The Effect of the Enhanced Recovery After Surgery Protocol on Lung Resection Surgical Outcomes at the University of North Carolina Hospitals

By

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Title: The Effect of the Enhanced Recovery After Surgery Protocol on Lung Resection Surgical Outcomes at the University of North Carolina Hospitals

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ABSTRACT

Introduction: The Enhanced Recovery After Surgery (ERAS) protocol is an evidence-based, multidisciplinary peri-operative care model that has been shown to reduce complications and hospital length of stay (LOS), improve cardiopulmonary function, and lead to earlier return of bowel function. While some thoracic ERAS studies have been inconclusive, others have shown that ERAS improves patient outcomes after lung resections and provides more cost-effective care. We aimed to investigate the effect of ERAS, in comparison to conventional care, on lung resection outcomes at the University of North Carolina (UNC) Hospitals.

Methods: In this retrospective cohort study, adult patients undergoing lung resections (wedge resection, segmentectomy, lobectomy, and bilobectomy) during the pre-ERAS (April 2014-September 2015) and post-ERAS (January 2016-May 2017) periods were identified from the UNC thoracic surgery database. Resections performed during the wash-in period (October-December 2015) were excluded. Relevant demographic, pre-operative, anesthesia, and surgical variables were collected. Pre- and post-ERAS cohorts were compared in terms of hospital LOS, post-operative complications, 30-day readmission and mortality.

Results: We identified 264 patients, half of which were exposed to ERAS. Pre- and post-ERAS groups were similar with respect to age, race, and comorbidities. There was no significant difference in hospital LOS, complications, or 30-day readmission between groups. There were only two cases of 30-day post-operative mortality in the post-ERAS group. Of the 163 patients in both groups who had hospital LOS greater than 3 days, 45 (28%) had pulmonary complications, half of which were prolonged air leaks for greater than 5 days.

Conclusions: Median hospital LOS, complications, and 30-day readmission did not differ significantly between the pre- and post-ERAS groups. Thoracic ERAS protocols should include interventions to reduce air leak and consider discharging patients with chest tubes placed to a Heimlich valve. ERAS has been shown to improve patient satisfaction, and this warrants further studies.

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LIST OF ABBREVIATIONS

ASA – American Society of Anesthesiologists

BMI – Body mass index

DLCO – Diffusing capacity for carbon monoxide

EHR – Electronic Health Record

ERAS – Enhanced Recovery After Surgery

ERATS – Enhanced Recovery After Thoracic Surgery

FEV1 – Forced expiratory volume in 1 second

ICB – Intercostal nerve block

LOS – Length of stay

OR – Operating room

PFT – Pulmonary function test

RATS – Robotic-assisted thoracoscopic surgery

RIFLE – Risk, Injury, Failure, Loss, End stage renal disease

STS – Society of Thoracic Surgeons

ThRCRI – Thoracic revised cardiac risk index

UNC – University of North Carolina

VATS – Video-assisted thoracoscopic surgery

INTRODUCTION

In the 1990s, Henrik Kehlet developed the Enhanced Recovery After Surgery (ERAS) protocol, an evidence-based, multidisciplinary peri-operative care model. Key principles of ERAS protocols include the following: pre-operative counseling; pre-operative nutrition (minimizing peri-operative fasting and carbohydrate loading up to 2 hours pre-operatively); standardized multimodal anesthetic and analgesic regimens (epidural and non-opioid analgesia); optimized antibiotic and thromboembolic prophylaxis; and early post-operative mobilization. This model has been shown to reduce complications and hospital length of stay (LOS), improve cardiopulmonary function, and lead to earlier return of bowel function and resumption of normal activity. The ERAS protocol was first adapted by the colorectal surgery discipline and has since been utilized by other surgical specialties, including vascular surgery, urologic surgery, and thoracic surgery[1,2].

In the field of thoracic surgery, the prototypical ERATS (Enhanced Recovery After Thoracic Surgery) pathway involves three phases. The first is the pre-operative phase which includes the following: pre-operative visit and assessment; patient education and explanation of ERAS; smoking cessation; pre-operative rehabilitation; admission on day of surgery; pre-operative carbohydrate drink; and avoidance of sedative pre-anesthetic medication. Next, the peri-operative phase incorporates prophylactic antibiotics, regional anesthesia with paravertebral catheters, avoidance of crystalloid overload, intra-operative warming, venous thromboembolism prophylaxis, avoidance of urinary catheter, minimally-invasive surgery (such as video-assisted thoracoscopic surgery [VATS] where possible), and single chest drain). Finally, the post-operative phase comprises of avoidance of post-operative intravenous fluids, avoidance of opiate analgesia, early feeding, targeted post-operative

nausea and vomiting therapy, use of incentive spirometry (pulmonary toileting), early mobilization within 24 hours, and early chest tube and urinary catheter removal[2,3].

In October 2015, the UNC Department of Anesthesiology gradually began to implement an ERAS pathway specific to the UNC Division of Cardiothoracic Surgery's Thoracic Surgery service. Since this ERAS pathway was fully implemented in January 2016, both UNC cardiothoracic anesthesiologists and surgeons have collected preliminary data and noted increased patient satisfaction with care, decreased peri-operative complications, decreased hospital LOS, and improved use of hospital resources[4,5].

Although the use of ERAS in lung resections began almost 20 years ago, ERATS protocols have not been studied as extensively as ERAS pathways in colorectal surgery. Initially, most of the evidence for ERATS was published in case-series; the lack of a control group in these studies increases risk of bias and limits the ability to attribute improvements in care to ERATS[6-8]. While some recent thoracic ERAS studies in the literature have been inconclusive[9], others have shown that ERAS improves patient outcomes after lung resections and provides more cost-effective care[10,11]. Objectives of this study were to (1) investigate the effect of ERAS, in comparison to conventional care, on lung resection outcomes at UNC Hospitals, and (2) determine the predictive demographic, pre-operative, anesthesia, or surgical factors that are associated with decreased hospital LOS, morbidity, and mortality.

METHODS

Study design:

In this retrospective cohort study, adult patients (age >18 years) undergoing lung resections (wedge resection, segmentectomy, lobectomy, and bilobectomy) during the pre-ERAS (April

2014-September 2015) and post-ERAS (January 2016-May 2017) periods were identified from the UNC thoracic surgery database. Only a patient's first thoracic surgery within this timeframe was eligible for inclusion. Resections performed during the ERAS wash-in period (October-December 2015) were excluded. Patients who simultaneously underwent esophagectomy (n=2), pneumonectomy (n=1), coronary artery bypass grafting (CABG, n=1) and trauma patients (n=4) were excluded.

The following demographic variables and baseline clinical characteristics were abstracted from the electronic health record (EHR): age, race, gender, weight, body mass index (BMI), comorbidities (hypertension, steroid use, congestive heart failure, coronary artery disease, peripheral vascular disease, pre-operative chemotherapy or radiation, prior cardiothoracic surgery, insulin-dependent diabetes mellitus, and renal insufficiency), smoking status, pulmonary function test (PFT) results, Karnofsky performance index[12], and thoracic revised cardiac risk index (ThRCRI, which assigns points for history of ischemic heart disease, cerebrovascular accident, creatinine >2, and pneumonectomy[13]). Anesthesia-related variables collected included the following: American Society of Anesthesiologists (ASA) score, baseline pulse oximetry measurement at room air, pre-operative laboratory values (hemoglobin, creatinine, bicarbonate), pre-operative medications (acetaminophen, pregabalin, celecoxib), total peri-operative anesthesia time, intra-operative nadir pulse oximetry measurement, intra-operative blood transfusion, total intra-operative crystalloid and colloid fluids, intra-operative medications (ketorolac, dexamethasone, vasopressin, norepinephrine), amount of intra-operative opioids (fentanyl, hydromorphone, oxycodone) in terms of morphine equivalents, intercostal nerve block (ICB) medications (bupivacaine [Marcaine], bupivacaine liposome injectable suspension [Exparel], or both), type of regional block (ICB, epidural, or both), and post-operative extubation in operating room (OR). The following

thoracic surgery-related variables were collected: procedure (wedge resection, segmentectomy, lobectomy, bilobectomy), primary diagnosis (benign lung disease, lung cancer, or metastatic lung cancer), lung cancer clinical and pathological staging (if applicable), and total surgery time.

