogeneity level. An $I^2$ of 25%, 50%, and 75% represented low, moderate, and considerable variance, respectively (28). A 2-sided P value of less than 0.05 was defined as statistical significance. In our study, random effects models were employed to estimate pooled effect sizes in order to reduce possible bias. Both Begg's and Egger's test were used to detect any potential publication bias within the meta-analyses (29,30). Significant publication bias was revealed if Begg's or Egger's P value <0.05.

We also conducted a sensitivity analysis, in which the impact of each study on the overall estimates could be detected by omitting individual studies sequentially, to further examine the stability of pooled estimates (27). The strong robustness of our meta-analysis was confirmed if there was no substantial variation between the adjusted results and the primary results (27).

To evaluate the efficacy of ERAS programs on postoperative complications in detail, a meta-analysis was then performed on 4 subgroups: pulmonary, cardiovascular, urinary, and surgical complications. The relevant complications were judged according to the criteria used in recent large-registry trials based on the French Society of Thoracic and Cardiovascular Surgery (SFCTCV) database (31).

All statistical analyses were conducted using the Review Manager software (RevMan version 5.3, the Nordic Cochrane Center, the Cochrane Collaboration, 2014) and Stata (version 14; StataCorp LLC, College Station, TX, USA).

## Results

### Literature search

A flow diagram outlining the searching procedures is presented in *Figure 2*. A total of 1,204 potential articles were identified, including 648 PubMed citations, 398 EMBASE citations, and 153 Cochrane Library citations. In addition, a manual search of the reference lists also yielded 5 relevant studies. After checking for duplicates, reviewing titles, abstracts, and full texts, 22 eligible articles were included in qualitative assessment (32-53). A total of 21 articles were finally included in our meta-analysis after excluding a study due to it being of low quality (53).

### Characteristics of the included studies

Baseline characteristics and major perioperative outcomes in each study are summarized in *Tables 2* and *3*. There were 19 cohort studies (34-52) and 2 RCTs (32,33) included in this review. The publication dates of the included articles ranged from 2006 to 2020. The sample size of the trials ranged from 34 to 1,957. All eligible articles were written in English.

### Patient characteristics

Through layers of screening, 6,480 patients were finally enrolled in our meta-analysis. Detailed participant characteristics are displayed in *Table 2* (more detailed baseline characteristics are presented in the Table S1). Approximately half of the participants were from North America (n=3,332; 51.4%), followed by 1,827 patients from Europe (28.2%), and 1321 patients from East Asia (20.4%).

A total of 2,617 patients were included in the ERAS group (40.4%), while 3863 patients were enrolled in the control group (59.6%).

### ERAS elements

Elaborate details of ERAS elements estimated in each study are summarized in *Tables 4,5*. The number of ERAS elements utilized in the ERAS group and control group ranged from 5 to 22 and 0 to 10, respectively. The most commonly used ERAS element in our included studies was preadmission education/counselling (adopted by 19 studies), followed by early ambulation (adopted by 18 studies). The ERAS elements that were least used in eligible studies were alcohol dependency management and anemia management (adopted by 1 study). Although ERAS elements varied across these 21 studies, they overlapped for some common components, as shown in *Tables 4,5*.

### Quality assessment

Quality assessment of the included studies is presented in *Tables 6-8*. Finally, all except for 1 of the included cohort studies (53) received a NOS score ≥6. The mean NOS score of included studies was 6.84 [6–8], suggesting that they were of acceptable quality. As for RCTs (32,33), 1 of the 2 articles included was not double-blinded and did not mention the allocation concealment. Both articles did not mention whether the results included incomplete outcome data and selective reporting. There were no other risks of bias identified.

### Effect of ERAS on outcome

#### Postoperative complications

As shown in *Table 3*, the overall postoperative complications rates in the ERAS group and the control group were 6.5–42.1% and 13.3–83.3%, respectively. Of the 18 studies that reported on overall postoperative complications (32-45,47,49-51), 9 reported that the ERAS group had decreased rates of overall postoperative complications (34,36,37,39,40,42-45), while the other half reported no significant difference between the 2 groups (32,33,35,38,41,47,49-51). The pooled RR of all 18 studies was 0.64 (95% CI: 0.52 to 0.78; P<0.0001), as shown in *Figure 3*, indicating a significant decrease of overall complications rates in the ERAS group. However, a significant heterogeneity was found by a random effects
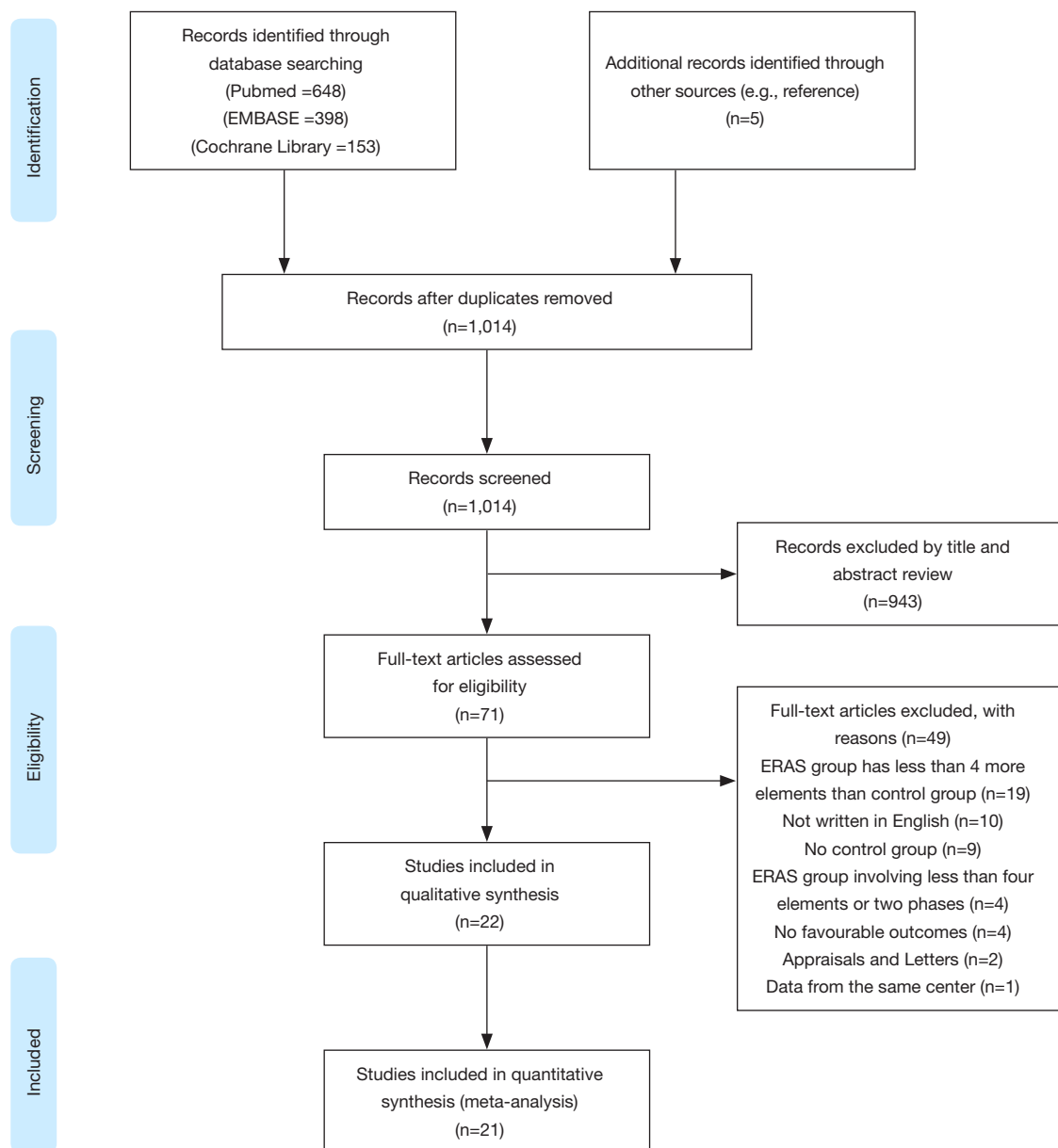
**Figure 2** PRISMA flow diagram of literature retrieval. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

model ($I^2$=63%; P<0.001). No publication bias was found using both Begg's test (P=0.363) and Egger's test (P=0.133).

To explore the source of high heterogeneity, we omitted the individual studies sequentially (27). Fortunately, we found a significantly reduced heterogeneity after excluding the studies performed by Gao *et al.* in 2015 ($I^2$=35%; P=0.08), as shown in *Figure 4*.

