Safety and Efficacy of Enhanced Recovery After Surgery in Patients Undergoing Minimally Invasive Pneumonectomy: A Systematic Review and Meta-Analysis

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Research article

Keywords: Enhanced recovery after surgery, Pneumonectomy, Thoracic surgery, Systematic review, Meta-analysis

Posted Date: September 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-837486/v1>

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Abstract

Background: The ERAS program has been widely used in thoracic surgery, but its effectiveness and safety in patients undergoing minimally invasive pneumonectomy remains uncertain.

Methods: We searched PubMed, Embase, the Cochrane Library, and Science Direct for studies published through April 5, 2021, that compared the Safety and Efficacy of ERAS versus conventional care after minimally invasive pneumonectomy. Outcome data, including length of stay, overall morbidity, and pulmonary complications, were extracted by two independent investigators and analyzed using STATA 15.1 software.

Results: 9 studies representing 2,332 patients were eligible for our analysis. Compared to conventional care, patients receiving an ERAS program had a shorter hospital stay (SMD=-0.51, 95 CI: -0.77 to -0.24), particularly postoperative hospital stay (SMD=-0.76, 95 CI: -1.07 to -0.46), and lower incidence rates of overall complications (OR= 0.79, 95% CI: 0.64-0.97) and pulmonary complications (OR= 0.51, 95%CI: 0.34-0.77), and bore less hospitalization costs (SMD=-0.39, 95 CI -0.52 to -0.25). But there was no difference in the frequency of readmission (OR=0.91, 95%CI: 0.57-1.45) and 30-day mortality (OR=0.50, 95 CI: 0.13-2.00) between patients accepting ERAS versus conventional care. In subgroup analysis, the incidence of overall complications in ERAS patients only undergoing minimally invasive lobectomy or segmentectomy was significantly lower versus non-ERAS individuals (OR=0.66, 95%CI: 0.50-0.89). But this difference was not statistically significant when compared to all ERAS patients (OR=0.93, 95%CI: 0.69-1.25).

Conclusion: ERAS is safe and effective in patients receiving minimally invasive pneumonectomy. Stronger evidence from large-sample, multicenter RCTs of ERAS following pneumonectomy is needed for better efficacy assessment.

1. Introduction

Minimally invasive technology has become more sophisticated and popular worldwide after decades of development and today supersedes conventional open thoracotomy. For example, video-assisted thoracoscopic surgery (VATS) has been recognized as the gold standard therapy for thoracic diseases[1]. It is estimated that the frequency of robot-assisted thoracoscopic surgery (RATS) worldwide rise to 17.5% in 2015[2]. However, a relatively high incidence of postoperative complications following minimally invasive pneumonectomy, about 10.2–38%[3, 4], as estimated, impedes a smooth recovery after the surgery, with delayed hospital stay[5] and lower quality of life[6]. Despite the rising cost of hospitalization, accordingly, the overuse of health care resources is also inevitable as the length of hospital stay extends[7]. Therefore, an appropriate rehabilitation approach to faster recovery after thoracic surgeries is urgently required.

Rehabilitation approaches for postoperative recovery have been a research hotspot for a decade. Enhanced recovery after surgery (ERAS), or called fast-track surgery (FTS), was first proposed by Danish surgeons Kehlet and Mogensen[8] in 1999, who applied this multidisciplinary approach in patients undergoing sigmoidectomy. Today, it has been accepted as a common type of nursing modality in modern surgical subspecialties. Standardized ERAS protocols[9–11] have been shown to minimize postoperative complications and hospital stay and expedite recovery after different types of surgery. These protocols often use multidisciplinary team-based approaches to deliver comprehensive perioperative rehabilitation, aiming at boosting surgical efficacy and patients' life quality.