Pre- and post-ERAS patients were compared in terms of hospital LOS, total number of post-operative complications, 30-day readmission and mortality. Pulmonary, cardiovascular, urologic, infectious, hematologic, gastrointestinal, neurologic, and miscellaneous complications were as defined by the Society of Thoracic Surgeons (STS)[14] (**Table 1).**

Statistical Analyses:

Patient demographics, surgical characteristics, and post-operative outcomes were compared between pre- and post-ERAS patients using Fisher's exact and Wilcoxon-Mann-Whitney tests, where appropriate. A p-value <0.05 was considered statistically significant.

Cox proportional hazard regression was used to estimate the effect of ERAS implementation on inpatient complications and 30-day readmission. For inpatient complications, patients were followed until discharge, and for 30-day readmission, patients were followed for up to 30-days post-discharge. Multivariable hazard regression was used to estimate the effect of ERAS on patient outcomes, after adjusting for age, sex, steroid use prior to surgery, ThRCRI, intra-operative crystalloids, intra-operative colloids, and intra-operative morphine equivalents. Age, crystalloids, colloids, and morphine equivalents were modeled as restricted cubic splines to allow for the most flexibility. Due to low incidence, some outcomes were unable to be modeled.

Crude and multivariable linear regression was used to assess the effect of ERAS on average length of stay after surgery. Multivariable models were adjusted for the same variables described above.

All analyses were performed in Stata SE version 15.1[15] (College Station, Texas).

Ethics Approval:

The institutional review board of the University of North Carolina at Chapel Hill provided ethical approval of the study (IRB# 15-1841).

RESULTS

Patient Baseline Characteristics:

Overall, 264 patients were included; 133 (50%) underwent surgery pre-ERAS and 131 (50%) underwent surgery post-ERAS implementation. In the pre-ERAS group, median age was 64 years, 50% were male, and median body mass index (BMI) was 27 kg/m^2. In terms of race, 100 (75%) were white, 27 (20%) were black, and 6 (5%) were of another race. For pre-operative PFTs, median forced expiratory volume in 1 second (FEV1) was 83%, and median diffusing capacity for carbon monoxide (DLCO) was 70%. Median Karnofsky performance index was 100. Regarding smoking status, 35 (26%) were never smokers, 69 (52%) were former smokers, 29 (22%) were current smokers; 34 (26%) smoked within four weeks of surgery. For primary diagnosis, 25 (19%) had benign lung disease, 77 (58%) had lung cancer, and 31 (23%) had metastatic lung cancer (**Table 2**).

In the post-ERAS group, median age was 61, 38% were male, and median BMI was also 27 kg/m^2. In terms of race, 92 (70%) were white, 28 (21%) were black, 11 (8%) were of another

race. For pre-operative PFTs, median FEV1 was 83%, and median DLCO was 75%. Median Karnofsky performance index was 90. Regarding smoking status, 36 (27%) were never smokers, 72 (55%) were former smokers, and 23 (18%) were current smokers; 29 (22%) smoked within four weeks of surgery. For primary diagnosis, 24 (18%) had benign lung disease, 69 (53%) had lung cancer, and 32 (24%) had metastatic lung cancer (**Table 2**).

Pre- and post-ERAS groups did not differ significantly in terms of age, race, BMI, comorbidities, smoking status, smoking within four weeks of surgery, pre-operative chemotherapy or radiation, history of prior cardiothoracic surgery, primary diagnosis, PFTs, Karnofsky performance index, ASA score, or ThRCRI. The two groups did, however, differ significantly with respect to gender (p=0.05) and history of steroid use (p=0.001); the pre-ERAS group had a higher percentage of males (50% vs. 38%), and fewer patients were on steroids compared to the post-ERAS group (35% vs 56%) (**Table 2**).

Intra-operative Characteristics:

In the pre-ERAS group, 85 (64%) had wedge resections, 0 (0%) had segmentectomies, 46 (35%) had lobectomies, and 2 (2%) had bilobectomies. Median surgery time was 121 minutes, and median anesthesia time was 159 minutes. Very few patients received the three pre-operative medications: acetaminophen (5%), pregabalin (4%), and celecoxib (1). In terms of intra-operative medications, 3 (2%) received ketorolac, 44 (33%) received dexamethasone, 9 (7%) received vasopressin, and 1 (1%) received norepinephrine. Median volume of crystalloids received was 2000 milliliters (mL), median volume of colloids received was 0 mL, and median amount of morphine equivalents received was 25 mg. For type of regional block, 90 (68%) received an ICB, 0 (0%) had an epidural, and 43 (32%) had both. All pre-ERAS patients received bupivacaine (Marcaine) as their ICB (**Table 3**).

In the post-ERAS group, 74 (56%) had wedge resections, 1 (1%) had a segmentectomy, 56 (43%) had lobectomies, and 0 (0%) had bilobectomies. Median surgery time was 119 minutes, and median anesthesia time was 173 minutes. Majority of patients received the three pre-operative medications: acetaminophen (78%), pregabalin (65%), and celecoxib (56%). In terms of intra-operative medications, 26 (20%) received ketorolac, 69 (53%) received dexamethasone, 51 (39%) received vasopressin, and 18 (14%) received norepinephrine. Median volume of crystalloids received was 800 mL, median volume of colloids received was 250 mL, and median amount of morphine equivalents received was 20 mg. For type of regional block, 102 (78%) had an ICB, 0 (0%) had an epidural, and 29 (22%) had both. Regarding type of ICB, 37 (28%) had bupivacaine (Marcaine), 61 (47%) had bupivacaine liposome injectable suspension (Exparel), and 33 (25%) had both (**Table 3**).

The pre- and post-ERAS groups differed significantly in terms of all three pre-operative medications ($p<0.0001$), robotic surgery ($p<0.0001$), all four intra-operative medications ($p=0.002$ for dexamethasone and $p<0.0001$ for others), type of ICB ($p<0.0001$), total crystalloids ($p<0.0001$), total colloids ($p<0.0001$), and morphine equivalents ($p<0.0001$). The post-ERAS group had significantly higher use of all of these medications. However, the two groups did not differ significantly with respect to procedure, surgery or anesthesia time, or regional block type (**Table 3**).

Post-operative Outcomes:

In the pre-ERAS group, median hospital LOS was 4 days, total number of post-operative complications was 57 (36 patients had complications [27%]), 11 (8%) were readmitted to the hospital within 30 days of surgery, and 0 (0%) died within 30 days of surgery (**Table 4**).

In the post-ERAS group, median hospital LOS was 4 days, total number of post-operative complications was 56 (44 patients had complications [34%]), 13 (10%) were readmitted to the hospital within 30 days of surgery, and 2 (2%) died within 30 days of surgery (**Table 4**).

The pre- and post-ERAS groups did not differ significantly in terms of median hospital LOS, post-operative complications, 30-day readmission and mortality (**Table 4**). In a subgroup analysis, median hospital LOS was 3 days for both wedge resection groups, and 5 days for both lobectomy groups. Similarly, there was no significant difference in the total number of post-operative complications and 30-days readmission rates within the wedge resection and lobectomy subgroups.

Of the 163 patients in both groups who had hospital LOS greater than 3 days, 45 (28%) had pulmonary complications, half of which were prolonged air leaks for greater than 5 days.

The Effect of ERAS on LOS and Associated Predictors:

When compared to pre-ERAS implementation, ERAS implementation did not have a significant effect on post-operative complications, hospital LOS, or 30-day readmission rates.