**In-hospital mortality**

A total of 13 studies reported in-hospital mortality (32,33,35,39-42,45-48,50,52), all of which reported no significant difference between the 2 groups. There were 11 deaths (0.4%) in the ERAS group and 28 deaths (0.7%) in the control group. However, 7 studies reported 0 events in both the experimental and control group (32,39-41,46,47,50); therefore, the pooled RD estimates with 95% CIs were applied. The results showed no significant difference in the mortality rates between the ERAS group and the control group (RD =0.00; 95% CI: −0.01 to 0.00; P=0.62) with low heterogeneity ($I^2$=0; P=1.00), as shown in

**Table 2** Baseline characteristics of included studies

| Study (year) | Country | Period | Study type | Sample size | | | Mean age | | Gender (Male Ratio) | | ERAS elements | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | ERAS | Con. | ERAS | Con. | ERAS | Con. | ERAS | Con. |
| Dong 2017 | China | 2012–2014 | RCT | 35 | 17 | 18 | 55.1 [44–65] | 56.6 [50–65] | 13 (76%) | 14 (78%) | 14 | 8 |
| Muehling 2008 | Germany | NR | RCT | 58 | 30 | 28 | 67 [45–81] | 64 [24–83] | 20 (66.7%) | 23 (82.1%) | 7 | 4 |
| Boujibar 2018 | France | 2014–2016 | RCS | 34 | 19 | 15 | 65 [59–71] | 69 [56–73] | 15 (78.9%) | 10 (66.6%) | 5 | 2 |
| Brunelli 2017 | UK | 2014–2017 | RCS | 600 | 235 | 365 | 69.7 [63–76] | 68.8 [63–75] | 99 (42%) | 146 (40%) | 15 | 8 |
| Chen 2020 | China | 2015–2017 | RCS | 337 | 169 | 168 | 57.6±10.23 | 57.22±8.95 | 110 (65.1%) | 109 (64.9) | 7 | 4 |
| Gao 2015 | China | 2008–2011 | PCS | 142 | 71 | 71 | 66.33±10.17 | 59.67±13.03 | 40 (56.3%) | 44 (62.0%) | 6 | 3 |
| Glogowaska 2017 | Poland | NR | PCS | 402 | 215 | 187 | 59 [49–67] | 55 [43–64] | 113 (52.6%) | 102 (54.5%) | 5 | 1 |
| Gonzalez 2018 | Switzerland | 2016–2017 | ACS | 100 | 50 | 50 | 64(44–87) | 68(51–81) | 24 (48%) | 18 (36%) | 16 | 10 |
| Haro,G 2019 | USA | 2015–2019 | PCS | 295 | 126 | 169 | 67 [59–72] | 67 [59–73] | 39 (31.0%) | 74 (43.8%) | 17 | 5 |
| Huang 2018 | China | 2016–2017 | RCS | 83 | 38 | 45 | 60.71±8.35 | 59.56±10.24 | 16 (42.1%) | 25 (55.6%) | 22 | 5 |
| Khandhar 2018 | USA | 2007–2016 | RCS | 404 | 304 | 100 | 66.2±10.5 | 66.2±10.0 | 178 (58.6%) | 53 (53.0%) | 11 | 2 |
| Li,M 2019 | China | 2016–2018 | RCS | 144 | 72 | 72 | 63.1±8.3 | 63.5±8.3 | 42 (58.3%) | 40 (55.6%) | 6 | 3 |
| Lv,H 2019 | China | 2017–2018 | PCS | 110 | 55 | 55 | 57.11±8.23 | 56.84±7.02 | 31 (56.4%) | 35 (63.6%) | 10 | 2 |
| Madani 2015 | Canada | 2011–2013 | RCS | 234 | 107 | 127 | 67±10 | 64±11 | 65 (61%) | 57 (45%) | 10 | 3 |
| Maruyama 2006 | Japan | 2000–2004 | RCS | 218 | 113 | 105 | 63(17–84) | 64(15–83) | 66 (58.4%) | 53 (50.5%) | 9 | 3 |
| Numan 2012 | Netherland | 2006–2008 | PCS | 169 | 75 | 94 | 60(21–78) | 58(24–83) | 43 (57.3%) | 55 (58.5%) | 8 | 0 |
| Rice,D 2020 | USA | NR | RCS | 246 | 123 | 123 | 62(20–89) | 61(22–82) | 65 (53%) | 66 (54%) | 11 | 5 |
| Salati 2012 | Italy | 2000–2010 | RCS | 464 | 232 | 232 | 68.2±9.4 | 67.7±10.8 | NR | NR | 5 | 0 |
| Shiono 2019 | Japan | 2013–2018 | RCS | 252 | 126 | 126 | 70 [65–76] | 70 [63–77] | 84 (66.7%) | 86 (68.3%) | 11 | 5 |
| Tahiri 2020 | Canada | 2015–2016 | RCS | 196 | 98 | 98 | 65.2±9.3 | 66.2±9.4 | 36 (36.7%) | 29 (29.6%) | 6 | 1 |
| Van Haren 2018 | USA | 2006–2016 | RCS | 1,957 | 342 | 1,615 | 66 [53–79] | 65 [50–80] | 162 (47.4%) | 808 (50%) | 10 | 5 |

[]= interquartile range; ( )=range; mean ± SD. NR, not reported; ERAS, enhanced recovery after surgery; Con., control; RCT, randomised controlled trail; PCS, prospective cohort study; RCS, retrospective cohort study; ACS, ambispective cohort study.

**Table 3** Outcomes of included studies

| Studies | Complication (%) | | Mortality (%) | | Readmission (%) | | Overall LOS (d) | | Postoperative LOS (d) | | Total cost (×10⁴) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ERAS | Con. | ERAS | Con. | ERAS | Con. | ERAS | Con. | ERAS | Con. | ERAS | Con. |
| Dong et al. | 4 (23.5) | 6 (33.3) | 0 | 0 | NR | NR | 18.1±1.4 | 27.4±6.6 | NR | NR | ¥: 2.99±0.27 | ¥: 3.72±0.36 |
| Muehling et al. | 8 (26.7) | 13 (46.4) | 1 (3.3) | 1 (3.6) | NR | NR | 11 (8–33) | 11 (7–34) | NR | NR | NR | NR |
| Boujibar et al. | 8 (42.1) | 12 (80.0) | NR | NR | NR | NR | 5 [4–8] | 7 [5–8] | NR | NR | NR | NR |
| Brunelli et al. | 53 (22.6) | 82 (22.4) | 6 (2.6) | 8 (2.2) | 17 (7.2) | 27 (7.4) | NR | NR | 5 [3–7] | 4 [3–7] | NR | NR |
| Chen et al. | 11 (6.5) | 32 (19.0) | NR | NR | NR | NR | NR | NR | 8.91±2.43 | 11.98±4.00 | ¥: 4.36±0.76 | ¥: 4.96±1.22 |
| Gao et al. | 12 (16.9) | 59 (83.3) | NR | NR | NR | NR | 14.54±4.71 | 19.21±9.89 | 7.21±3.18 | 11.07±4.66 | ¥: 4.01±0.47 | ¥: 3.69±0.37 |
| Glogowska et al. | 32 (14.9) | 37 (19.8) | NR | NR | NR | NR | 7 [6–8] | 8 [7–10] | NR | NR | NR | NR |
| Gonzalez et al. | 12 (24.0) | 24 (48.0) | 0 | 0 | 1 (2.0) | 1 (2.0) | NR | NR | 4 (1–16) | 7 (2–21) | €: 1.59 [1.51–1.75] | €: 2.04 [1.91–2.30] |
| Haro,G et al. | 25 (19.8) | 61 (36.1) | 0 | 0 | 8 (6.4) | 9 (5.3) | 2.9 [1.9–3.8] | 4.1 [3.0–5.1] | NR | NR | $: 1.77 [1.39–2.21] | $: 2.10 [1.72–2.62] |
| Huang et al. | 4 (10.5) | 6 (13.3) | 0 | 0 | NR | NR | NR | NR | 6.58±3.87 | 8.69±4.40 | NR | NR |
| Khandhar et al. | 74 (24.3) | 35 (35.5) | 0 | 2 (2.0) | 15 (4.9) | 6 (6.0) | NR | NR | 1 [1–1.25] | 2 [1–4] | NR | NR |
| Li,M et al. | 10 (13.9) | 20 (27.8) | NR | NR | NR | NR | NR | NR | 8.94±2.38 | 12.01±3.97 | NR | NR |
| Lv, H et al. | 9 (16.4) | 20 (36.4) | NR | NR | NR | NR | NR | NR | 6.55±1.20 | 8.59±1.62 | NR | NR |
| Madani et al. | 40 (37.4) | 64 (50.4) | 1 (1.0) | 0 | 7 (6.5) | 6 (4.7) | 6 [5–7] | 7 [6–10] | NR | NR | NR | NR |
| Maruyama et al. | NR | NR | 0 | 0 | NR | NR | 18.6±1 | 29.4±2 | 13.3±0.9 | 22.4±2 | $: 1.31±0.28 | $: 1.44±0.43 |
| Numan et al. | 13 (17.3) | 13 (13.8) | 0 | 0 | 2 (26.7) | 9 (9.6) | 6.3 [4–7] | 7.5 [5–9] | NR | NR | NR | NR |
| Rice,D et al. | NR[a] | NR[a] | 1 (0.8) | 1 (0.8) | 5 (40.7) | 4 (32.5) | 4.9 no SD | 5.4 no SD | NR | NR | NR | NR |
| Salati et al. | 42 (18.1) | 38 (16.4) | NR | NR | 13 (5.6) | 12 (5.2) | NR | NR | 5.8±3.5 | 8.6±4.7 | NR | NR |
| Shiono et al. | 16 (12.7) | 24 (19.1) | 0 | 0 | 3 (2.4) | 6 (4.8) | NR | NR | 4 (4–18) | 5 (3–25) | NR | NR |
| Tahiri et al. | 23 (23.4) | 28 (28.6) | NR | NR | 5 (5.1) | 4 (4.1) | NR | NR | 3 [2–5] | 5 [4–6] | NR | NR |
| VanHaren et al. | NR[a] | NR[a] | 2 (0.6) | 16 (1) | 13 (3.8) | 54 (3.3) | 4 [1–7] | 5 [2–8] | NR | NR | NR | NR |

[]= interquartile range; ( )=range; { }=95% CI; mean ± SD. [a], not report overall postoperative complications but more detailed complications. NR, not reported; ERAS, enhanced recovery after surgery; LOS, length of stay; Con., Control; ¥, RMB; €, euro; $, dollar.