Despite the surge of ERAS programs in common surgeries, its applications for thoracic surgeries remain limited[12], most of which are adopted in patients following thoracotomy[13–15]. There are very few studies of ERAS regimens for minimally invasive pneumonectomy. Though they have tried to prove the efficacy and advantages of an ERAS pathway, their inconsistent conclusions only provide unconvincing evidence. For instance, Khandhar et al.[16] found an ERAS program shortened length of stay (LOS) in patients undergoing minimally invasive pneumonectomy. But this conclusion was not validated in the study conducted by Brunelli et al[17]. Some studies[18, 19] reported a lower incidence of complications after ERAS programs, but the study by Tahiri et al[20]. did not yield the same result. Given the controversy on ERAS programs for minimally invasive pneumonectomy, we, for the first time, precisely assessed its safety and efficacy through meta-analysis.

2 Methods

This meta-analysis was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement[21] and was registered on the PROSPERO database (CRD 42021236271).

2.1 Search strategy

Two researchers (QK and ZWB) independently searched PubMed, Embase, The Cochrane Library, and ScienceDirect databases for relevant articles published through April 5, 2021. Studies were identified using a combination of free-text keywords and MeSH headings as follows: enhanced recovery after surgery or ERAS, fast-track surgery or FTS, clinical pathway, critical pathway, multimodal perioperative care, accelerated rehabilitation, pneumonectomy, lobectomy, and segmentectomy. The bibliography of the articles selected was reviewed to identify additional related publications.

2.2 Inclusion and exclusion criteria

The pre-set inclusion criteria were designed from four dimensions: subjects, interventions, controls, and outcomes. Studies were included if they fulfilled all of the following criteria. (I) Subjects: patients must undergo minimally invasive pneumonectomy, either VATS or RATS. No restrictions were imposed regarding the basic characteristics of patients. (II) Interventions: as there is no consensus on ERAS/FTS components, we utilized a relevant criterion described elsewhere, defining that no less than four ERAS elements that covered at least two perioperative stages were applied in one study[22]. (III)

Controls: conventional nursing care was carried out in patients undergoing minimally invasive pneumonectomy. (IV) Outcomes: the primary endpoints incorporated LOS, overall morbidity, and pulmonary complications, including atelectasis (diagnosed using a bronchofiberscope), confirmed or suspected pneumonia, respiratory failure requiring invasive or non-invasive mechanical ventilation[23, 24]. Secondary endpoints were hospitalization cost, 30-day mortality, and frequency of readmission. Studies were excluded if they were (I) non-full-text English-language articles, (II) studies on thoracotomy, (III) comments, meta-analysis, case reports, letters, protocols, or (IV) duplicates; or data (V) were incomplete or unavailable.

2.3 Data extraction

Two well-trained researchers (ZL and SC) were designated to independently review articles according to the eligibility criteria, extract data from each eligible study using a prepiloted data extraction form, and cross-checked the records. Any disagreements were solved by discussion between them or consultation with a third researcher. Study information was categorized into three dimensions: basic information (e.g., the first author's name, year of publication, country, study type, etc.), demographic and clinical characteristics (age, gender, interventions, and outcome indicators), and results of bias risk assessment.

2.4 Bias risk assessment of included studies

The methodology quality of the studies included was assessed by two researchers (CXL and PJH) independently using the 8-item Newcastle-Ottawa scale (NOS). Each study was appraised on three dimensions: selection, comparability, and outcome for non-randomized studies, and assigned to a range of 0–9 points. Studies with a score of 7 and beyond were considered to have a low risk of bias or high quality. Evaluation results were cross-checked, and any disagreements were addressed by discussion or consultation with a third researcher.

2.5 Statistical analysis

All statistical analyses were performed using STATA software version 15.1. We estimated median or interquartile range from the studies included to obtain a pooled estimate of means and standard deviations (SD)[25, 26]. Odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were calculated for dichotomous variables and the standard mean deviations (SMDs) with their 95% CIs for continuous data. We quantified between-study heterogeneity using I^2 statistics and the Chi-square-based Q test: If $I^2 > 50\%$ and $P < 0.10$, which suggested significant heterogeneity, a random-effects model was applied; otherwise, a fixed-effects model was chosen. To identify potential sources of heterogeneity or the effect of excision area on the efficacy of ERAS protocols, we performed subgroup analyses based on surgical types. Leave-one-out sensitivity analysis was carried out by omitting one study and pooling the OR or SMD for the rest in each turn. Publication bias was visually inspected using funnel plots and statistically assessed using Egger's test[27, 28]. A P -value of < 0.05 was considered statistically significant.