When adjusted for sex, age, prior steroid use, thoracic revised cardiac risk index, intra-operative crystalloids, intra-operative colloids, and intra-operative morphine equivalents, the adjusted hazard ratio (HR) for any post-operative complications was 1.23 (95% confidence interval [CI], 0.61-2.48; p=0.56) (**Table 5**). When adjusted for the same variables listed above, the adjusted HR for 30-day readmissions was 2.25 (95% CI, 0.61-8.29; p=0.22) (**Table 5**). When adjusted for the same variables listed above, the adjusted change in estimate

(CIE) of ERAS implementation on hospital LOS was 0.15 (95% CI, -1.43-1.73; p=0.85) **(Table 5)**.

DISCUSSION

In this retrospective cohort study, patients who underwent lung resections in the pre- and post-ERAS had similar baseline characteristics and only differed significantly with respect to gender and history of steroid use. In terms of intra-operative characteristics, the two groups differed significantly in terms of all three pre-operative medications, all four intra-operative medications, all three types of ICB, total crystalloids, total colloids, and total morphine equivalents given; all of these variables correspond with key components of the ERAS protocol, such as goal-directed fluid management and multimodal anesthetic and analgesic regiments (with judicious use of opioid pain medications). ERAS also requires careful consideration of blood transfusions, and none of the study patients underwent intra-operative blood transfusions.

As ERAS protocols prefer shorter incisions and use of laparoscopic approach when possible, the majority of our patients had minimally-invasive VATS procedures[16] (only three in each group underwent conversion to thoracotomy). Fifteen patients in the post-ERAS group underwent robotic-assisted thoracoscopic surgery (RATS), which has been shown to reduce hospital LOS, 30-day mortality, and post-operative blood transfusion when compared to VATS and thoracotomy procedures[17]. These minimally-invasive surgical techniques are also important from a cost perspective, as studies have shown that the average cost of inpatient procedures (wedge resections and lobectomies) with VATS and RATS are both lower than that of an open thoracotomy approach[18-20]. One cost-minimization analysis demonstrated that utilizing VATS for the 50,000 lobectomies performed in the United States each year,

compared to open lobectomy via posterolateral thoracotomy, would result in cost savings of approximately $100 million[20].

Median hospital LOS, total number of post-operative complications, 30-day readmission and mortality rates did not differ significantly between the pre- and post-ERAS groups. There was no significant difference in the total number of post-operative complications and 30-day readmission rates within the wedge resection and lobectomy subgroups as well. There were only two cases of post-operative mortality in the post-ERAS group.

Median hospital LOS was four days for both groups overall, three days for both VATS wedge resection groups, and five days for both VATS lobectomy groups; these medians are comparable to, or even lower than, national medians demonstrated in other studies[19,21-23]. This result was consistent with a recent study by Brunelli et al., which showed no statistically significant benefit from ERAS implementation on outcomes such as hospital LOS, cardiopulmonary complications, 30- and 90-day mortality, and readmissions[9]. However, our study results contradict two other recent studies: Madani et al. and Paci et al. Both found that ERAS was associated with significantly decreased hospital LOS and complications with no difference in readmission. In addition, one study also found that ERAS in lung resections was associated with societal cost savings ($4,396 Canadian dollars)[10,11].

For our study, there are a few potential explanations for why rates of healthcare utilization and complications were not significantly lower in the post-ERAS group compared with the pre-ERAS group. Firstly, our data represents a snapshot of ERAS implementation for lung resections at a single academic medical center, and our sample size is relatively small. Secondly, the UNC Thoracic Surgery service had low post-operative complication rates

before ERAS implementation, and the median hospital LOS was already consistent with the national median[19,21-23]; thus, it would be difficult to notice a significant difference in outcomes associated with ERAS implementation. Of note, the UNC Thoracic Surgery service even won the 2018 UNC Excellence in Quality Award; concurrent efforts to improve patient safety and surgical outcomes render it more challenging to determine the overall effect of ERAS during this time period[24].

Next, pre-ERAS care may have already involved sufficient ERAS components to result in good outcomes. For example, one of the key elements of ERAS in thoracic surgery is the utilization of VATS, and almost all of our pre-ERAS patients had VATS procedures. Similarly, pre-operative counseling and antibiotic prophylaxis are variables that were also present before ERAS. In addition, minimally-invasive VATS lung resections may already be associated with low procedural risk and an uncomplicated recovery, and ERAS may not be required[9].

Furthermore, pulmonary air leaks often prolong hospital LOS and thus may affect the ability to measure differences in hospital LOS before and after ERAS. Of the 163 patients in both groups who had hospital LOS greater than 3 days, 45 (28%) had pulmonary complications, half of which were prolonged air leaks (greater than 5 days, as defined by the STS[14]). Using the national hospital billing database Premier, Yoo et al. recently estimated the economic burden of air leaks to be $6,512 higher than those without any air leak complications[25]. While the post-operative phase of ERAS in thoracic surgery involves early post-operative mobilization, early removal of chest tubes and drains, and early transition to oral pain medications, it does not address air leaks. Therefore, we recommend that thoracic ERAS

protocols should include interventions to reduce air leak and consider discharging patients with prolonged air leak home earlier with chest tubes placed to a Heimlich valve[26].

Finally, a recent study by Horattas et al. suggested that ERAS in colorectal surgery results in enhanced patient satisfaction scores and improvements in pain management[27]. Given the multimodal anesthetic and analgesic regimens in ERAS, patient satisfaction scores and pain scores are variables that could differ significantly between the pre- and post-ERAS groups. The UNC Thoracic Surgery service has collected preliminary data that shows improved patient satisfaction scores, decreased opioid equivalents, and better patient pain scores with ERAS implementation. Since we did not include these variables for this study, further analysis is warranted.

Strengths of this study include the initial comparability of the pre- and post-ERAS groups, the large number of variables collected, and minimal missing data. However, our study does have limitations, including its small sample size from a single academic medical center. The UNC Thoracic Surgery service has significant discharge delay due to patients' lack of access to transportation to get home; this factor may have skewed our data as well. The lack of a concurrent control group could also introduce bias given that other factors that contribute to health care utilization and complication rates may have changed over the same time frame. As previously mentioned, the utilization of VATS is one of the key elements of ERAS in thoracic surgery, and having VATS as a common variable for the majority of both the pre- and post-ERAS patients could potentially mask the effect of other ERAS elements on surgical outcomes[9]. Lastly, this study focused on objective outcomes (hospital LOS, total number of post-operative complications, 30-day readmission and mortality). Future studies

could investigate the effect of ERAS on patient-reported outcomes, such as quality of life, patient satisfaction scores, and pain scores.

Conclusion:

Our results demonstrated that median hospital LOS, complications, and 30-day readmission and mortality did not differ between the pre-ERAS and post-ERAS lung resection groups. Thoracic ERAS protocols should include interventions to reduce air leak and consider discharging patients with chest tubes placed to a Heimlich valve given that air leaks are associated with increased hospital LOS. ERAS has been shown to improve patient satisfaction after lung resections – an important consideration in the era of patient-informed decisions regarding choice of lung surgeons – and further studies are warranted to continue improving lung resection outcomes.