**Table 4** Detailed ERAS elements of included studies (I)

| ERAS elements | Dong | Muehling | Boujibar | Brunelli | Chen | Gao | Glogowaska | Gonzalez | Haro | Huang | Khandhar |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Preoperative interventions** | | | | | | | | | | | |
| Preadmission education/counselling | √ | √ | √[a] | √[a] | √ | | √[a] | √[a] | √[a] | √[a] | √[a] |
| Preoperative nutrition improvement | | | | √[a] | | | | √[a] | | √[a] | |
| Smoking cessation | | | √[a] | | | | | | √[a] | √[a] | √[a] |
| Alcohol dependency management | | | | | | | | | | √[a] | |
| Anaemia management | | | | | | | | | | √[a] | |
| Preoperative cardiopulmonary function assessment | √ | | √ | √ | √ | √ | | | √[a] | √ | √ |
| Preoperative airway management | | | | | | √[a] | | | | √[a] | |
| Preoperative anti-infective treatment | | | | √ | | √[a] | | √ | √ | √[a] | |
| Preoperative fasting and carbohydrate treatment | √[a] | √ | | √[a] | | | | √[a] | | √[a] | |
| Venous thromboembolism prophylaxis | | | | | | | | √ | √[a] | √[a] | |
| Physical exercise training | | | √[a] | | √ | √[a] | √[a] | | | √[a] | √[a] |
| **Intraoperative interventions** | | | | | | | | | | | |
| Prevention of intraoperative hypothermia | √[a] | √ | | √[a] | | | | √ | | √[a] | √[a] |
| Standard anesthetic protocol | √ | √ | | √ | | | | √ | √ | √ | √[a] |
| Protective lung ventilation | √ | | | | | | | √ | √[a] | √ | |
| Thoracotomy with muscle-/nerve-sparing technique | √ | | | | | | | | √ | | |
| Minimally invasive surgery (VATS) | | | √ | √ | √ | | | √ | √[a] | √ | √ |
| Single chest tube placement | √ | | | √ | | | | √[a] | | √[a] | √[a] |
| Perioperative fluid management | √ | | | √ | | | | √ | √ | √[a] | √[a] |
| **Postoperative interventions** | | | | | | | | | | | |
| Postoperative airway management/pulmonary rehabilitation | | | | | √ | | √[a] | | √[a] | √ | |
| Rational use of analgesics | √[a] | √[a] | | √[a] | √[a] | √ | | √ | √ | | √[a] |
| PONV control | | | | √[a] | √[a] | | | √[a] | √[a] | √[a] | |
| Standardized chest tube management | √ | | | √ | | | | √[a] | √[a] | √[a] | |
| Early removal of urinary catheter | √[a] | | | √ | | | | | √[a] | √[a] | |
| Early oral feeding | √[a] | √[a] | | √[a] | | | | √ | √[a] | | |
| Early ambulation (out of bed) | √[a] | √[a] | | √ | √[a] | | √[a] | √ | √[a] | √[a] | √[a] |

[a], included in ERAS group but not in control group. ERAS, enhanced recovery after surgery; VATS, video-assisted thoracoscopic surgery; PONV, postoperative nausea and vomiting.

**Table 5** Detailed ERAS elements of included studies (II)

| ERAS elements | Studies | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Li M | Lv H | Madani | Maruyama | Numan | Rice | Salati | Shiono | Tahiri | Van Haren |
| **Preoperative interventions** | | | | | | | | | | |
| Preadmission education/counselling | √ | √ | √[a] | √[a] | √[a] | √ | √[a] | √[a] | | √ |
| Preoperative nutrition improvement | | | | | | √[a] | | | | |
| Smoking cessation | √[a] | | √[a] | | | | | | | |
| Alcohol dependency management | | | | | | | | | | |
| Anaemia management | | | | | | | | | | |
| Preoperative Cardiopulmonary function assessment | | | | | | | | √ | | |
| Preoperative airway management | | | | | | | | | | |
| Preoperative anti-infective treatment | | | | | √[a] | | | √ | | √ |
| Preoperative fasting and carbohydrate treatment | | √ | | | | √[a] | | | | √ |
| Venous thromboembolism prophylaxis | | | | | | | | | | |
| Physical exercise training | √ | | √[a] | | | | | √[a] | | |
| **Intraoperative interventions** | | | | | | | | | | |
| Prevention of intraoperative hypothermia | | √[a] | | | | | | | | |
| Standard anesthetic protocol | | √[a] | √ | √ | | √[a] | | √ | | √[a] |
| Protective lung ventilation | | | | √ | | | | | | |
| Thoracotomy with muscle-/nerve-sparing technique | | | | | √[a] | | | | | |
| Minimally invasive surgery (VATS) | | | | √ | √[a] | √ | √[a] | | √ | |
| Single chest tube placement | | | | | | √[a] | √[a] | √[a] | | √[a] |
| Perioperative fluid management | | | | | | √ | | | | √ |
| **Postoperative interventions** | | | | | | | | | | |
| Postoperative airway management/ pulmonary rehabilitation | | √[a] | √ | | √[a] | | √[a] | | √[a] | |
| Rational use of analgesics | √ | √[a] | √ | √[a] | √[a] | √ | | √ | √[a] | √[a] |
| PONV control | | | | | | | | √ | | |
| Standardized chest tube management | √[a] | √[a] | √[a] | √[a] | √[a] | √[a] | √[a] | √[a] | √[a] | √[a] |
| Early removal of urinary catheter | | √[a] | √[a] | √[a] | | | | | | |
| Early oral feeding | | √[a] | √[a] | √[a] | | √[a] | | √[a] | √[a] | √[a] |
| Early ambulation (out of bed) | √[a] | √[a] | √[a] | √[a] | √[a] | √ | | √[a] | √[a] | √ |

[a], included in ERAS group but not in control group. ERAS, enhanced recovery after surgery; VATS, video-assisted thoracoscopic surgery; PONV, postoperative nausea and vomiting.

**Table 6** Detailed quality assessment of cohort studies (I)

| Items of NOS | Studies | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Boujibar | Brunelli | Chen | Gao | Glogowska | Gonzalez | Haro | Huang | Jin X[a] | Khandhar |
| Selection | | | | | | | | | | |
| Representativeness of the exposed cohort | * | * | * | * | * | * | | | * | * |
| Selection of the non-exposed cohort | * | * | * | * | * | * | * | * | * | * |
| Ascertainment of exposure | * | * | * | * | * | * | * | * | | * |
| Demonstration that outcome of interest was not present at start of study | | | | * | * | | * | | | |
| Comparability | | | | | | | | | | |
| Comparability of cohorts on basis of the design or analysis | ** | ** | ** | ** | * | * | ** | ** | * | * |
| Outcome | | | | | | | | | | |
| Assessment of outcome | | * | | | * | * | * | | | * |
| Was follow-up long enough for outcomes to occur | * | * | * | * | * | * | * | * | * | * |
| Adequacy of follow up of cohorts | | * | | | * | | * | * | | * |
| Total | 6 | 8 | 6 | 7 | 8 | 6 | 8 | 6 | 4 | 7 |

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. Studies rates ≥6 are eligible. [a], not qualified study. NOS, Newcastle-Ottawa Scale.

*Figure 5*. No publication bias was found using both Begg's test (P=1.00) and Egger's test (P=0.632).

**Readmission rate**

A total of 11 of the included studies mentioned the rates of readmission (35,39,40,42,45,47-52), and only 1 study found that the ERAS group had a lower readmission rate than the control group (47). There were 89 (4.9%) and 138 (4.5%) participants who were readmitted to hospital within 30 days in the ERAS group and control group, respectively. The pooled analysis of 11 available studies showed no significant difference in readmission rate between the ERAS group and control group (RR =1.00; 95% CI: 0.76 to 1.32; P=0.99) with low heterogeneity (I²=0; P=0.90), as shown in *Figure 6*. No publication bias was found using both Begg's test (P=0.276) and Egger's test (P=0.305).

**LOS**

Regarding LOS, we analyzed 2 outcomes: overall LOS and postoperative LOS. A total of 11 studies reported overall LOS (32-34,37,38,40,45-48,52) and 12 studies reported postoperative LOS (35-37,39,41-44,46,49-51). However, only 3 studies presented overall LOS in the format of mean ± SD (32,37,46); therefore, we performed a qualitative analysis instead of meta-analysis of overall LOS. Among the 11 studies that reported overall LOS, 9 indicated that the ERAS-treated patients had a significantly shortened overall LOS (32,37,38,40,45-48,52), while the remaining 2 studies found that the difference was not significant (33,34), as shown in *Table 3*. Among the 12 studies reporting postoperative LOS, all but 1 (35) reported significantly shortened postoperative LOS in the ERAS group. However, only 7 provided the data of mean ± SD (36,37,41,43,44,46,49). The pooled analysis of 7 eligible studies indicated that participants in the ERAS group had significantly shorter postoperative LOS (SMD =−1.58; 95% CI: −2.38 to −0.79; P<0.0001) with a significantly high heterogeneity (I²=98%; P<0.0001) between studies (*Figure 7*). No publication bias was found using both Begg's test (P=0.072) and Egger's test (P=0.113).