3. Results

3.1 Study selection and characteristics

As shown in Fig. 1, our database query initially identified 2,592 relevant articles, and 1,755 of them were retained after duplicates were discarded. After the title and abstract reviewing, 88 studies highly relevant to ERAS programs following minimally invasive pneumonectomy remained for full-text reading. Among them, 51 studies only appraising less than 4 ERAS elements, 10 studies on thoracotomy, 8 using other controls rather than conventional care, and one non-English study were ruled out. Besides, another 9 studies were excluded as they mixed thoracotomical and minimally invasive pneumonectomical data. Ultimately, 9 case-control trials (CCTs)[16, 18–20, 29–33] representing 2,332 patients were included for the subsequent meta-analysis. Study characteristics and clinical data at baseline and post-operation were summarized in Tables 1–3. The ERAS protocol of each CCT included was listed in Table 4.

Table 1
Study characteristics

Study	Year	Country	Design	Type of surgery	Surgical procedures	ERAS items	Sample size		Outcomes reported	NOS score
							ERAS	Control		
Maruyama et al.	2006	Japan	CCT	VATS	LB,ST WR PN	10	113	105		7
Khandhar et al.	2018	U.S.A	CCT	VATS	LB	8	304	100		8
Gonzalez et al.	2018	Switzerland	CCT	VATS	LB,ST	12	50	50		7
Huang et al.	2018	China	CCT	VATS	LB	12	38	45		7
Martin et al.	2018	U.S.A	CCT	VATS	LB,WR SLB others	9	81	162		8
Van et al.	2018	U.S.A	CCT	VATS,RATS	LB,ST WR PN SR BL,	7	129	506		8
Haro et al.	2019	U.S.A	CCT	VATS,RATS	LB,ST WR	10	67	79		9
Tahiri et al.	2020	Canada	CCT	VATS	LB	6	98	98		7
Forster et al.	2021	Switzerland	CCT	VATS	LB	12	140	167		9
Abbreviations: BL, bilobectomy; CCT, controlled clinical trial; LB, lobectomy; PN, pneumonectomy; RATS,robotic-assisted thorascopic surgery; ST, segmentectomy; SR, sleeve resection; SLB, Surgical lung biopsy; VATS, video-assisted thorascopic surgery, WR, wedge resection.										
Notes: Length of hospital stay; Overall complications; Pulmonary complications; Hospitalization cost; Hospital readmission; 30-day mortality.										

Table 2
Clinical characteristics of all patients included at baseline

Study	Age		ASA		BMI		FEV1		DLCO	
	ERAS	Control	ERAS	Control	ERAS	Control	ERAS	Control	ERAS	Control
Maruyama et al.	63(17–84)	64(15–83)	NA	NA	NA	NA	NA	NA	NA	NA
Khandhar et al.	66.2 ± 10.5	66.2 ± 10.0	NA	NA	NA	NA	87.5 ± 19.6	86.6 ± 19.9	75.7 ± 27.0	72.7 ± 22.7
Gonzalez et al.	64[44–87]	68[51–81]	II 33 III 17	II 24 III 26	NA	NA	92 ± 18	81 ± 20	76 ± 17	74 ± 21
Huang et al.	60.71 ± 8.35	59.56 ± 10.24	NA	NA	NA	NA	94.09 ± 10.09	92.02 ± 16.00	NA	NA
Martin et al.	63.5 ± 13	61.3 ± 15.6	NA	NA	29.2(8.6)	27(7.5)	81(24)	80.5(32)	69.5(25)	71(27)
Van et al.	66(13)	65(15)	I 10.8% II 13.5% III 74.9% IV 0.9%	I 6.3% II 24.1% III 68.5% IV 1.2%	NA	NA	86(26)	87(25)	80(23)	79(27)
Haro et al.	67(59–72)	67(59–73)	NA	NA	NA	NA	91(80–107)	86(72–100)	72(65–90)	80(71–95)
Tahiri et al.	65.2 ± 9.3	66.2 ± 9.4	NA	NA	26.9 ± 5.9	27.5 ± 5.6	92.9 ± 18.6	86.8 ± 22	84.4 ± 23.3	83.1 ± 20.9
Forster et al.	67(59–72)	67(60–74)	2.5 ± 0.5	2.5 ± 0.5	25.4 ± 5.7	25.2 ± 4.7	85.8 ± 20.3	89.8 ± 22.3	72.6 ± 20	74.1 ± 18.5
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; DLCO = diffusing capacity of the lungs for carbon monoxide; ERAS, enhanced recovery after surgery; FEV1, forced expiratory volume in 1 second; NA, Not available, not reported; SD = standard deviation.										
Notes: Continuous Variables are presented as median (interquartile range), median[range]and mean ± SD.										