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Table 1. Post-operative events defined by the Society of Thoracic Surgeons[1]

Post-operative event	Definition
Unexpected return to OR	Primary reason for return to OR was bleeding, anastomotic leak following esophageal surgery, bronchopleural fistula, empyema, chylothorax requiring surgical ligation of thoracic duct, or other
Pulmonary complication	Air leak >5 days duration, atelectasis requiring bronchoscopy, pleural effusion requiring drainage, pneumonia, acute respiratory distress syndrome, respiratory failure, bronchopleural fistula, pulmonary embolus, pneumothorax, initial vent support >48 hours, reintubation, tracheostomy, tracheobronchial injury, or other pulmonary event
Cardiovascular complication	Atrial arrhythmia requiring medication, ventricular arrhythmia requiring medication, myocardial infarct, deep vein thrombosis requiring medication, or other cardiovascular event
Urologic complication	Urinary tract infection, urinary retention requiring catheterization, or discharged with Foley catheter
Infection complication	Empyema, sepsis, another infection requiring intravenous antibiotics, or surgical site infection (none, superficial, deep, organ space [empyema, mediastinitis])
Hematologic complication	Postoperative packed red blood cells given
Gastrointestinal complication	Gastric outlet obstruction, ileus, anastomotic leak requiring medication only, dilation esophagus within post-operative period, conduit necrosis requiring surgery, delayed conduit emptying requiring intervention or maintenance of nasogastric drainage >7 days post-operatively, Clostridium difficile infection, or other gastrointestinal event
Neurological complication	New central neurological event, recurrent laryngeal nerve paresis or paralysis, delirium, or other neurological event
Miscellaneous complication	Chylothorax requiring drainage or medication, other events requiring OR with general anesthesia, unexpected admission to intensive care unit, new renal failure per RIFLE criteria

Abbreviations: OR, operating room; RIFLE criteria, Risk, Injury, Failure, Loss, End stage renal disease

[1]The Society of Thoracic Surgeons (STS). General Thoracic Surgery Database Training Manual. STS National Database. https://www.sts.org/sites/default/files/documents/STSThoracicTrainingManualV2_41.master.pdf. Accessed June 10, 2018.

Table 2. Patient baseline characteristics, stratified by pre- and post- ERAS implementation

	Before ERAS 133 (50%)	After ERAS 131 (50%)	p-value
Age, in years, median (IQR)	64 (55 – 70)	61 (54 – 68)	0.19
Male, n (%)	67 (50)	50 (38)	**0.05**
Race, n (%)			
White	100 (75)	92 (70)	0.41
Black	27 (20)	28 (21)	0.88
Other	6 (5)	11 (8)	0.22
BMI, median (IQR)	27 (24 – 33)	27 (23 – 31)	0.26
Comorbidities, n (%)			
Hypertension	73 (55)	60 (46)	0.18
Congestive heart failure	12 (9)	4 (3)	0.07
Coronary artery disease	20 (15)	13 (10)	0.26
Peripheral vascular disease	13 (10)	13 (10)	0.99
Diabetes, insulin-dependent	6 (5)	3 (2)	0.50
Renal insufficiency	5 (4)	6 (5)	0.77
Smoking status, n (%)			
Never	35 (26)	36 (27)	0.89
Former	69 (52)	72 (55)	0.62
Current	29 (22)	23 (18)	0.44
Smoked within 4 weeks of surgery, n (%)	34 (26)	29 (22)	0.56
Steroid use, n (%)	47 (35)	73 (56)	**0.001**
Pre-operative chemotherapy, n (%)	29 (22)	19 (15)	0.15
Pre-operative radiation, n (%)	27 (20)	15 (11)	0.06
Prior cardiothoracic surgery, n (%)	15 (11)	17 (13)	0.71
Primary diagnosis, n (%)			
Benign lung disease	25 (19)	24 (18)	0.99
Lung cancer	77 (58)	69 (53)	0.46
Metastatic lung cancer	31 (23)	32 (24)	0.89
FEV1, %, median (IQR)	83 (72 – 97)	83 (66 – 97)	0.88
DLCO, %, median (IQR)	70 (57 – 84)	75 (62 – 87)	0.16
Karnofsky scale, %, median (IQR)	100 (90 – 100)	90 (90 – 100)	0.44
ASA, n (%)			
1	0 (0)	0 (0)	–
2	13 (10)	12 (9)	0.99
3	96 (72)	98 (75)	0.68
4	24 (18)	21 (16)	0.74
Thoracic revised cardiac risk index, n (%)			
0	104 (78)	1112 (86)	0.15
1 – 1.5	25 (19)	15 (11)	0.12
≥2	4 (3)	4 (3)	0.99

Abbreviations: ERAS, enhanced recovery after surgery; IQR, interquartile range; BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide

Table 3. Intra-operative characteristics, stratified by pre- and post- ERAS implementation

	Before ERAS 133 (50%)	**After ERAS 131 (50%)**	**p-value**
Pre-operative medications, n (%)			
Acetaminophen	7 (5)	102 (78)	**<0.0001**
Pregabalin	5 (4)	85 (65)	**<0.0001**
Celecoxib	1 (1)	73 (56)	**<0.0001**
Procedure, n (%)			
Wedge resection	85 (64)	74 (56)	0.22
Segmentectomy	0 (0)	1 (1)	0.50
Lobectomy	46 (35)	56 (43)	0.21
Bilobectomy	2 (2)	0 (0)	0.50
Robotic surgery, n (%)	0 (0)	15 (11)	**<0.0001**
Thoracotomy, n (%)	3 (2)	3 (2)	0.99
Surgery time, minutes, median (IQR)	121 (67 – 182)	119 (81 – 193)	0.34
Anesthesia time, minutes, median (IQR)	159 (113 – 217)	173 (126 – 232)	0.18
Intra-operative medications, n (%)			
Ketorolac	3 (2)	26 (20)	**<0.0001**
Dexamethasone	44 (33)	69 (53)	**0.002**
Vasopressin	9 (7)	51 (39)	**<0.0001**
Norepinephrine	1 (1)	18 (14)	**<0.0001**
Regional block type, n (%)			
Intercostal nerve block	90 (68)	102 (78)	0.07
Epidural	0 (0)	0 (0)	–
Intercostal nerve block + epidural	43 (32)	29 (22)	0.07
Intercostal nerve block type, n (%)			
Bupivacaine (Marcaine)	133 (100)	37 (28)	**<0.0001**
Bupivacaine liposome injectable suspension (Exparel)	0 (0)	61 (47)	**<0.0001**
Bupivacaine (Marcaine) + Bupivacaine liposome injectable suspension (Exparel)	0 (0)	33 (25)	**<0.0001**
Transfusion, n (%)	0 (0)	0 (0)	–
Total crystalloids, mL, median (IQR)	2000 (900 – 1600)	800 (496 – 1100)	**<0.0001**
Total colloids, mL, median (IQR)	0 (0 – 0)	250 (0 – 500)	**<0.0001**
Morphine equivalents, mg, median (IQR)	25 (22 – 32)	20 (15 – 25)	**<0.0001**

Abbreviations: ERAS, enhanced recovery after surgery; IQR, interquartile range

Table 4. Postoperative inpatient outcomes, length of stay, and 30-day readmission, stratified by pre- and post- ERAS implementation

	Before ERAS 133 (50%)	**After ERAS 131 (50%)**	**p-value**
Inpatient complications, n (%)			
Pulmonary	20 (15)	20 (15)	0.99
Cardiovascular	12 (9)	9 (7)	0.65
Urinary	10 (8)	17 (13)	0.16
Infection	2 (2)	1 (1)	0.99
Hemolytic	2 (2)	2 (2)	0.99
Gastrointestinal	2 (2)	0 (0)	0.50
Neurological	5 (4)	1 (1)	0.21
Other	4 (3)	6 (5)	0.54
Any complication, n (%)	36 (27)	44 (34)	0.28
30-day mortality, n (%)	0 (0)	2 (2)	0.25
30-day readmission, n (%)	11 (8)	13 (10)	0.67
Length of stay, days, median (IQR)	4 (2 – 6)	4 (2 – 6)	0.74

Abbreviations: ERAS, enhanced recovery after surgery; OR, operating room; IQR, interquartile range

Table 5. Crude and adjusted effect of ERAS implementation, compared to pre-ERAS implementation, on inpatient complications, length of stay, and 30-day readmission