**Table 7** Detailed quality assessment of cohort studies (II)

| Items of NOS | Studies | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Li M | Lv H | Madani | Maruyama | Numan | Rice | Salati | Shiono | Tahiri | VanHaren |
| Selection | | | | | | | | | | |
| Representativeness of the exposed cohort | * | * | * | * | * | * | * | * | * | * |
| Selection of the non-exposed cohort | * | * | * | * | * | * | * | * | * | * |
| Ascertainment of exposure | * | * | * | * | * | * | * | * | * | * |
| Demonstration that outcome of interest was not present at start of study | | * | | | * | | | | | |
| Comparability | | | | | | | | | | |
| Comparability of cohorts on basis of the design or analysis | ** | ** | ** | ** | ** | ** | ** | ** | * | * |
| Outcome | | | | | | | | | | |
| Assessment of outcome | | | * | | * | * | * | * | * | * |
| Was follow-up long enough for outcomes to occur | * | * | * | * | | * | * | * | * | * |
| Adequacy of follow up of cohorts | | | | | * | * | | | | |
| Total | 6 | 7 | 7 | 6 | 8 | 8 | 7 | 7 | 6 | 6 |

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. Studies rates ≥6 are eligible. [a], not qualified study. NOS, Newcastle-Ottawa Scale.

**Table 8** Detailed quality assessment of RCTs

| Items of Cochrane Collaboration's Quality assessment Tool | Studies | |
|---|---|---|
| | Dong *et al.* | Muehling *et al.* |
| Random sequence generation (selection bias) | (+) | (+) |
| Allocation concealment (selection bias) | (+) | (?) |
| Blinding of participants and personnel (performance bias) | (+) | (−) |
| Blinding of outcome assessment (detection bias) | (+) | (−) |
| Incomplete outcome data (attrition bias) | (?) | (?) |
| Selective reporting (reporting bias) | (?) | (?) |
| Other bias | (+) | (+) |
| Total | 5 | 2 |

(+): low risk of bias; (−): high risk of bias; (?): unclear risk of bias. RCTs, randomised controlled trails.

## Total cost of hospitalization

A total of 6 studies mentioned total cost of hospitalization (32,36,37,39,40,46), but only 4 studies presented data as mean ± SD (32,36,37,46). Due to the small number of studies reporting this outcome, we performed a qualitative review instead of a meta-analysis. Of these 4 studies, 3 reported a significantly lower cost of hospitalization in the ERAS group (32,36,46); however, the studies performed by Gao *et al.* in 2015 found that the ERAS group had a much higher cost of hospitalization (37). The remaining 2 studies
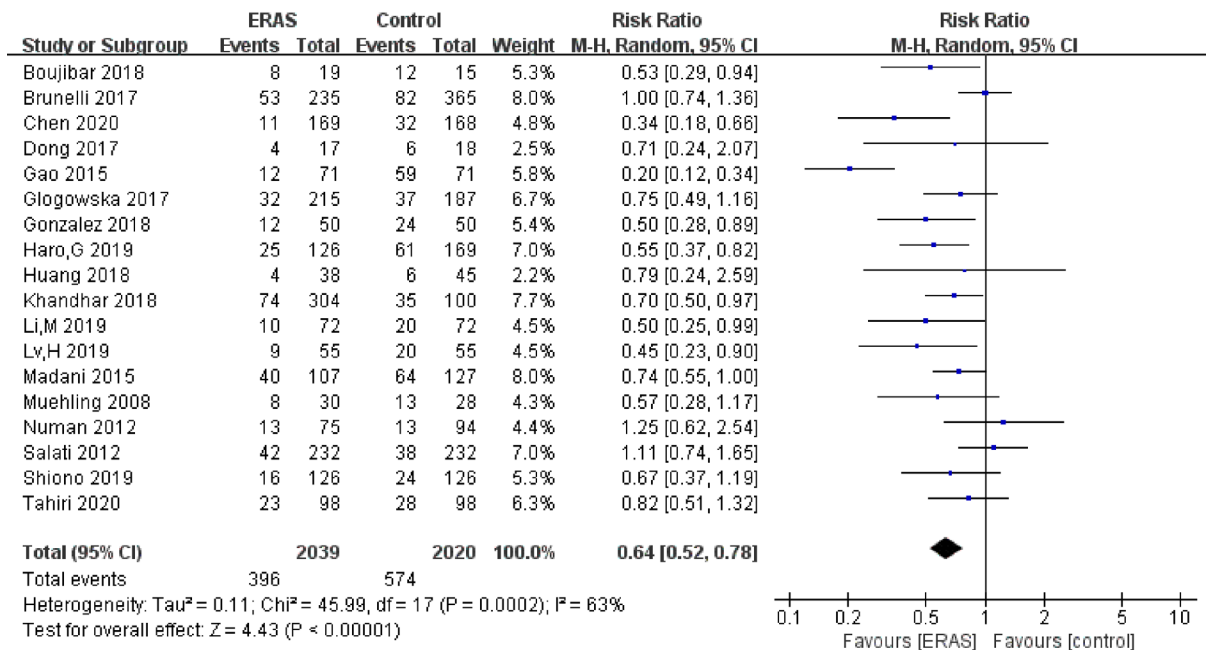
| Study or Subgroup | ERAS Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Boujibar 2018 | 8 | 19 | 12 | 15 | 5.3% | 0.53 [0.29, 0.94] |
| Brunelli 2017 | 53 | 235 | 82 | 365 | 8.0% | 1.00 [0.74, 1.36] |
| Chen 2020 | 11 | 169 | 32 | 168 | 4.8% | 0.34 [0.18, 0.66] |
| Dong 2017 | 4 | 17 | 6 | 18 | 2.5% | 0.71 [0.24, 2.07] |
| Gao 2015 | 12 | 71 | 59 | 71 | 5.8% | 0.20 [0.12, 0.34] |
| Glogowska 2017 | 32 | 215 | 37 | 187 | 6.7% | 0.75 [0.49, 1.16] |
| Gonzalez 2018 | 12 | 50 | 24 | 50 | 5.4% | 0.50 [0.28, 0.89] |
| Haro,G 2019 | 25 | 126 | 61 | 169 | 7.0% | 0.55 [0.37, 0.82] |
| Huang 2018 | 4 | 38 | 6 | 45 | 2.2% | 0.79 [0.24, 2.59] |
| Khandhar 2018 | 74 | 304 | 35 | 100 | 7.7% | 0.70 [0.50, 0.97] |
| Li,M 2019 | 10 | 72 | 20 | 72 | 4.5% | 0.50 [0.25, 0.99] |
| Lv,H 2019 | 9 | 55 | 20 | 55 | 4.5% | 0.45 [0.23, 0.90] |
| Madani 2015 | 40 | 107 | 64 | 127 | 8.0% | 0.74 [0.55, 1.00] |
| Muehling 2008 | 8 | 30 | 13 | 28 | 4.3% | 0.57 [0.28, 1.17] |
| Numan 2012 | 13 | 75 | 13 | 94 | 4.4% | 1.25 [0.62, 2.54] |
| Salati 2012 | 42 | 232 | 38 | 232 | 7.0% | 1.11 [0.74, 1.65] |
| Shiono 2019 | 16 | 126 | 24 | 126 | 5.3% | 0.67 [0.37, 1.19] |
| Tahiri 2020 | 23 | 98 | 28 | 98 | 6.3% | 0.82 [0.51, 1.32] |
| **Total (95% CI)** | | **2039** | | **2020** | **100.0%** | **0.64 [0.52, 0.78]** |
| Total events | 396 | | 574 | | | |

Heterogeneity: Tau² = 0.11; Chi² = 45.99, df = 17 (P = 0.0002); I² = 63%
Test for overall effect: Z = 4.43 (P < 0.00001)



**Figure 3** Meta-analysis of overall postoperative complications in the ERAS *vs.* control group. ERAS, enhanced recovery after surgery.