Table 3
Postoperative outcomes

Study	Length of hospital stay (days)		Overall complications		pulmonary complications		30-day mortality		Hospital readmission		Hospitalization cost (\$)	
	ERAS	Control	ERAS	Control	ERAS	Control	ERAS	Control	ERAS	Control	ERAS	Control
Maruyama et al.	13.3 ± 9.57 ^b 18.6 ± 10.63 ^a	22.4 ± 20.49 ^b 29.4 ± 20.49 ^a	NA	NA	NA	NA	NA	NA	NA	NA	13093 ± 2976.4	14439 ± 4406.2
Khandhar et al.	1(1-1.25) ^b	2(1-4) ^b	41	18	2	6	0	2	15	6	NA	NA
Gonzalez et al.	7[2-21] ^b	4[1-16] ^b	12	24	8	19	0	0	1	1	15945 ± 4313.91	20360 ± 6706.62
Huang et al.	6.58 ± 3.87 ^b	8.69 ± 4.40 ^b	4	6	1	2	0	0	NA	NA	NA	NA
Martin et al.	3.28 ± 3.6 ^a	3.54 ± 2.5 ^a	29	55	2	5	1	2	2	11	14870 ± 11552	20169 ± 13295
Van et al.	NA	NA	59	241	23	126	1	3	5	17	NA	NA
Haro et al.	2.0(1.8-3.1) ^a	3.0(2.1-4.2) ^a	12	19	NA	NA	0	0	6	3	16200(13200-20400)	18000(13800-22700)
Tahiri et al.	3(2-5) ^a	5(4-6) ^a	23	28	NA	NA	NA	NA	5	4	NA	NA
Forster et al.	5(4-10) ^a	7(5-12) ^a	41	61	NA	NA	0	0	5	9	NA	NA
Abbreviation: ERAS, enhanced recovery after surgery; NA, Not available, not reported;												
Notes: Continuous Variables are presented as median (interquartile range), median [range] and mean ± SD; a = Overall length of hospital stay; b = Postoperative length of hospital stay.												

Table 4. ERAS protocols implemented in eligible CCTs

ERAS elements	Eligible CCTs								
	Maruyama et al.	Khandhar et al.	Gonzalez et al.	Huang et al.	Martin et al.	Van et al.	Haro et al.	Tahiri et al.	Forster et al.
Preoperative interventions									
patient education	✓	✓	✓	✓	✓	✓	✓	✓	✓
Shortened fasting						✓			
Prophylactic antibiotics	✓			✓					✓
Respiratory drug intervention				✓					
Cardiopulmonary exercise testing				✓					
Optimized diets			✓	✓	✓				✓
Intraoperative interventions									
Epidural anesthesia/analgesia	✓		✓	✓	✓	✓	✓		✓
Protective lung ventilation					✓		✓		
Intraoperative warming		✓	✓	✓			✓		✓
Postoperative interventions									
Enhanced postoperative analgesia		✓	✓	✓	✓	✓	✓	✓	✓
Optimized chest tube management	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intravenous fluid restriction	✓	✓	✓	✓	✓		✓		✓
early removal of drainage tube or catheter	✓	✓	✓					✓	✓
Encourage early oral feeding	✓		✓		✓	✓	✓	✓	✓
Encourage early mobilization	✓	✓	✓	✓	✓	✓	✓	✓	✓
PONV			✓	✓			✓		✓

Abbreviation: CCT, controlled clinical trial; ERAS, enhanced recovery after surgery; PONV, postoperative nausea and vomiting.