	Crude		Adjusted[a]	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Inpatient complications				
Pulmonary	1.01 (0.54, 1.87)	0.99	0.83 (0.27, 2.58)	0.75
Cardiovascular	0.74 (0.31, 1.76)	0.49	0.91 (0.25, 3.29)	0.88
Urinary	1.74 (0.80, 3.80)	0.17	0.82 (0.24, 2.86)	0.76
Infection	0.44 (0.04, 4.88)	0.51	NA	–
Hemolytic	1.02 (0.14, 7.20)	0.99	NA	–
Gastrointestinal	NA	–	NA	–
Neurological	0.19 (0.02, 1.66)	0.13	NA	–
Other	1.52 (0.43, 5.38)	0.52	1.12 (0.14, 8.98)	0.91
Any complication	1.23 (0.79, 1.92)	0.36	1.23 (0.61, 2.48)	0.56
30-day mortality	NA	–	NA	–
30-day readmission	1.21 (0.52, 2.82)	0.65	2.25 (0.61, 8.29)	0.22
	CIE (95% CI)	**p-value**	**CIE (95% CI)**	**p-value**
Length of stay, days	0.18 (-0.86, 1.22)	0.74	0.15 (-1.43, 1.73)	0.85

Abbreviations: HR, hazard ratio; CI, confidence interval; CIE, change in estimate; NA, not analyzable

[a] Adjusted for sex, age, prior steroid use, thoracic revised cardiac risk index, intra-operative crystalloids, intra-operative colloids, and intra-operative morphine equivalents; age, crystalloids, colloids, and morphine equivalents were modeled as restricted cubic splines

Appendix: The effect of the Enhanced Recovery After Surgery protocol on surgical outcomes after lung resection: a systematic review

Introduction

In the 1990s, Henrik Kehlet developed the Enhanced Recovery After Surgery (ERAS) protocol, an evidence-based, multidisciplinary peri-operative care model. Key principles of ERAS protocols include the following: pre-operative counseling; pre-operative nutrition (minimizing peri-operative fasting and carbohydrate loading up to 2 hours pre-operatively); standardized multimodal anesthetic and analgesic regimens (epidural and non-opioid analgesia); optimized antibiotic and thromboembolic prophylaxis; and early post-operative mobilization. This model has been shown to reduce complications and hospital length of stay (LOS), improve cardiopulmonary function, and lead to earlier return of bowel function and resumption of normal activity. The ERAS protocol was first adapted by the colorectal surgery discipline and has since been utilized by other surgical specialties, including vascular surgery, urologic surgery, and thoracic surgery[1,2].

In the field of thoracic surgery, the prototypical ERATS (Enhanced Recovery After Thoracic Surgery) pathway involves three phases. The first is the pre-operative phase, which focuses on patient education and smoking cessation. Next, the peri-operative phase incorporates regional anesthesia with paravertebral catheters and intercostal nerve blocks, along with minimally-invasive surgery (such as video-assisted thoracoscopic surgery [VATS] where possible), and single chest drain). Finally, the post-operative phase emphasizes the use of incentive spirometry (pulmonary toileting), early mobilization within 24 hours, and early chest tube and urinary catheter removal. Throughout the three phases, goal-directed fluid therapy and avoidance of opiate analgesia is encouraged [2,3].

Although the use of ERAS in lung resections began almost 20 years ago, ERATS protocols have not been studied as extensively as ERAS pathways in colorectal surgery. Most of the evidence for ERATS has been published in case-series reports, but the lack of a control group in these studies increases the risk of bias[4-6]. In 2016, Fiore et al. published a systematic review of six comparative studies (five were non-randomized trials) on ERAS in lung resections; however, due to the high risk of bias of the included studies, the authors determined that their results were inconclusive[7]. The following year, Li et al. published a systematic review of seven randomized-controlled trials on this topic, but all of the study participants were from China, Europe, and the Middle East[8]. Recently, a few retrospective cohort studies of ERAS in lung resections have been conducted in the United States and Canada, demonstrating that ERATS improves patient outcomes after lung resections and provides more cost-effective care[9-11]. Thus, in this systematic review, we aimed to identify recent studies (published in the past five years) and relied on existing systematic reviews of older studies to synthesize the evidence as a whole regarding the effect of ERAS, in comparison to conventional care, on surgical outcomes of adult patients undergoing lung resections.

Methods

Eligibility criteria

This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[12]. We developed inclusion and exclusion criteria with respect to populations, interventions, comparators, outcomes, timing, setting, and study designs (shown in **Appendix Table 1**). Studies enrolling adults (age >18 years) who underwent lung resections and compared an ERAS intervention with conventional

care (no ERAS) were eligible. In terms of outcomes, hospital LOS, 30-day mortality, post-operative complications (as defined by the Society of Thoracic Surgeons in **Table 1**[13]) were eligible. Only English language studies published within the past five years (2013-2018) were included. Eligible study designs included the following: randomized controlled trials (RCTs), retrospective cohort studies, prospective cohort studies, case-control studies, and systematic reviews (**Appendix Table 1**). We set the publication time limit as the last five years because we aimed to capture the most recent relevant studies. We also included recent systematic reviews that covered studies published earlier than the past 5 years in order to assess whether results of recent studies were consistent with studies published in the past.

Data Sources and Searches

We searched PubMed and the Cochrane Library from April 3, 2013 to April 3, 2018, limited to English-language articles. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe adult populations who underwent lung resections and various synonyms of the ERAS intervention (such as enhanced recovery, fast-track, and multimodal optimization) (**Appendix Table 2**). Similarly, we also searched for unpublished studies using ClinicalTrials.gov.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using the Covidence online platform[14] for relevance based on the eligibility criteria described above (and shown in **Appendix Table 1**). Abstracts marked as relevant by both reviewers were reviewed

again at the full-text stage. During review of full-text articles, disagreements between reviewers were resolved by consensus.

Data Collection Process and Data Items

We designed and used structured data extraction forms to gather pertinent information from each article, including information about the methods and populations, interventions, comparators, outcomes, timing, setting, and study designs. The following details were collected from each study: publication data (authors and year); setting (nation); source population (total sample size, number of patients in ERAS group and control group, type of surgical procedures, and operative approach [open thoracotomy vs. VATS]); study design and duration; ERAS interventions used; and outcome data (hospital LOS, 30-day mortality, and post-operative complications). All data extractions were reviewed for completeness and accuracy by a second investigator. Disagreements between data extractors were resolved by consensus.

Risk of Bias Analysis

To assess the risk of bias in individual studies, we used Cochrane's risk of bias tool[15] to assess randomized controlled trials, the Newcastle-Ottawa Scale[16] to assess observational studies (both prospective and retrospective cohort studies), and the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) 2[17] tool to assess systematic reviews. Two investigators assigned the risk of bias for each study, and disagreements were resolved by consensus. We did not exclude any studies based on their risk of bias but describe common sources of bias in the results section. Heterogeneity in terms of surgical populations (including different types of lung resections and surgical approaches [VATS or open thoracotomies]) and ERAS intervention

components, together with varying statistical methods and outcome measures across the studies, precluded any attempt at meta-analysis.

Results

Results of Literature Searches

Upon initial search (see search terms in **Appendix Table 2**), 314 unique articles were identified. Three additional unpublished studies were found in ClinicalTrials.gov. The 317 articles were screened by title and abstract, and 254 were excluded based on the aforementioned eligibility criteria (Table 1). Full-texts of those marked as potentially relevant (63 articles) were screened again using the same eligibility criteria; of these, eight met full eligibility criteria. Reasons for exclusion at the full-text stage are shown in **Appendix Figure 1**.

Study Characteristics

Of the eight included studies, two were systematic reviews; one included seven RCTs (with a meta-analysis)[8], and the other included one RCT, one case-control study, two prospective cohort studies, and two retrospective cohort studies[7]. The systematic review by Fiore et al. included all studies that compared the effect of ERAS versus conventional care on lung resection outcomes, while the one by Li et al. used the same eligibility criteria but only included RCTs.