| Study or Subgroup | ERAS Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Boujibar 2018 | 8 | 19 | 12 | 15 | 5.0% | 0.53 [0.29, 0.94] |
| Brunelli 2017 | 53 | 235 | 82 | 365 | 10.7% | 1.00 [0.74, 1.36] |
| Chen 2020 | 11 | 169 | 32 | 168 | 4.3% | 0.34 [0.18, 0.66] |
| Dong 2017 | 4 | 17 | 6 | 18 | 1.8% | 0.71 [0.24, 2.07] |
| Glogowska 2017 | 32 | 215 | 37 | 187 | 7.5% | 0.75 [0.49, 1.16] |
| Gonzalez 2018 | 12 | 50 | 24 | 50 | 5.2% | 0.50 [0.28, 0.89] |
| Haro,G 2019 | 25 | 126 | 61 | 169 | 8.1% | 0.55 [0.37, 0.82] |
| Huang 2018 | 4 | 38 | 6 | 45 | 1.5% | 0.79 [0.24, 2.59] |
| Khandhar 2018 | 74 | 304 | 35 | 100 | 9.9% | 0.70 [0.50, 0.97] |
| Li,M 2019 | 10 | 72 | 20 | 72 | 3.9% | 0.50 [0.25, 0.99] |
| Lv,H 2019 | 9 | 55 | 20 | 55 | 3.9% | 0.45 [0.23, 0.90] |
| Madani 2015 | 40 | 107 | 64 | 127 | 10.8% | 0.74 [0.55, 1.00] |
| Muehling 2008 | 8 | 30 | 13 | 28 | 3.7% | 0.57 [0.28, 1.17] |
| Numan 2012 | 13 | 75 | 13 | 94 | 3.8% | 1.25 [0.62, 2.54] |
| Salati 2012 | 42 | 232 | 38 | 232 | 8.2% | 1.11 [0.74, 1.65] |
| Shiono 2019 | 16 | 126 | 24 | 126 | 5.0% | 0.67 [0.37, 1.19] |
| Tahiri 2020 | 23 | 98 | 28 | 98 | 6.7% | 0.82 [0.51, 1.32] |
| **Total (95% CI)** | | **1968** | | **1949** | **100.0%** | **0.70 [0.60, 0.82]** |
| Total events | 384 | | 515 | | | |

Heterogeneity: Tau² = 0.03; Chi² = 24.54, df = 16 (P = 0.08); I² = 35%
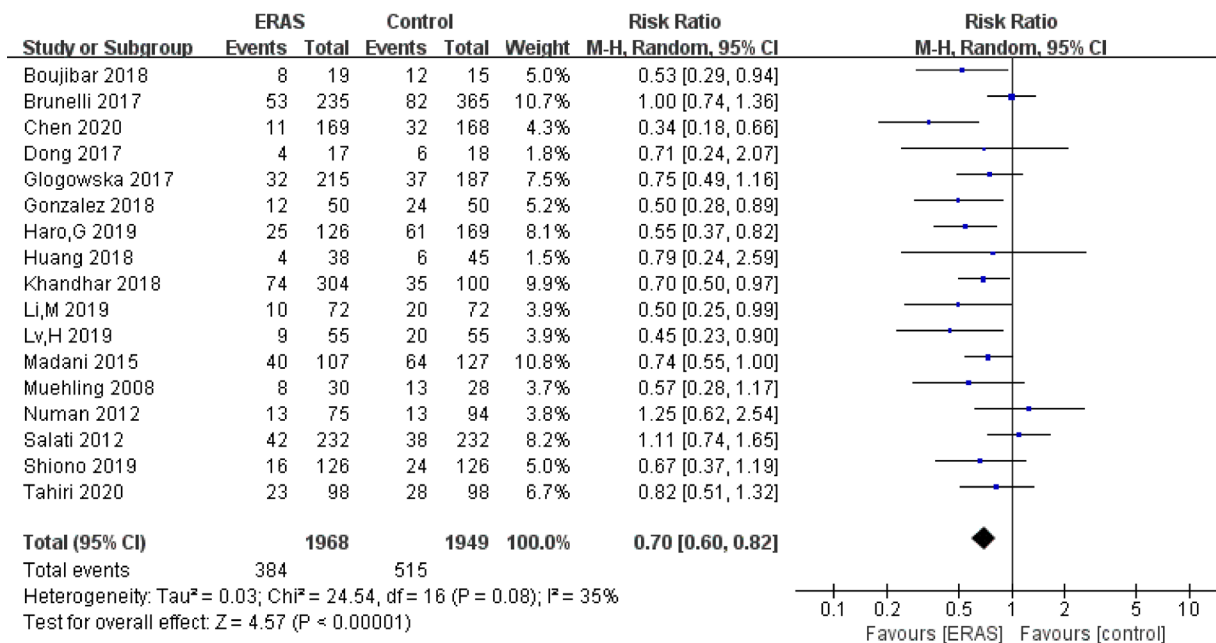Test for overall effect: Z = 4.57 (P < 0.00001)



**Figure 4** Meta-analysis of overall postoperative complications in ERAS *vs.* control group after excluding the study by Gao *et al.* ERAS, enhanced recovery after surgery.
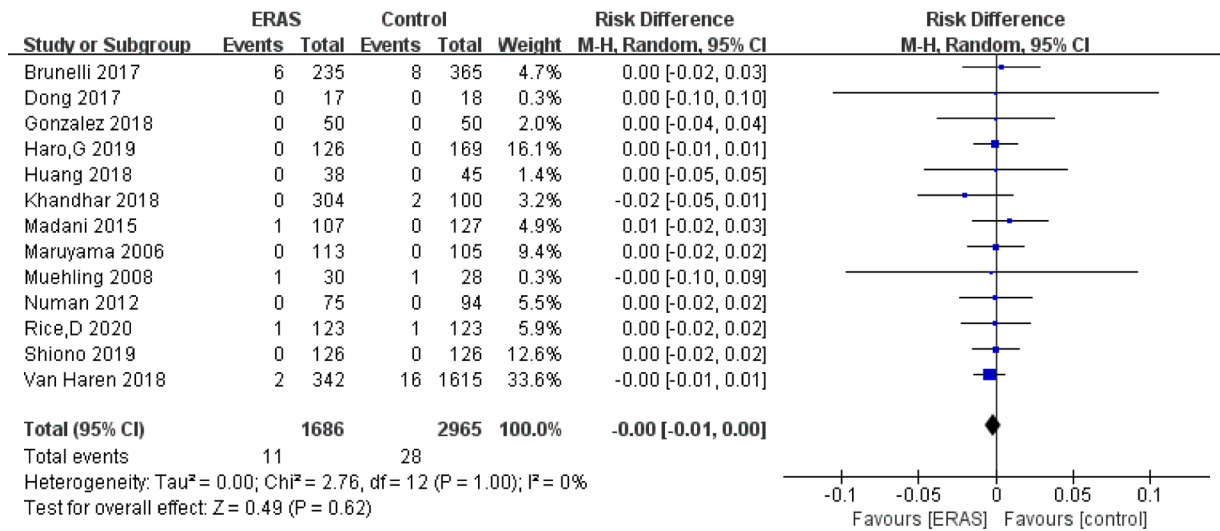
**Figure 5** Meta-analysis of in-hospital mortality in the ERAS *vs.* control group. ERAS, enhanced recovery after surgery.
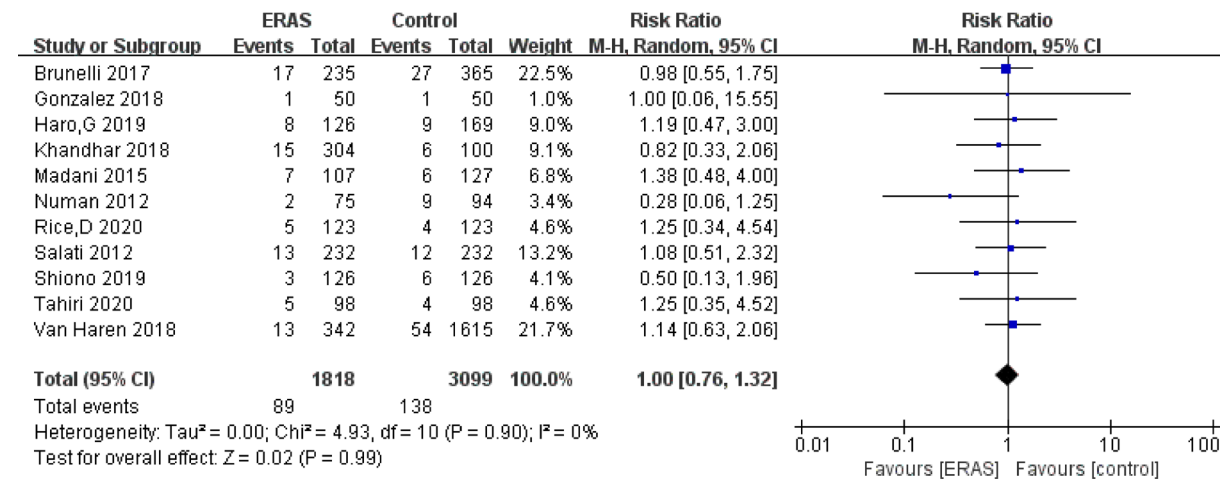


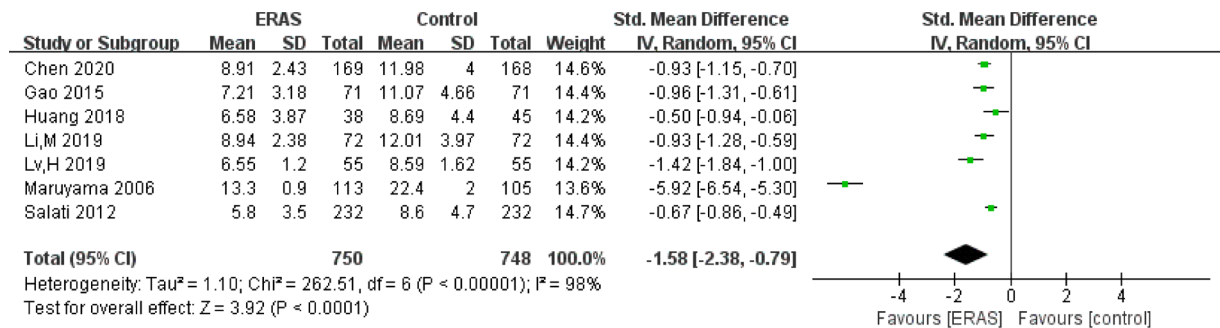**Figure 6** Meta-analysis of readmission rate in the ERAS *vs.* control group. ERAS, enhanced recovery after surgery.