3.2 Quality assessment

Then, the 9 studies included were subject to bias risk assessment using the 8-item NOS checklist. Among others, 5 studies scored 8–9 points were rated as high-quality, and the rest 4 scored 7 were graded as moderate-quality evidence. More details were illustrated in Table 5.

Table 5
Quality assessment of CCTs based on the Newcastle-Ottawa scale

Author	Year	Selection	Comparability	Exposure/Outcome	Total Score
Maruyama	2006	***	**	**	7
Khandhar	2018	****	**	**	8
Gonzalez	2018	***	**	**	7
Huang	2018	***	**	**	7
Martin	2018	****	**	**	8
Van	2018	****	**	**	8
Haro	2019	****	**	***	9
Tahiri	2020	***	**	**	7
Forster	2021	****	**	***	9
Abbreviation: CCT, controlled clinical trial.					

3.3 Length of hospital stay

Among the 8 studies included, 5 compared the overall LOS between ERAS versus non-ERAS patients, and 4 of them specially analyzed postoperative LOS. The study conducted by Van et al.[30] was excluded as their data were merely expressed as percentages, from which the results of the sample mean and standard deviation could not be pooled. After that study was discarded, substantial heterogeneity was found between studies for LOS (overall LOS: $I^2 = 78.7\%$ and $P = 0.001$; postoperative LOS: $I^2 = 71.4\%$ and $P = 0.015$). The sensitivity analysis did not show significant changes in the pooled ORs with 95% CIs for LOS after each article was omitted (Additional file 1A). Thus, a random-effects model was selected for meta-analysis. As shown in Fig. 2A, both overall (SMD=-0.51; 95%CI: -0.77 to -0.24) and postoperative LOS (SMD=-0.76; 95%CI: -1.07 to -0.46) were significantly shortened in ERAS patients versus non-ERAS ones. Neither funnel plots nor the Egger's test indicated evident publication bias in the pooled estimates of LOS ($P = 0.895$) (Fig. 3A).

3.4 Overall complications

Eight out of the 9 studies reported the overall incidence of postoperative complications in 2114 patients undergoing minimally invasive pneumonectomy. A fixed-effects model ($I^2 = 0.0\%$ and $P = 0.544$) was utilized concerning the low heterogeneity across the studies. Patients receiving ERAS regimens showed a significantly lower incidence of postoperative complications versus non-ERAS individuals (OR = 0.79, 95%CI: 0.64 to 0.97, Fig. 2B). In subgroup analysis, ERAS protocols remarkably reduced postoperative complications in patients only receiving minimally invasive lobectomy or segmentectomy compared to non-ERAS ones (OR = 0.66, 95%CI: 0.50 to 0.89, Fig. 2B). But this difference was not statistically significant in the comparison between all ERAS patients versus non-ERAS controls (OR = 0.93, 95%CI: 0.69 to 1.25, Fig. 2B). The funnel plot (Fig. 3B) showed no evident publication bias, which was subsequently supported by Egger's test ($P = 0.208$). Sensitivity analysis demonstrated that the effect of ERAS regimens on postoperative complications was not unduly affected by a particular study (Additional file 1B).

3.5. Pulmonary complications

Five studies assessed the incidence of pulmonary complications in 1465 patients. Forster et al.[29] estimated the frequency of cardiopulmonary complications, so their data on pulmonary complications were unavailable and not included in our analysis. A fixed-effects model ($I^2 = 33.8\%$ and $P = 0.196$) was employed for analysis. Again, the ERAS group exhibited a lower incidence of pulmonary complications versus non-ERAS individuals (OR = 0.51, 95% CI: 0.34 to 0.77, Fig. 2C).