The six individual studies (6,051 participants in total) identified in our searches for recent studies (published between 2015 and 2018) included one RCT, one prospective cohort study, and four retrospective cohort studies[9-11,18-20]. Studies were set in diverse countries, including China, Canada, the United States, and the United Kingdom. Individual study sample sizes

ranged from 35 to 2886. All studies included a comparison between pre- and post-ERAS groups, and all ERAS participants received key components of the thoracic ERAS protocol (**Appendix Table 3**). While most studies enrolled patients who underwent various types of lung resections with different surgical approaches (VATS vs. open thoracotomies), one study only included open pulmonary lobectomies[9], one study only included pneumonectomies[18], and two studies only included VATS procedures[19,20]. All studies reported on LOS and complication rates, while only 5 studies reported on 30-day readmission rates and 4 reported on 30-day mortality rates.

Risk of Bias Analysis

Most of the studies were determined to have low risk of bias overall. Both systematic reviews were deemed to be low risk of bias as their only missing component on the AMSTAR 2 checklist was discussion regarding funding and conflicts of interest. Selection bias was low in all studies: pre- and post-ERAS groups in all studies had similar baseline characteristics, and as most of the studies were prospective or retrospective cohort studies that involved EHR review, all studies had complete follow-up with all patients accounted for. We rated one RCT as having a low-medium risk of bias due to small sample bias (n = 35) and the potential for confounding bias, although it had low risk of selection bias, performance bias, detection bias, attrition bias, and reporting bias[18]. There was low risk of measurement bias in these studies that involved EHR review. Three studies had a potential for confounding bias, as they did not mention which covariates they adjusted for in their statistical analysis[10,18,19]. Each individual study was conducted at a single academic medical center; thus, their results would have low applicability to other hospital settings in other nations (**Appendix Tables 4-6**).

Summary of Results

The two included systematic reviews both reported a significant decrease in hospital LOS in the ERAS group (one reported a difference of 1.2-9.1 days), which is consistent with results from five of the six individual studies. While one systematic review found no difference in post-operative complication rates[7], the other included a meta-analysis of 486 participants and reported a risk ratio (RR) of 0.64 (95% confidence interval [CI], 0.51-0.80)[8]; similarly, three of the six individual studies also described a significant decrease in post-operative complications, especially pulmonary complications. None of the studies reported a significant decrease in 30-day or 90-day readmission or mortality. Notably, one study found no significant differences in LOS, post-operative complication rates, 30- and 90-day readmission and mortality between the pre- and post-ERAS groups[20] (**Appendix Table 3**).

Discussion

In summary, these studies provide modest evidence that ERAS improves surgical outcomes in the field of thoracic surgery. While most studies reported a significant decrease in hospital LOS, half of the studies noted a significant decrease in post-operative complications. None of the studies, however, found a significant decrease in 30-day or 90-day readmission or mortality. A few studies noticed a significant decrease in post-operative pain[19] and both societal and medical costs in the ERAS group (mean difference in societal cost -$4,396 Canadian per patient[10], and difference in medical costs of $7,300 Chinese Yuan[18]); further studies are warranted to study the cost and effect of ERAS on patient-reported outcomes such as pain and patient satisfaction scores.

Although these studies have a low risk of bias overall, this body of literature is not without its limitations. In the systematic review by Fiore et al., the authors highlight the potential for confounding bias in observational studies and thus the need for well-designed RCTs to provide conclusive evidence about the effect of ERAS in lung resection outcomes[7]. Some of these studies only included patients who underwent VATS lung resections; since the utilization of VATS is one of the key elements of ERAS in thoracic surgery, Brunelli et al. discuss that operating with VATS in both pre- and post-ERAS patients could potentially mask the effect of other ERAS elements on surgical outcomes[20]. The different surgical populations (including different types of lung resections and surgical approaches [VATS or open thoracotomies]) and ERAS intervention components in these studies, together with varying statistical methods and outcome measures across the studies, renders it difficult to perform a meta-analysis.

Conclusion

Although the reviewed studies do not clearly establish the magnitude of benefit of ERAS on post-operative hospital LOS, complications, 30- and 90-day readmission and mortality, the results are promising given that most studies consistently found significantly decreased LOS with ERAS implementation. Future research, including future RCTs, should be conducted with larger sample sizes to better determine the association between ERAS and surgical outcomes of lung resections. Studies regarding the effect of ERAS on patient-reported outcomes such as pain scores and patient satisfaction scores are also warranted.

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Appendix Table 1. Systematic review eligibility criteria

PICOTSS	Inclusion Criteria	Exclusion Criteria
Population(s)	Patients age >18 who undergo lung resections (+/- video-assisted thoracoscopic surgery [VATS])	Children age <18, pregnant women, adults who undergo other types of thoracic surgery (such as esophagectomies)
Interventions	Enhanced Recovery After Surgery (ERAS) protocol	Conventional care (no ERAS intervention); just single components of ERAS (not all key elements of ERAS protocol)
Comparators	ERAS vs. pre-ERAS protocol for thoracic surgery	No comparison (all patients had ERAS intervention); non-concordant historical controls
Outcomes	Hospital length of stay (LOS), 30-day mortality, post-operative complications (as defined by the STS in **Table 1**[1])	All other outcomes
Timing	Studies within the last 5 years (2013-2018)	Studies older than 2013
Settings	Inpatient hospital settings	Other non-hospital settings
Study Designs	Randomized controlled trials, retrospective cohort studies, prospective cohort studies, case-control studies, systematic reviews	Non-systematic reviews, case reports, case series, cross-sectional studies, and modelling studies (such as cost-effectiveness analyses)

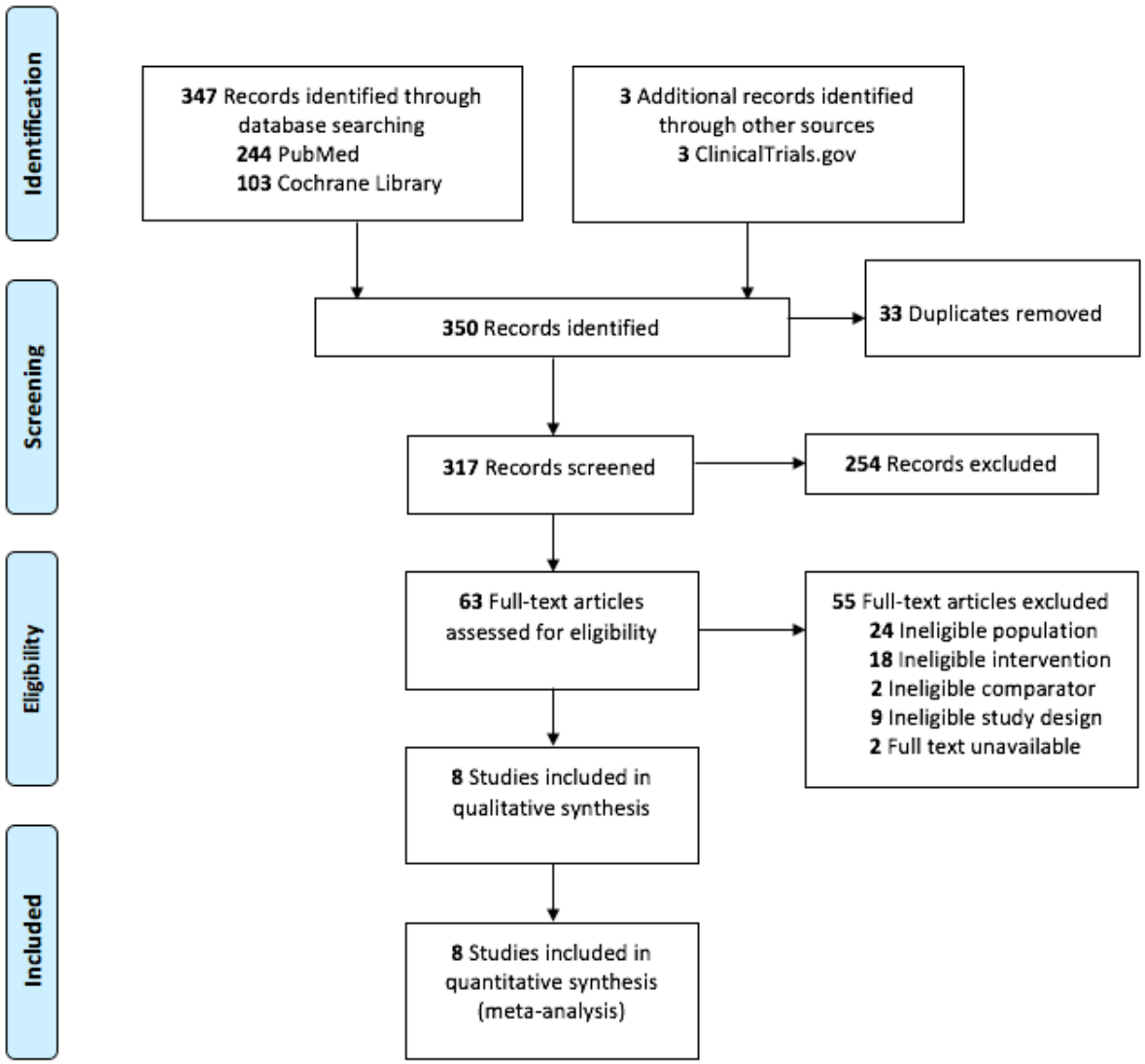
[1]The Society of Thoracic Surgeons (STS). General Thoracic Surgery Database Training Manual. STS National Database. https://www.sts.org/sites/default/files/documents/STSThoracicTrainingManualV2_41.master.pdf. Accessed June 10, 2018.

