Title:

Effects of perioperative exercise interventions on lung cancer patients: an overview of systematic reviews

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Abstract

Aims and Objectives: To identify, appraise, and summarize systematic reviews of exercise interventions for surgical lung cancer patients.

Background: Low exercise capacity, reduced pulmonary function, impaired health-related quality of life, and postoperative pulmonary complications are common in surgical lung cancer patients. Numerous systematic reviews address these health problems and examine the effects of exercise intervention. However, differences in the quality and scope of the systematic reviews and discordant findings from the reviews make it difficult for decisions-makers to interpret the evidence and establish best practices in the clinical settings.

Design: Overview of systematic reviews.

Methods: This overview was conducted following the PRISMA guideline. A literature search of PubMed, CINAHL, EMBASE, Cochrane Library, SPORTDiscus and PEDro was conducted (October 2019). Peer-reviewed systematic reviews of randomized controlled trials focusing on the effects of exercise interventions for lung cancer patients who underwent surgery were included. The methodological quality of included reviews was assessed using AMSTAR 2. The results of reviews with meta-analysis were synthesized and presented by each health outcome.

Results: Seven systematic reviews published between 2013 and 2019 were included. High/moderate quality evidence showed that postoperative exercise interventions could increase the exercise capacity and muscle strength, and low/very-low quality evidence showed that postoperative exercise interventions may increase the physical component of health-related quality of life and decease dyspnea. Low quality evidence showed that preoperative exercise interventions may increase exercise capacity and pulmonary function, decrease the risk of postoperative pulmonary complications and reduce the length of hospital stay.

Conclusions: Postoperative and preoperative exercises have the potential to improve health outcomes in surgical lung cancer patients. Further research is needed to evaluate the effects of different types of exercise and varying amounts of exercise.

Relevance to clinical practice: This study provides evidence to support the implementation of exercise interventions for surgical lung cancer patients.

KEYWORDS

lung cancer; surgery; preoperative care; postoperative care; physical therapy; exercise; overview of systematic review

What does this paper contribute to the wider global community?

- This overview of systematic review provided a summary of evidence that examined the effects of exercise interventions for lung cancer patients.
- This overview listed the health outcomes that could be improved by exercise interventions.
- Future research needs to focus on evaluating the effects of different types of exercise and varying amounts of exercise.

1 INTRODUCTION

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death worldwide (World Health Organization, 2018). Global cancer statistics estimate that 2.09 million new cases of lung cancer were diagnosed and 1.76 million lung cancer deaths occurred worldwide in 2018 (Bray et al., 2018; World Health Organization, 2018). Surgical resection is one of the main treatments for lung cancer, especially for non-small cell lung cancer (NSCLC). In the United States, 56% of patients with stage I and II NSCLC and 18% of patients with stage III NSCLC undergo surgery with either wedge resection, sleeve resection, lobectomy or pneumonectomy (Miller et al., 2019). While surgery is an effective treatment for lung cancer, lung cancer patients who underwent surgery tend to experience decreased exercise capacity (Ha, Ries, Mazzone, Lippman, & Fuster, 2018), reduced pulmonary function (Kim et al., 2015), impaired health-related quality of life (HRQoL) (Ha et al., 2018; Handy et al., 2002; Poghosyan, Sheldon, Leveille, & Cooley, 2013), and a high risk of postoperative pulmonary complications (PPCs) (Agostini et al., 2010; Flores et al., 2009; Lugg et al., 2016; Stephan et al., 2000).

Exercise is defined as “planned, structured, and repetitive bodily movement to improve or maintain one or more components of physical fitness” (Caspersen, Powell, & Christenson,

1985). The exercise guidelines for cancer survivors report that specific doses of aerobic training, resistance training or a combination could improve common cancer-related health outcomes (Campbell et al., 2019). Additionally, respiratory muscle training (RMT) is sometimes recommended to increase the strength of respiratory muscles for people with lung disease (Hill, Cecins, Eastwood, & Jenkins, 2010). These types of exercise (aerobic training, resistance training and RMT) may contribute to improved health outcomes of surgical lung cancer patients.

Numerous systematic reviews address postoperative health problems and examine the effects of preoperative and/or postoperative exercise interventions on lung cancer patients following surgery (Cavalheri et al., 2019; Cavalheri & Granger, 2017; Cavalheri, Tahirah, Nonoyama, Jenkins, & Hill, 2013a, 2013b; Crandall, Maguire, Campbell, & Kearney, 2014; J. Li et al., 2017; X. Li et al., 2019; W. Liu et al., 2013; X. Liu, Wang, & Xie, 2019; Mainini et al., 2016; Ni et al., 2017; Pouwels et al., 2015; Rodriguez-Larrad, Lascurain-Aguirrebena, Abecia-Inchaurregui, & Seco, 2014; Rosero et al., 2019; Sebio Garcia, Yáñez Brage, Giménez Moolhuyzen, Granger, & Denehy, 2016; Sommer et al., 2018; Steffens, Beckenkamp, Hancock, Solomon, & Young, 2018; Wang, Liu, Jia, & Xie, 2019). However, these reviews vary in inclusion criteria and methodological quality, and this leads to inconsistent findings. Some reviews report inconsistent findings about the effect of exercise interventions on specific outcomes, e.g. pulmonary function (Cavalheri & Granger, 2017; Rosero et al., 2019; Sebio Garcia et al., 2016) and exercise capacity (Cavalheri et al., 2019; J. Li et al., 2017). The varied methodology and inconsistent findings make it difficult for decision-makers to interpret the evidence and establish best practices in the clinical settings.