3.6 Hospitalization cost

Four studies, including 311 ERAS patients and 396 non-ERAS controls, calculated the cost of treatment during the whole period. A fixed-effects model ($I^2 = 39.6\%$ and $P = 0.174$) was utilized. The results supported reduced hospitalization costs for ERAS patients (SMD =-0.39, 95%CI: 0.52 to -0.25, Fig. 4A).

3.7 Hospital readmission

We assessed the frequency of readmission in ERAS versus non-ERAS patients from 7 studies ($n = 2031$). No significant difference in the readmission rate was observed between ERAS versus non-ERAS (OR = 0.91, 95%CI: 0.57 to 1.45) in a fixed-effects model ($I^2 = 0.0\%$ and $P = 0.639$), as depicted in Fig. 4B.

3.8. 30-day mortality

We evaluated the safety endpoint, 30-day mortality, based on 7 studies representing 1,792 patients. Of the 7 studies, four reported zero deaths in both ERAS and non-ERAS groups. Using a fixed-effects model ($I^2 = 27\%$ and $P = 0.254$), the meta-analysis demonstrated no significant difference in 30-day mortality between the two groups (OR = 0.50, 95%CI: 0.13 to 2.00, Fig. 4C).

4 Discussion

To the best of our knowledge, this is the first meta-analysis of ERAS protocols tailored for minimally invasive pneumonectomy. Our results demonstrate that compared with traditional nursing, these ERAS programs shorten LOS, minimizes postoperative complications, particularly pulmonary complications, and reduces hospitalization costs without a rise in the risk of readmission and postoperative death.

One of the most important goals of an ERAS pathway is to shorten the LOS for patients post-operation, which in turn is conducive to a shorter bed turnover time and more cost-effective use of medical resources[34]. As we expected, ERAS achieved that aim in this meta-analysis, featuring a shorter LOS of patients undergoing minimally invasive pneumonectomy, consistent with that observed in patients experiencing thoracotomy[35, 36]. All of the eight studies included yielded the same result, except for one by Martin et al.[31] that only showed a borderline decrease in the LOS. A synergy of ERAS elements, specially tailored for minimally invasive pneumonectomy, can result in a significant outcome improvement[37]. The current data on each element, though insufficient to determine which one weighs the heaviest on those improvements, show that patients perceived efficacy after receiving some ERAS components, such as early removal of chest drainage tubes and early mobilization. Some studies[38, 39] ascertained that early removal of chest drainage tubes and early mobilization are independent predictors of a shorter LOS. However, delayed chest tube drainage will accordingly increase various degrees of chest pain, resulting in delayed ERAS implementation and longer recovery in the hospital[40]. Khandhar et al.[16] designed an ERAS program for VATS lobectomy, requiring a 250-ft walk within an hour after chest tube removal, and found the median LOS was one day shorter in ERAS patients versus non-ERAS controls. Similarly, Kuroda et al.[41] proved that chest tube removal and early activity at 4–6 hours post-operation lead to earlier hospital discharge versus conventional care (the reduction of hospitalization to ≤ 3 postoperative days). All these studies applied early mobilization, an important ERAS element, which is assumed to be a significant contributor to a shorter LOS. In addition, a clear definition of the discharge criteria described in ERAS protocols reduces the likelihood of a longer LOS of patients.