**Figure 7** Meta-analysis of postoperative LOS in the ERAS *vs.* control group. LOS, length of stay; ERAS, enhanced recovery after surgery.

**Table 9** Meta-analysis for effects of the ERAS program on postoperative complications

| Outcomes | Number of studies | Sample size[a] | | | RR (95% CI) | Heterogeneity (I²) | P value | Publication bias | | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | ERAS | Con. | | | | Begg's (P) | Egger's (P) | |
| Overall complications | 18 | 4,059 | 2,039 | 2,020 | 0.64 (0.52, 0.78) | 63% | <0.001 | 0.363 | 0.133 | Significant |
| Subgroup analysis | | | | | | | | | | |
| Pulmonary | 13 | 4,450 | 1,613 | 2,837 | 0.58 (0.45, 0.75) | 56% | <0.001 | 0.161 | 0.049 | Significant |
| Cardiovascular | 13 | 4,708 | 1,756 | 2,952 | 0.73 (0.59, 0.89) | 0% | 0.003 | 1.000 | 0.967 | Significant |
| Urinary | 8 | 3,176 | 1,044 | 2,132 | 0.53 (0.32, 0.88) | 0% | 0.01 | 0.536 | 0.858 | Significant |
| Surgical | 8 | 3,147 | 942 | 2,205 | 0.64 (0.42, 0.97) | 13% | 0.04 | 0.902 | 0.029 | Significant |

[a], studies of Van Haren and Rice D did not provide overall postoperative complications but detailed data of subgroup complications. ERAS, enhanced recovery after surgery; RR, relative risk; Con., control; CI, confidence interval.

reported data as a median with interquartile range (IQR) or 95% CI (39,40), both of which showed a lower total cost in the ERAS group than in the control group, as shown in *Table 3*.

*Subgroup analysis*

In order to assess the effects of ERAS programs on postoperative complications in detail, we performed a subgroup analysis as follows: pulmonary complications, cardiovascular complications, urinary complications, and surgical complications. There were 13 studies included in the subgroup of pulmonary complications (32,33,35-37,39,41-45,48,52), 13 in the subgroup of cardiovascular complications (32,33,35-39,41,42,44,45,48,52), 8 in the subgroup of urinary complications (32,33,37,39,42,45,48,52), and 8 in the subgroup of surgical complications (33,37-39,43-45,52).

The meta-analysis of results in all subgroups are summarized in *Table 9*. As shown in *Figure 8*, the synthesized estimates using random effects model revealed that all subgroups of complications were significantly decreased in the patients who were treated with the ERAS program. However, the meta-analysis of the pulmonary subgroup showed a moderate heterogeneity (I²=55.6%; P=0.008). The other 3 subgroup analyses did not present any significant heterogeneity. Egger's test detected a slight publication bias of meta-analysis of pulmonary complications subgroup (P=0.049) and surgical complication subgroup (P=0.029). No other publication bias was found using both Begg's test and Egger's test in other subgroup analyses, as shown in *Table 9*.

*Sensitivity analysis*

We performed sensitivity analysis by omitting individual studies sequentially. None of the pooled RRs based on the remaining studies in each group of meta-analysis was out of the estimated range, as shown in *Figure 9*. No substantial variation was found between adjusted pooled estimates and primary pooled estimates. The strong robustness of our meta-analysis was thus confirmed.

**Discussion**

Through this meta-analysis, we found that patients treated with the ERAS program had a lower risk of developing postoperative complications and a decreased postoperative LOS. However, in terms of in-hospital mortality and readmission rate, there was no significant difference between the ERAS group and the control group. Qualitative assessment revealed significantly decreased overall LOS and total hospitalization costs in the ERAS group.