Overviews of systematic reviews typically compare, summarize and synthesize results from multiple systematic reviews (Smith, Devane, Begley, & Clarke, 2011). With syntheses of all the related findings from included reviews, overviews help provide decision-makers with easily available evidence.

2 AIM

The aim of this overview is to identify, appraise, and summarize systematic reviews of exercise interventions for surgical lung cancer patients.

3 METHODS

This study was conducted and reported following the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Mother, Liberati, Tetzlaff, & Altman, 2009) (see Supplementary File 1).

3.1 Search strategy

A literature search of PubMed, CINHAL, Embase, Cochrane Library, SPORTDiscus, and

PEDro (Physiotherapy Evidence Database) using related terms and filters was conducted on October 15th, 2019. Details of the search strategy are shown in Appendix 1. No limits were applied to the databases in terms of publication date or language.

3.2 Selection of reviews

Two authors independently screened the studies identified by the search strategy. The authors excluded studies based on the titles and abstracts and then independently assessed the remaining studies for eligibility based on the full texts. Disagreements were resolved by consensus. The inclusion criteria for the selection of relevant studies were: systematic reviews (with or without meta-analysis) which 1) include randomized controlled trials (RCTs); 2) include subjects who were lung cancer patients (NSCLC or other type of lung cancer) underwent any type of surgery; 3) include exercise interventions of either aerobic exercises, resistance training, respiratory muscle training or any combination; 4) report at least one of the following outcomes: exercise capacity, pulmonary function, HRQoL, PPCs, muscle strength and LOS, and 5) are full, peer-reviewed articles published in English. Systematic reviews that include both non-RCTs and RCTs were excluded.

3.3 Data extraction

Data were extracted using a standardized form, which included participants characteristics, types of interventions, outcomes, syntheses methods, pooled anticipated absolute/relative effects for outcomes meta-analyzed, quality of evidence (GRADE) and main conclusions. The first author abstracted data and the second author verified it for accuracy. Disagreements were resolved by consensus.

3.4 Quality assessment of included reviews

The methodological quality of the included systematic reviews was independently assessed by two authors using AMSTAR 2 (Shea et al., 2017). Disagreements were resolved in group meetings. AMSTAR 2 is the revised version of AMSTAR (A MeaSurement Tool to Assess systematic Reviews). AMESTAR 2 is composed of 16 items scored as “yes”, “no”, “partial yes” and “no meta-analysis”. The overall quality is categorized as “high”, “moderate”, “low” and “critically low” (Shea et al., 2017).

3.5 Data analysis and synthesis

We constructed figures to visualize the overlap of reviews in terms of the included RCTs (Kitsiou, Pare, & Jaana, 2015) and to demonstrate the types of exercises included in each RCT. To summarize the evidence on the effects of exercise interventions, we synthesized the results of meta-analyses and constructed “Summary of findings” tables for each outcome. We

reported outcomes which were examined in more than one systematic review. The number of participants, types of interventions, anticipated absolute effects/ relative effects and quality of evidence (GRADE) were reported in "Summary of findings" tables.

4 RESULTS

4.1 Search results

As shown in Figure 1, the database search (up to October 15th, 2019) yielded 176 citations after removal of 65 duplicate references. We screened titles and abstracts and retrieved 32 full-text articles. After full text review, 24 additional articles did not meet eligibility criteria (list of articles and reasons for exclusion are shown in Appendix 2). Seven systematic reviews (eight references as one systematic review was published in duplicate) were included in this overview. Six of the seven reviews included meta-analyses (Cavalheri et al., 2019; Cavalheri & Granger, 2017; Cavalheri et al., 2013a; J. Li et al., 2017; Mainini et al., 2016; Rosero et al., 2019; Sommer et al., 2018). One review (Cavalheri et al., 2019) is an updated version of the old one (Cavalheri et al., 2013a).

4.2 Characteristics of included studies

The participants characteristics, types of interventions, syntheses methods and main conclusions of the seven systematic reviews are reported in Table 1. The reviews were published between 2013 and 2019. The number of RCTs included in each review ranged from three to ten.

4.2.1 Overlap of reviews

The RCTs included in the systematic reviews are presented in Figure 2 and 3 to show the overlap of the reviews. Ten RCTs (12 references) were included in the postoperative group (see Figure 2), and 13 RCTs were included in the preoperative exercise intervention group (see Figure 3).