Appendix Table 2. Systematic review detailed search strategy

Database	Search Terms
PubMed	(("enhanced recovery" OR "fast-track" OR fasttrack OR "accelerated rehabilitation" OR ERAS OR FTS OR "rapid recovery" OR "early recovery" OR "multimodal optimization" OR "early mobilization") AND (lung OR lungs OR pulmon*) AND (resect* OR surger* OR surgic* OR operation* OR operativ*)) AND "last 5 years"[PDat] AND English[lang]
Cochrane Library[1]	("enhanced recovery" OR "fast-track" OR fasttrack OR "accelerated rehabilitation" OR ERAS OR FTS OR "rapid recovery" OR "early recovery" OR "multimodal optimization" OR "early mobilization") AND (lung OR lungs OR pulmon*) AND (resect* OR surger* OR surgic* OR operation* OR operativ*)

[1]Note: Also added search limit of past 5 years under "Title/Abstract" drop-down menu.

Appendix Figure 1. PRISMA flow diagram of disposition of articles[1]



[1]Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-analyses of Studies that Evaluate Health Care Interventions: Explanation and Elaboration. *Ann Intern Med*. 2009;151:W-65--W-94.

Appendix Table 3. Summary characteristics of included studies

#	Reference	Setting	Source population	Study design and duration	ERAS interventions used	Outcomes reported
1.	Fiore et al. 2016	Systematic review that included 2 studies from the United States (1997 and 1998), 3 studies from Europe (2008-2012), and 1 study from Japan (2006)	Total sample size was 1612 participants (821 ERAS vs. 791 control). Sample size of included studies ranged from 58-464 (most studies had half of sample exposed to ERAS). 2 studies involved only patients undergoing lobectomy, and 4 studies involves a variety of lung resection procedures (ranging from wedge resection to pneumonectomy). One study included only VATS procedures, and one study only included thoracotomies.	Systematic review (included 1 RCT, 2 retrospective cohort studies, 2 prospective cohort studies, and 1 case-control study).	Most included studies had the following ERAS components: pre-operative patient education/counseling and prophylactic antibiotics, intra-operative epidural anesthesia/analgesia, and post-operative standardized chest tube management, early removal of epidural catheter, early removal of oxygen support, early feeding, and early mobilization.	The 1 RCT reported no differences in hospital LOS, but all the nonrandomized studies reported decreased LOS (difference 1.2-9.1 days). There were no significant differences in readmissions, overall complications, and mortality rates. Two nonrandomized studies also reported decreased hospital costs in the ERAS group.
2.	Li et al. 2017	Systematic review that included 4 studies from China (2010-2017), 2 studies from Europe (2008 and 2017), and 1 study from the Middle East (2011).	Total sample size was 486 (243 ERAS vs. 243 control). Majority of patients were diagnosed with primary non small cell lung cancers (n=472). 326 patients (67%) underwent lobectomy, 78 (16%) underwent pneumonectomy, and 82 (17%) underwent sublobar resections. Most of the patients had standard posterolateral thoractomy (n=392, 81%), and only 94 (19%) had VATS procedures.	Systematic review (included 7 RCTs); study duration ranged from 1-3 years	Most included studies had the following ERAS components: pre-operative patient education/counseling and intensive pulmonary physiologic therapy, post-operative epidural analgesia/nonsteroidal analgesic painkillers, intravenous fluid restriction, early oral feeding, and early ambulation.	Meta-analysis demonstrated that ERAS group had significantly lower morbidity rates (RR=0.64; p<0.001), especially the rates of pulmonary (RR=0.43; p<0.001) and surgical complications (RR=0.46; p=0.010). There was no significant difference in inpatient mortality or cardiovascular complications. Qualitatively, most studies reported significantly shorter hospital LOS, ICU stay, and decreased hospitalization costs in the ERAS group.
3.	Madani et al. 2015	Canada (single academic center)	Sample size n = 234 (107 ERAS vs. 127 control). Only open pulmonary lobectomies.	Retrospective cohort study (August 2011-October 2013)	ERAS intervention included pre-operative patient education/counselling, opioid-sparing pain control, preferred extubation in the OR or PACU, early and structured mobilization, early feeding and optimization of nutritional status, standardized drain management, and target discharge with written patient goals for each post-operative day.	The ERAS group had decreased LOS (median, 6 [IQR, 5–7] vs 7 [6–10] days; p<0.05), total complications (40 [37%] vs 64 [50%]; p<0.05), urinary tract infections (3 [3%] vs 15 [12%]; p<0.05), and chest tube duration (median, 4 [IQR, 3–6] vs 5 [4–7] days; p<0.05), with no difference in readmissions (7 [7%] vs 6 [5%]; p<0.05) or chest tube reinsertion (4 [4%] vs 6 [5%]; p<0.05). Decreased LOS was driven by patients without complications (median, 5 [IQR, 4–6] vs 6 [5–7] days; p<0.05).
4.	Paci et al. 2017	Canada (single academic center)	Sample size n = 133 (75 ERAS vs. 58 control). All elective lung resections (except pneumonectomies and extended resections).	Prospective before/after cohort study (August 2011-August 2013)	ERAS intervention included pre-operative patient education/counselling, opioid-sparing pain control, preferred extubation in the OR or PACU, early and structured mobilization, early feeding and optimization of nutritional status, standardized drain management, and target discharge with written patient goals for each post-operative day.	The ERAS group had shorter median (IQR) LOS (4 [3 to 6] days vs 6 [4 to 9] days, p<0.01), decreased total complications (32% vs 52%, p=0.02), and decreased pulmonary complications (16% vs 34%, p=0.01, with no difference in readmissions. There was a trend towards less post-discharge caregiver burden for the ERAS group (53 ± 90 hours vs 101 ± 252 hours, p=0.17. Overall societal costs were lower in the ERAS group (mean difference per patient: –$4,396 Canadian; 95% confidence interval –$8,674 to $618 Canadian).