It is worthy of note that pronounced heterogeneity was observed between the five LOS studies (overall LOS: $I^2 = 78.7\%$ and $P = 0.001$; postoperative LOS: $I^2 = 71.4\%$ and $P = 0.015$). Five factors may potentially contribute to a substantial degree of heterogeneity. First, disagreement between practitioners is the most significant contributor as anesthesiologists, physiotherapists, dietitians, nurses, and clinicians involved in a multidisciplinary team who conducts an ERAS program often make clinical decisions based on their experience, attributed to the lack of consensus ERAS guidelines. Second, differences in selection of ERAS elements employed, either in number or type, and the clinical stage of chest disease in different studies contribute to the heterogeneity of LOS. Third, a lack of recommendations for standardized ERAS implementation, such as the time to start early mobilization, a threshold of drainage volumes for chest tube removal, and different drug regimens (type or dose), may lead to significant heterogeneity between studies. Moreover, there inevitably exist some objective differences between VATS and RATS after we eliminated the studies of open chest surgeries, which could be a source of heterogeneity. Last but not the least, most of the studies included only reported results from a single center, and interhospital differences in health-related conditions, associated with economic status in localities, may be a critical reason for the high heterogeneity between these studies. Despite the significant heterogeneity, our sensitivity analysis and publication bias assessment showed our results were stable.

Postoperative complications can delay early recovery and diminish long-term life quality in patients post-operation, and some of the severe complications may even cause death. Thus, minimizing postoperative complications is one of the most significant criteria to evaluate the feasibility of an ERAS program[42]. In an ERAS pathway, various interventions can be delivered for a lower incidence of postoperative complications. For example, preoperative education and psychological counseling can help improve chest incision pain, nausea, and anxiety after minimally invasive pneumonectomy[43]. Shortening preoperative fasting time helps lower insulin resistance[44]. Air leakage from the lung post-operation can be prevented through preoperative physiotherapy and physical exercise[45]. And the likelihood of postoperative respiratory failure, associated with impaired skeletal muscle, may be substantially minimized through early mobilization[14]. A synergy of ERAS elements can achieve the best performance for patient recovery post-operation[46]. Our results demonstrated that the synergy of various ERAS elements for minimally invasive pneumonectomy decreased the incidence of overall and pulmonary complications after the surgery. Wang et al.[35] retrospectively analyzed 1,749 cases undergoing pneumonectomy and found that the incidence of complications remarkably decreased in the ERAS group (OR = 0.601, 95%CI:0.434 to 0.824), consistent with our results. Paci et al.[12] came to the same conclusion. But in some studies of minimally invasive pneumonectomy, ERAS protocols failed to prevent postoperative complications, although they were proved to be safe[17, 20]. They believed minimally invasive pneumonectomy itself was so non-invasive that ERAS interventions merely had little effect on the reduction in complication probabilities[47]. Licker et al.[48] conducted a randomized controlled trial representing 151 patients and ascertained that the ERAS program for lung cancer resection significantly improved the aerobic exercise capacity of patients post-operation, but failed to reduce early postoperative complications. Khoury et al.[36] also reported no significant differences in the median LOS and the frequency of postoperative complications after ERAS compared to the results before ERAS was implemented. A rational explanation for the insignificant efficacy of ERAS in these studies is that an ERAS program introduced for minimally invasive pneumonectomy, whose noninvasiveness has already reduced postoperative complications, may only moderately improve patient prognosis, and any other independent factors may mask its efficacy.

Regarding the best performance, an ERAS program could be less effective for patients undergoing minimally invasive surgery (MIS). Some studies attempted to assess the efficacy of ERAS in different surgeries in terms of surgical types (e.g., wedge resection, segmentectomy, lobectomy, and pneumonectomy) and approaches. However, this design can be a source of statistical biases in clinical outcomes. Our subgroup analysis stratified by types of pneumonectomy revealed that postoperative complications were only reduced in ERAS patients receiving minimally invasive lobectomy or segmental pneumonectomy versus non-ERAS controls. There was no significant difference in the incidence of complications in patients following anatomic lobectomy versus non-anatomical lobectomy. Reasonable speculation is that ERAS for minimally invasive pneumonectomy might reduce postoperative complications in patients undergoing anatomical pneumonectomy rather than non-anatomical pneumonectomy that are dissection-less, time-saving, and trauma-less for fewer complications when combined with MIS. So the advantage of postoperative ERAS for non-anatomical pneumonectomy is very small[30]. However, there are no other studies to confirm the hypothesis we proposed only based on phenomenon.