The role of the ERAS program in lung cancer surgery has been extensively studied, and the ERAS Association has formulated detailed guidelines, illustrating the benefits of its various components (24,25). According to our best knowledge, this review is an updated meta-analysis to explore the impact of the ERAS program on patients undergoing lung cancer surgery. This meta-analysis covers all the provisions of the standardized PRISMA report (23). Compared with previous studies (20,21), ours has the following advantages. To begin with, in order to increase the sample size and improve the credibility of the results, we included both RCTs and cohort studies,
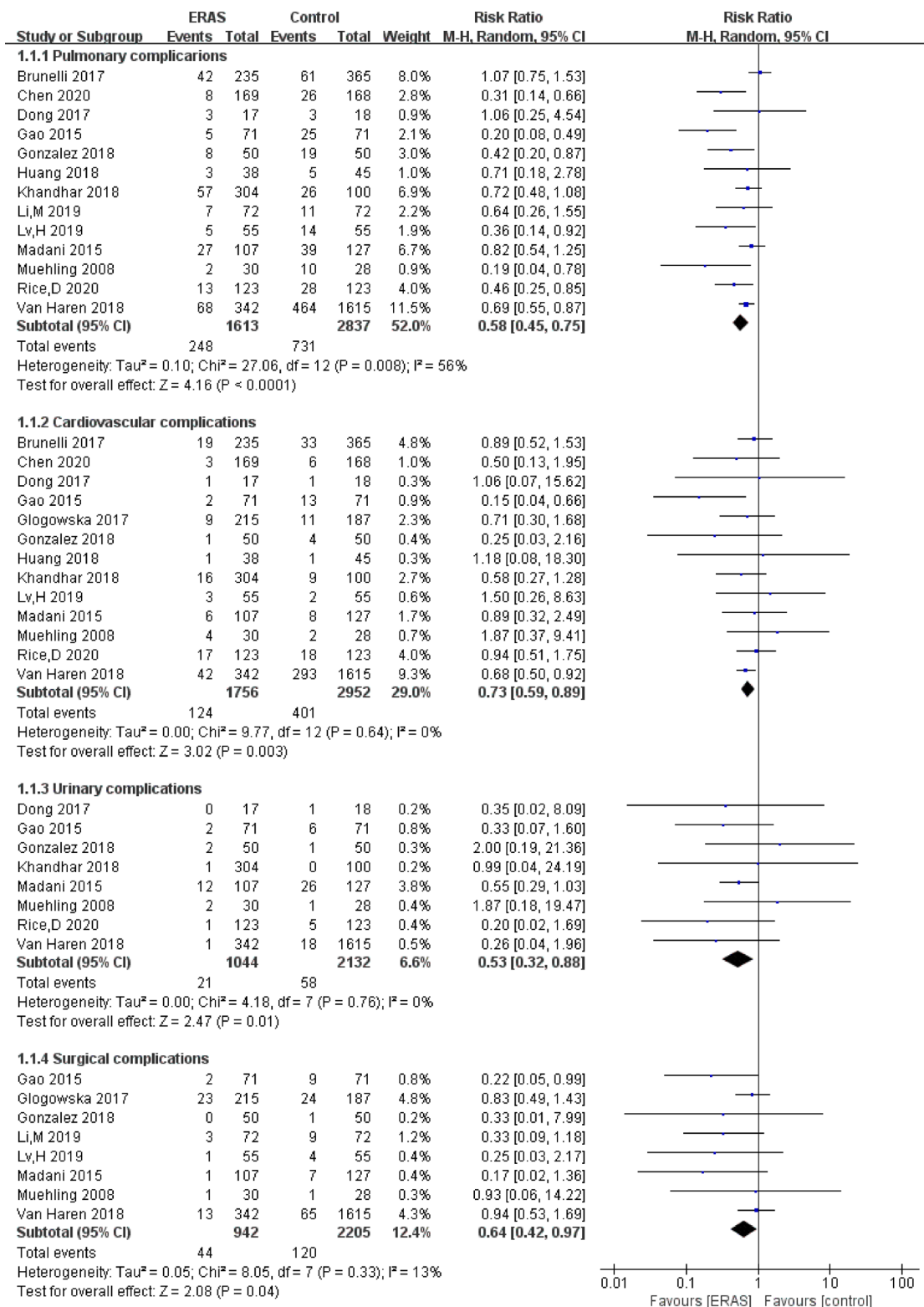
| Study or Subgroup | ERAS Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.1.1 Pulmonary complicarions** | | | | | | |
| Brunelli 2017 | 42 | 235 | 61 | 365 | 8.0% | 1.07 [0.75, 1.53] |
| Chen 2020 | 8 | 169 | 26 | 168 | 2.8% | 0.31 [0.14, 0.66] |
| Dong 2017 | 3 | 17 | 3 | 18 | 0.9% | 1.06 [0.25, 4.54] |
| Gao 2015 | 5 | 71 | 25 | 71 | 2.1% | 0.20 [0.08, 0.49] |
| Gonzalez 2018 | 8 | 50 | 19 | 50 | 3.0% | 0.42 [0.20, 0.87] |
| Huang 2018 | 3 | 38 | 5 | 45 | 1.0% | 0.71 [0.18, 2.78] |
| Khandhar 2018 | 57 | 304 | 26 | 100 | 6.9% | 0.72 [0.48, 1.08] |
| Li,M 2019 | 7 | 72 | 11 | 72 | 2.2% | 0.64 [0.26, 1.55] |
| Lv,H 2019 | 5 | 55 | 14 | 55 | 1.9% | 0.36 [0.14, 0.92] |
| Madani 2015 | 27 | 107 | 39 | 127 | 6.7% | 0.82 [0.54, 1.25] |
| Muehling 2008 | 2 | 30 | 10 | 28 | 0.9% | 0.19 [0.04, 0.78] |
| Rice,D 2020 | 13 | 123 | 28 | 123 | 4.0% | 0.46 [0.25, 0.85] |
| Van Haren 2018 | 68 | 342 | 464 | 1615 | 11.5% | 0.69 [0.55, 0.87] |
| **Subtotal (95% CI)** | | **1613** | | **2837** | **52.0%** | **0.58 [0.45, 0.75]** |
| Total events | 248 | | 731 | | | |
| Heterogeneity: Tau² = 0.10; Chi² = 27.06, df = 12 (P = 0.008); I² = 56% | | | | | | |
| Test for overall effect: Z = 4.16 (P < 0.0001) | | | | | | |
| | | | | | | |
| **1.1.2 Cardiovascular complications** | | | | | | |
| Brunelli 2017 | 19 | 235 | 33 | 365 | 4.8% | 0.89 [0.52, 1.53] |
| Chen 2020 | 3 | 169 | 6 | 168 | 1.0% | 0.50 [0.13, 1.95] |
| Dong 2017 | 1 | 17 | 1 | 18 | 0.3% | 1.06 [0.07, 15.62] |
| Gao 2015 | 2 | 71 | 13 | 71 | 0.9% | 0.15 [0.04, 0.66] |
| Glogowska 2017 | 9 | 215 | 11 | 187 | 2.3% | 0.71 [0.30, 1.68] |
| Gonzalez 2018 | 1 | 50 | 4 | 50 | 0.4% | 0.25 [0.03, 2.16] |
| Huang 2018 | 1 | 38 | 1 | 45 | 0.3% | 1.18 [0.08, 18.30] |
| Khandhar 2018 | 16 | 304 | 9 | 100 | 2.7% | 0.58 [0.27, 1.28] |
| Lv,H 2019 | 3 | 55 | 2 | 55 | 0.6% | 1.50 [0.26, 8.63] |
| Madani 2015 | 6 | 107 | 8 | 127 | 1.7% | 0.89 [0.32, 2.49] |
| Muehling 2008 | 4 | 30 | 2 | 28 | 0.7% | 1.87 [0.37, 9.41] |
| Rice,D 2020 | 17 | 123 | 18 | 123 | 4.0% | 0.94 [0.51, 1.75] |
| Van Haren 2018 | 42 | 342 | 293 | 1615 | 9.3% | 0.68 [0.50, 0.92] |
| **Subtotal (95% CI)** | | **1756** | | **2952** | **29.0%** | **0.73 [0.59, 0.89]** |
| Total events | 124 | | 401 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 9.77, df = 12 (P = 0.64); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.02 (P = 0.003) | | | | | | |
| | | | | | | |
| **1.1.3 Urinary complications** | | | | | | |
| Dong 2017 | 0 | 17 | 1 | 18 | 0.2% | 0.35 [0.02, 8.09] |
| Gao 2015 | 2 | 71 | 6 | 71 | 0.8% | 0.33 [0.07, 1.60] |
| Gonzalez 2018 | 2 | 50 | 1 | 50 | 0.3% | 2.00 [0.19, 21.36] |
| Khandhar 2018 | 1 | 304 | 0 | 100 | 0.2% | 0.99 [0.04, 24.19] |
| Madani 2015 | 12 | 107 | 26 | 127 | 3.8% | 0.55 [0.29, 1.03] |
| Muehling 2008 | 2 | 30 | 1 | 28 | 0.4% | 1.87 [0.18, 19.47] |
| Rice,D 2020 | 1 | 123 | 5 | 123 | 0.4% | 0.20 [0.02, 1.69] |
| Van Haren 2018 | 1 | 342 | 18 | 1615 | 0.5% | 0.26 [0.04, 1.96] |
| **Subtotal (95% CI)** | | **1044** | | **2132** | **6.6%** | **0.53 [0.32, 0.88]** |
| Total events | 21 | | 58 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.18, df = 7 (P = 0.76); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.47 (P = 0.01) | | | | | | |
| | | | | | | |
| **1.1.4 Surgical complications** | | | | | | |
| Gao 2015 | 2 | 71 | 9 | 71 | 0.8% | 0.22 [0.05, 0.99] |
| Glogowska 2017 | 23 | 215 | 24 | 187 | 4.8% | 0.83 [0.49, 1.43] |
| Gonzalez 2018 | 0 | 50 | 1 | 50 | 0.2% | 0.33 [0.01, 7.99] |
| Li,M 2019 | 3 | 72 | 9 | 72 | 1.2% | 0.33 [0.09, 1.18] |
| Lv,H 2019 | 1 | 55 | 4 | 55 | 0.4% | 0.25 [0.03, 2.17] |
| Madani 2015 | 1 | 107 | 7 | 127 | 0.4% | 0.17 [0.02, 1.36] |
| Muehling 2008 | 1 | 30 | 1 | 28 | 0.3% | 0.93 [0.06, 14.22] |
| Van Haren 2018 | 13 | 342 | 65 | 1615 | 4.3% | 0.94 [0.53, 1.69] |
| **Subtotal (95% CI)** | | **942** | | **2205** | **12.4%** | **0.64 [0.42, 0.97]** |
| Total events | 44 | | 120 | | | |
| Heterogeneity: Tau² = 0.05; Chi² = 8.05, df = 7 (P = 0.33); I² = 13% | | | | | | |
| Test for overall effect: Z = 2.08 (P = 0.04) | | | | | | |

**Figure 8** Subgroup analyses of the effects of the ERAS program on pulmonary, cardiovascular, urinary, and surgical complications following lung cancer surgery. ERAS, enhanced recovery after surgery.
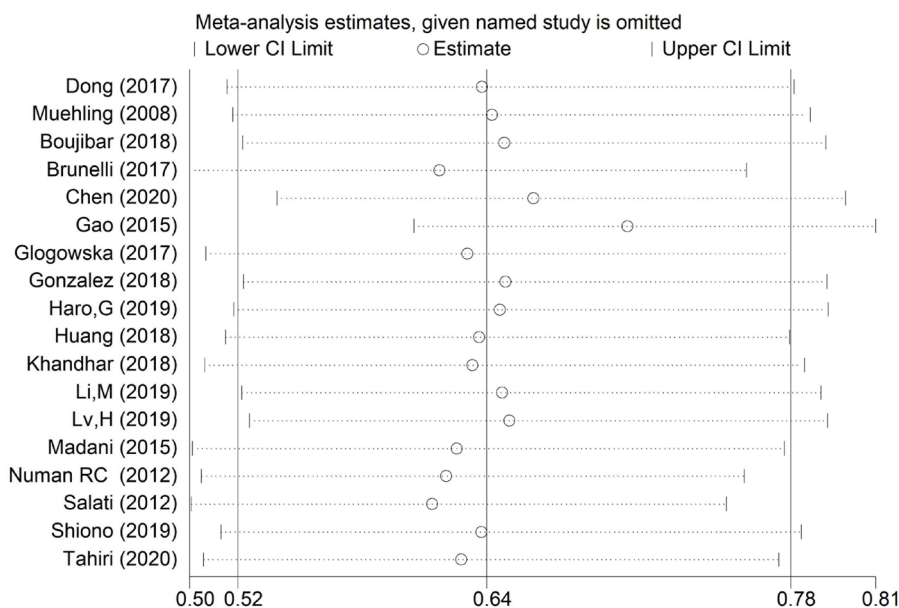
**Figure 9** Sensitivity analysis of meta-analysis.

involving 10 countries and regions. Second, according to the recently published guidelines and previous review (19-21,24,25), we formulated a fresh ERAS protocol composed of 25 elements covering 3 phases. Meanwhile, we emphasized the difference between the ERAS group and the control group (the difference between the 2 groups needed exceed 3 ERAS elements), which was different from Li's study (21). Third, we analyzed the impact of the ERAS program on readmission rate and postoperative LOS and conducted a more comprehensive subgroup analysis including pulmonary, cardiovascular, urinary, and surgical complications. Therefore, this review has become the latest and most comprehensive review of the ERAS literature on lung cancer surgery.

Lung surgery can precipitate a series of physical and psychological stress responses, which can cause critical trauma to the body and postoperative complications (54,55). The ERAS program can effectively reduce the psychological and physical stress of patients, thereby reducing the occurrence of postoperative complications (56,57). Postoperative inflammatory response is the main cause of postoperative complications (58,59). The study by Dong *et al.* (32) showed that postoperative inflammatory factors such as interleukin-6 (IL-6) in the ERAS group were significantly reduced, indicating that the ERAS program can weaken the postoperative inflammatory response of patients. Notably, we found that ERAS can effectively

reduce the incidence of postoperative cardiovascular complications, which is in contrast to the results of previous studies (20,21).