5.	Van Haren et al. 2018	United States (single academic medical center)	Sample size n = 2886 (324 ERAS vs. 929 transitional period vs. 1615 control). Included patients undergoing pulmonary resection for primary lung cancer (both VATS and open thoracotomy).	Retrospective cohort study (January 2006-December 2016)	ERAS intervention included pre-operative patient education, preventive analgesia, peri-operative steroids, opioid-sparing analgesia, total intravenous anesthesia, goal-directed fluid therapy, regional analgesia with pre-incisional posterior intercostal nerve blockage and local wound infiltration with long-acting liposomal bupivacaine, early ambulation, early oral intake, and early chest tube removal.	For all patients, LOS decreased in both ERAS and transitional periods compared to pre-ERAS (4[3] vs. 4[3] vs. 5[3] days, p<0.001). Pulmonary complications were decreased with ERAS compared to transitional and Pre-ERAS (19.9% vs. 28.2% vs. 28.7%, p=0.004). Cardiac complications decreased with ERAS (12.3% vs. 13.1% vs. 18.1%, p=0.001). There was less thoracic epidural use (2.9% vs. 44.5% vs. 75.5%, p<0.001). There were no differences in hospital readmission or mortality rates. Following thoracotomy, ERAS was associated with decreased LOS, less ICU readmission, and decreased frequency of pneumonia, atrial arrhythmias, and need for home oxygen (all p<0.05). ERAS was independently associated with decreased pulmonary (p=0.046) and cardiac complications (p=0.001) on logistic regression after thoracotomy, but not minimally invasive surgery.
6.	Dong et al. 2017	China (single academic medical center)	Sample size n = 35 (17 ERAS vs. 18 control). All patients with non small cell lung cancer and only pneumonectomies.	Randomized controlled trial (June 2012-March 2014).	ERAS intervention included pre-operative patient education, pre-operative carbohydrate diet, intra-operative warming, post-operative analgesia with patient-controlled epidural analgesia and oral nonsteroidal analgesic painkillers, early post-operative feeding, chewing gum to promote bowel movements, early removal of urinary catheter, and early post-operative ambulation.	In the ERAS group, latency to the first postoperative flatus (1.5 ± 0.6 versus 3. 1 ± 0.8 s in controls, p<0.0001), C-reactive protein (71.36 ± 5.48 versus 80.71 ± 8.32 mg/L in at POD 7, p<0.0001), the length of hospital stay (18.1 ± 1.4 versus 27.4 ± 6.6 days, p<0.0001), and the medical costs (29.9 ± 2.7 versus 37.2 ± 3.6 thousand Chinese Yuan, p<0.0001) were significantly reduced. The ERAS group also had a relatively lower postoperative complication rate (23.5% of 17 versus 33.3% of 18 in control group) although it was statistically insignificant.
7.	Huang et al. 2018	China (single academic medical center)	Sample size n = 83 (38 ERAS vs. 45 control). All patients with non small cell lung cancer and only uni-portal VATS procedures.	Retrospective cohort study (January 2016-February 2017).	ERAS intervention included pre-operative patient education, alcohol and tobacco cessation 2-4 weeks pre-operatively, pre-operative respiratory function exercises, pre-operative carbohydrate loading, prophylactic antibiotics, intra-operative warming, intra-operative anesthesia (with general anesthesia, local anesthesia, and intercostal nerve block), goal-directed fluid therapy, post-operative analgesia (opioid-sparing and oral non-steroidal anti-inflammatory analgesics), post-operative aerosol inhalation with respiratory function training, early ambulation, and early removal of urinary catheter and chest tubes.	The ERAS group had better visual analogue scale (VAS, to estimate wound pain) on the third post-operative day (3.11 vs. 3.69; p=0.003), shorter chest tube duration (5.26 vs. 7.02; p=0.021), and shorter length of hospital stay (6.58 vs. 8.69; p=0.024). There were no significant differences between the groups in terms of operative duration, number of lymph nodes retrieved, blood loss, VAS on the first post-operative day, or complication rate.
8.	Brunelli et al. 2017	United Kingdom (single academic medical center)	Sample size n = 600 (235 ERAS vs. 365 control). 561 VATS lobectomies and 39 VATS segmentectomies.	Retrospective cohort study (April 2014-January 2017).	ERAS intervention included pre-operative patient education, pre-operative carbohydrate loading, pre-operative and intra-operative warming, no prolonged fasting, post-operative discharge when criteria met, early mobilization, early oral feeding, nausea and vomiting prevention, goal-directed fluid therapy, and opioid-sparing analgesia.	Between the pre- and post-ERAS groups, there were no significant differences in LOS (ERAS median 5 days vs pre–ERAS 4, p=0.44), cardiopulmonary complication rates (22.6% vs 22.4%, p=0.98), 30-day mortality rates (3.8% vs 2.2%, p=0.31), and 90-day mortality rates (4.7% vs 3.0%, p=0.37). No significant differences were noted in terms of 30-day (7.2% vs 7.4%, p=0.94) or 90-day readmission rates (9.8% vs 12.3%, p=0.34). The risk-adjusted cardiopulmonary morbidity rates were similar in the 2 periods (p=0.76), whereas the risk-adjusted 30-day mortality was significantly higher in the ERAS period compared with the pre–ERAS mortality (p=0.0004).

Abbreviations: RCT, randomized controlled trials; ERAS, enhanced recovery after surgery; RR, risk ratio; IQR, interquartile range; OR, operating room; PACU, post-anesthesia care unit; ICU, intensive care unit; LOS, length of stay; VATS, video-assisted thoracoscopic surgery

Appendix Table 4. Risk of bias analysis for randomized controlled trials[1]

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

[1]Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *BMI*. 2011;343:d5928. doi: 10.1136/bmj.d5928.

Appendix Table 5. Risk of bias analysis for observational studies[1]

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

						of epidural catheter, extent of surgical resection, pathologic stage, ASA score, and pre-existing COPD.	submitted to STS database and subject to independent review for accuracy).			
7.	Huang et al. 2018	Truly representative of the average	Drawn from the same community as the exposed cohort	Secure record (HER)	Yes	Pre- and post-ERAS groups were very similar in baseline characteristics. Did not mention which covariates were adjusted for.	Data collected from electronic hospital charts.	Unclear how long patients were followed for post-operative complicatio ns – authors stated short follow-up time.	Complete follow-up – all subjects accounted for (retrospective chart review)	Selection: 4/4; Comparability: 1/2; Outcome: 3/3
8.	Brunelli et al. 2017	Truly representative of the average	Drawn from same community as the exposed cohort	Secure record (EHR)	Yes	Pre- and post-ERAS groups were very similar in baseline characteristics. Adjusted for age, sex, BMI, FEV1, DLCO, presence of underlying coronary artery disease, cerebrovascular disease, diabetes, performance score, and duration of surgery.	Data collected from a prospectively maintained quality-improvement institutional database.	Yes - 30-day and 90-day post-operative outcomes	Complete follow-up - all subjects accounted for (retrospective chart review)	Selection: 4/4; Comparability: 2/2; Outcome: 3/3

Abbreviations: EHR, electronic health record; ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; STS, Society of Thoracic Surgeons; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of carbon monoxide

[1]Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. The Ottawa Hospital Research Institute. doi:10.2307/632432.

Appendix Table 6. Risk of bias analysis for systematic reviews[1]

	Fiore et al. 2016	**Li et al. 2017**
Did the research questions and inclusion criteria for the review include components of PICO[1]?	Yes	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
Did the review authors use a comprehensive literature search strategy?	Yes	Yes
Did the review authors perform study selection in duplicate?	Yes	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes
Did the review authors provide a list of excluded studies and justify the conclusions?	Yes	Yes
Did the review authors describe the included studies in adequate detail?	Yes	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	Yes - Cochrane ROB tool	Yes - Jadad score
Did the review authors report on the sources of funding for the studies included in the review?	No	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A	Yes
If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	Yes
Did the review authors account for risk of bias in individual studies when interpreting/discussing the results of the review?	Yes	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No

Abbreviations: PICO, Population, intervention, comparator group, outcome; ROB, Risk of bias

[1]Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.