Patient compliance is another common factor influencing the best performance of ERAS protocols. Forster et al.[49] and Rogers et al.[39] showed a strong association of a lower incidence of postoperative complications with better compliance. During ERAS implementation, multiple challenges, such as lack of institutional support, poor teamwork, difficulty to optimize patient management[29], and interpatient variability[20], result in a significant disparity in the overall compliance rate of an ERAS protocol among studies. That may also contribute to the substantial difference in the incidence of complications between studies.

We also assessed hospitalization costs between ERAS versus non-ERAS, a dimension we are very curious about. Compared with conventional care, the total cost during hospitalization was lower in the ERAS group. But there were no significant differences in readmission rate and 30-day mortality between the two groups. We speculate that reduced postoperative complications and shorter LOS are the main contributors to lower hospitalization costs as severe complications are factors increasing readmission rate and postoperative mortality. Gonzalez et al.[18] and Forster et al.[29] found that the ERAS program did not reduce severe postoperative complications, which confirmed our speculation. It is worth noting that in our meta-analysis, only 2 patients died after ERAS implementation due to postoperative complications, further confirming that ERAS protocols are safe for minimally invasive pneumonectomy. However, as the insufficient sample size that results in the lack of statistical efficiency may reduce the accuracy of our analysis, our conclusion still needs to be validated by larger-sample, multicenter trials.

4.1 Limitation

Although we have carefully conducted this meta-analysis of the evidence currently available, we must point out some of the limitations of this study. All the studies included were CCTs, and a lack of RCTs determines less credibility of our conclusion. Besides, some of our results (e.g., LOS) have pronounced

heterogeneity, and the lack of means to reduce heterogeneity may lead to a certain bias in the final results. Moreover, the impact of ERAS compliance on clinical outcomes has not yet been evaluated, which makes it impossible for us to make a strong conclusion about ERAS in minimally invasive pneumonectomy. Finally, due to the lack of supporting data, a thorough meta-analysis for some significant indicators, for example, quality of life, is currently unavailable.

5 Conclusions

In conclusion, this is the first meta-analysis of ERAS programs tailored for minimally invasive pneumonectomy. Our results demonstrate that ERAS can improve postoperative outcomes, particularly shorter LOS, to minimize overall morbidity, pulmonary complications, and hospitalization costs without increases in readmission rate and postoperative mortality. Therefore, ERAS is safe and effective for minimally invasive pneumonectomy. Future studies with larger samples and conducted at multiple centers are required to validate the efficacy of ERAS.

Abbreviations

Fast track surgery, FTS

Video-assisted thoracoscopic surgery, VATS

Robot-assisted thoracoscopic surgery, RATS

Enhanced recovery after surgery, ERAS

Newcastle-Ottawa scale, NOS

Odds ratio, OR

Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA

Standard mean difference, SMD

Confidence interval, CI

Standard deviation, SD

Controlled clinical trial, CCT

Length of hospital stay, LOS

Randomized controlled trial, RCT

Declarations

Acknowledgements

We would like to thank all the investigators, surgeons, and patients who participated in this study.

Funding

None.

Availability of data and materials

All the data used in the study can be obtained from the original articles.

Authors' contributions

XJJ designed the study; QK and ZWB interpreted data and drafted the manuscript; ZL and SC screened documents and extracted data; CXL and PJH conducted the statistical analyses; MHP and LXL reviewed the results and made critical comments on the manuscript. All authors approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

All analyses were based on previous published studies; thus, no consent for publication is required.

Ethics approval and consent to participate

All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

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Figures

Figure 1
Flow diagram of studies assessed and included.

Figure 2

Forest plots of primary endpoints (ERAS vs. non-ERAS). A: Forest plots of the overall and postoperative length of hospital stay; B: Forest plots of overall complications following anatomical and non-anatomical pneumonectomy; C: Forest plots of pulmonary complications.

Figure 3

Funnel plots of primary endpoints. A: Funnel plots of the length of hospital stay; B: Funnel plots of overall complications.

Figure 4

Forest plots of (A) hospitalization cost, (B) hospital readmission, and (C) 30-day mortality between ERAS versus non-ERAS patients.

Supplementary Files

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