The meta-analysis of overall postoperative complications showed a high heterogeneity ($I^2$=63%; P<0.001). Fortunately, after excluding Gao's study from 2015 (37), the heterogeneity of the meta-analysis was reduced significantly ($I^2$=35%; P=0.08). Hence, we focused on Gao's study. In this study, the author included 142 high-risk patients (heavy smokers, airway hyperresponsiveness, hypopulmonary function) as the participants. The complication rate of the control group was 83.31%, 5 times more than that of the ERAS group (16.9%), which far exceeded the results of other studies. The probability of postoperative complications is much higher for high-risk patients than for those with normal risk due to deficient lung function, more microbial colonization in the respiratory tract, and low immunity (60,61). Meanwhile, some components in the ERAS program, such as preoperative assessment of cardiopulmonary function, preoperative exercise, prophylactic antibiotics, and the application of respiratory drugs could significantly improve the lung function of high-risk patients and enhance their tolerance to surgery (24), thereby reducing the incidence of postoperative complications to a greater extent. Muehling *et al.* performed a subgroup analysis of patients with FEV1% <75% in 2008, and found the same results (33).

This further implies that the ERAS program may bring greater benefits to high-risk patients, which can become the focus of future research.

Compared with the previous meta-analysis, one novelty of our research was the analysis of the impact of the ERAS program on the readmission rate. The results indicated that the readmission rate of patients in the ERAS group did not increase significantly compared with the control group. However, some of the eligible studies were not sufficiently transparent in terms of readmission, which might have reduced the credibility of the results to some extent. In addition, there was a significant reduction in LOS and no significant increase in in-hospital mortality, which demonstrated that the implementation of the ERAS program in lung cancer surgery can effectively accelerate postoperative recovery without threating patient safety.

Although this review found that the patients treated with the ERAS program have a significantly shortened postoperative LOS, it also showed significantly high heterogeneity ($I^2$=98%; P<0.001). The reasons for this heterogeneity may be various and include variability in the ERAS components, surgical procedures, inclusion criteria, and traditional control standards between countries. Heterogeneity can also be attributed to some clinical factors, such as the technical level of hospitals and surgeons, patient compliance with the ERAS program, surgical procedures, conflicting evaluations of results, and others.

The cost-benefit analysis conducted in our study also indicated that the ERAS program has obvious economic benefits for lung cancer surgery. Among the 6 studies mentioning hospitalization expenses, 5 articles (based on 1,127 patients) reported that the hospitalization expenses of the ERAS group were significantly lower than those of the control group. In contrast, the study conducted by Gao *et al.* in 2015 showed that the overall hospitalization costs of patients in the ERAS group were slightly higher than those in the control group, which might have been due to the prolonged preoperative hospital stay and the additional cost of pulmonary rehabilitation (approximately 1,000 RMB) (37). It might also have been caused by differences in economic and medical expenses between countries. Unfortunately, we are unable to further assess the impact of the huge differences in the socioeconomic level and health care between the East and the West.

In other surgical fields, minimally invasive surgery serves as a key element of the ERAS program (62). It has been shown that VATS reduces complications after lung resection and effectively shortens the length of hospital stay (6,63).

Conceptually, VATS seems to be the ideal surgical method for the ERAS program to improve postoperative results. Therefore, we originally planned to conduct a subgroup analysis on the impact of ERAS on open surgery and VATS, but due to the insufficient data on open surgery, our idea was not implemented, but could be considered in a future meta-analysis.

This review had some limitations. First, the majority of the included studies were cohort studies, and only 2 RCTs were included. Moreover, the majority of eligible cohort studies were separate-sample pre-post-test designs. These types of studies have some limitations, such as nonparallel controls and cohort selection, which might have introduced biases and reduced the reliability of the results. Second, the ERAS protocols of the included studies were significantly different, and the implementation standards of the ERAS program varied between each country and region, possibly producing bias and reducing the credibility of the results. In addition, there were differences in patient compliance with the ERAS program (64,65), which might have led to obvious heterogeneity in the results. Third, we did not analyze patient-reported outcomes such as pain score and QoL because published research did not provide these types of data. We encourage future research to be more focused on this aspect. Finally, a certain language-based bias might have arisen due to the requirement of full-text English language literature; future meta-analyses should include studies written in other languages.

## Conclusions

This meta-analysis is the most up-to-date and comprehensive review of the literature on the ERAS program for lung cancer surgery. Implementation of the ERAS program in lung cancer surgery can not only significantly reduce the risks of overall postoperative complications and hospitalization costs, but also shorten the LOS without increasing the rate of in-hospital mortality and readmission. In short, the ERAS program is an effective and safe strategy and should be recommended for lung cancer surgery.

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## Footnote

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**Table S1** Additional baseline characteristics of included studies

| Study (year) | Mean BMI (kg/m²) | | FEV1 (% predicted) | | Surgical procedures | | Extent of resection | |
|---|---|---|---|---|---|---|---|---|
| | ERAS | Con. | ERAS | Con. | ERAS | Con. | ERAS | Con. |
| Dong 2017 | 26.8 [18.5-30.0] | 25.6 [18.7-29.8] | 2.9 [2.5-3.9][a] | 2.8 [2.5-3.7][a] | OPEN | OPEN | Pne | Pne |
| Muehling 2008 | NR | NR | 2.05 (0.68-4.5)[a] | 2.4 (1.4-2.8)[a] | NR | NR | Lob =20; Pne =3; Sle =1; Wed =6 | Lob =20; Pne =1; Sle =2; Wed =5 |
| Boujibar 2018 | 26.6 [23.7-30.4] | 25.0 [22.5-30] | 61 [54-67] | 61 [58-71] | V/RATS | V/RATS | Lob | Lob |
| Brunelli 2017 | 27.3 [24-30] | 27 [24-30] | 89.2 [74-105] | 89.2 [73-106] | VATS | VATS | Lob; Seg | Lob; Seg |
| Chen 2020 | NR | NR | NR | NR | NR | NR | Lob | Lob |
| Gao 2015 | NR | NR | NR | NR | OPEN =29; VATS =42 | OPEN =32; VATS =39 | Lob | Lob |
| Glogowaska 2017 | NR | NR | 90 [80-104] | 95 [83-101] | NR | NR | Lob =61; Wed =147 Pne =7 | Lob =46; Wed =136 Pne =5 |
| Gonzalez 2018 | 24.9 (median) | 23.5 (median) | 92±18 | 81±20 | VATS | VATS | Lob =32; Seg =18 | Lob =30; Seg =20 |
| Haro,G 2019 | NR | NR | 91 [80-107] | 86 [72-100] | OPEN =47; V/RATS =79 | OPEN =102; V/RATS =67 | Lob =62; Sublob =64 | Lob =81; Sublob =88 |
| Huang 2018 | NR | NR | 94.09±10.09 | 92.02±16.00 | VATS | VATS | Lob; Wed | Lob; Wed |
| Khandhar 2018 | NR | NR | NR | NR | VATS | VATS | Lob | Lob |
| Li,M 2019 | NR | NR | 98.25±11.89 | 97.89±11.44 | VATS | VATS | NR | NR |
| Lv,H 2019 | NR | NR | NR | NR | NR | NR | NR | NR |
| Madani 2015 | 27±6 | 27±5 | 87±24 | 92±22 | OPEN | OPEN | Lob | Lob |
| Maruyama 2006 | NR | NR | NR | NR | VATS | VATS | Lob =64; Seg+Wed =46; Pne+Bilob =3 | Lob =58; Seg+Wed =46; Pne+Bilob =1 |
| Numan RC 2012 | 25 [22-27] | 26 [23-28] | 95 [82-104] | 92 [77-101] | OPEN =50; VATS =25 | OPEN =79; VATS =15 | Lob+Seg =34; Wed =31; Other =10 | Lob+Seg =42; Wed =38; Other =14 |
| Rice,D 2020 | NR | NR | NR | NR | OPEN =73; V/RATS =50 | OPEN =73; V/RATS =50 | Wed+Seg =46; Lob =69; Pne+Sle =8 | Wed+Segm:46; Lob =69; Pne+Sle =8 |
| Salati 2012 | 26.3±4.8 | 26.5±3.8 | 84.6±18.5 | 85.7±19 | NR | NR | Lob | Lob |
| Shiono 2019 | 22.8 [20.4-24.5] | 22.6 [20.9-25.] | 74 [67.5-78.7] | 73.8 [68-80.5] | OPEN | OPEN | Lob =94; Seg =32 | Lob =100; Seg =26 |
| Tahiri 2020 | 26.9±5.9 | 27.5±5.6 | 92.9±18.6 | 86.8±22 | VATS | VATS | Lob | Lob |
| Van Haren 2018 | NR | NR | 86 [60-112] | 87 [62-112] | OPEN =166; V/RATS =176 | OPEN =1095; V/RATS =520 | Lob =239; Pne =15; Sle =14; Wed =60; Seg =32 | Lob =1202; Pne =91; Sle =81; Wed =237; Seg =125 |

[ ] = interquartile range; ( ) = range; mean ± SD; [a]: Not report FEV1 (% predicted) but FEV1 values. NR, Not Reported; ERAS, Enhanced Recovery After Surgery; Con., Control; BMI, Body Mass Index; VATS, Video-assisted Thoracoscopic Surgery; RATS, Robotic-assisted Thoracic Surgery; Pne, Pneumonectomy; Lob, Lobectomy; Bilob, Bilobectomy; Sle, Sleeve resection; Wed, Wedge resection; Seg, Segmentectomy