4.2.2 Participants

As shown in Table 1, the number of participants included in the systematic reviews ranged from 167 to 676. The average age of participants ranged from 54 to 72.5 years. Five reviews (Cavalheri et al., 2019; Cavalheri & Granger, 2017; Cavalheri et al., 2013a; Mainini et al., 2016; Rosero et al., 2019) only included patients diagnosed with NSCLC, while two reviews (J. Li et al., 2017; Sommer et al., 2018) included participants with any type of lung cancer. None of the reviews had restrictions on the type of surgery.

4.2.3 Interventions

Four reviews (Cavalheri et al., 2019; Cavalheri et al., 2013a; J. Li et al., 2017; Sommer et al., 2018) reported postoperative exercise interventions, two reviews (Cavalheri & Granger, 2017; Rosero et al., 2019) reported preoperative exercise interventions, and one review

(Mainini et al., 2016) reported both postoperative and preoperative interventions. Regarding the type of exercises, three reviews (Cavalheri & Granger, 2017; Cavalheri et al., 2013b; Rosero et al., 2019) described the inclusion criteria for intervention as "aerobic exercise, resistance exercise, respiratory muscle training or any combination", one review (Cavalheri et al., 2019) described the intervention as "aerobic exercise, resistance exercise, or a combination", one review (Mainini et al., 2016) had no restriction on the type of exercise, and one review (J. Li et al., 2017) described the inclusion criteria for intervention as "aerobic exercise, resistance exercise, ambulation or mobility exercise" although it included one RMT study (Brocki, Andreasen, Langer, Souza, & Westerdahl, 2016).

4.2.4 Outcomes

Outcomes reported in the systematic reviews is shown in Appendix 3. The frequency of the outcomes reported in the seven systematic reviews is: exercise capacity (7/7, 100%), pulmonary function (6/7, 86%), HRQoL (6/7, 86%), PPCs (4/7, 57%), muscle strength (2/7, 29%), LOS (2/7, 29%), dyspnea (2/7, 29%) and fatigue (2/7, 29%).

4.3 Methodological quality of the included systematic reviews

The quality of the reviews is presented in Appendix 4. Three Cochrane reviews (Cavalheri et al., 2019; Cavalheri & Granger, 2017; Cavalheri et al., 2013a) were of high quality, two reviews (Mainini et al., 2016; Sommer et al., 2018) were of low quality, and two reviews (J. Li et al., 2017; Rosero et al., 2019) were of critically low quality.

4.4 Effects of interventions

The evidence from six meta-analyses (Cavalheri et al., 2019; Cavalheri & Granger, 2017; Cavalheri et al., 2013a; J. Li et al., 2017; Rosero et al., 2019; Sommer et al., 2018) was synthesized to show the effects of postoperative or preoperative exercise interventions.

4.4.1 Exercise capacity

The effects on exercise capacity were examined in all six meta-analyses (Table 2). Three reviews (Cavalheri et al., 2019; Cavalheri et al., 2013a; Sommer et al., 2018) reported significantly increased exercise capacity after postoperative exercise interventions. One review (J. Li et al., 2017) showed no significant difference in exercise capacity after postoperative exercise interventions but that review included a study that examined the effects of RMT alone without aerobic training or resistance training of the lower extremities (Brocki et al., 2016). The strongest evidence (high and moderate quality) comes from a high-quality meta-analysis which found a significant 57.26 (95% CI: 34.34-80.18) meters increase in 6MWD and 2.97 (95% CI: 1.93-4.02) mL/kg/min increase in VO_2 peak (Cavalheri et al., 2019).

Two reviews (Cavalheri & Granger, 2017; Rosero et al., 2019) reported statistically significant increases in exercise capacity (mean difference=18.23m, 95% CI: 8.50-27.96) after preoperative exercise interventions. However, the quality of the evidence was reported to be low (Cavalheri & Granger, 2017).

4.4.2 Pulmonary function

Five systematic reviews examined the effects on pulmonary function. (Cavalheri et al., 2019; Cavalheri & Granger, 2017; Cavalheri et al., 2013a; J. Li et al., 2017; Rosero et al., 2019) (Table 3). Three reviews of postoperative exercise studies (Cavalheri et al., 2019; Cavalheri et al., 2013a; J. Li et al., 2017) found no significant improvement on pulmonary function. Two reviews of preoperative exercise studies (Cavalheri & Granger, 2017; Rosero et al., 2019) showed no significant increase on FEV1, but findings were inconsistent with respect to FVC. One meta-analysis (Cavalheri & Granger, 2017) showed a statistically significant increase in FVC (mean difference=2.97 % predicted, 95% CI: 1.78-4.16), and another meta-analysis (Rosero et al., 2019) reported no significant difference.

4.4.3 PPCs

Four reviews examined the effects on PPCs (Cavalheri & Granger, 2017; Cavalheri et al., 2013a; J. Li et al., 2017; Rosero et al., 2019) (Table 4). Two reviews of postoperative exercise studies (Cavalheri et al., 2013a; J. Li et al., 2017) reported no significant difference. In contrast, two reviews of preoperative exercise studies (Cavalheri & Granger, 2017; Rosero et al., 2019) found statistically significant decreases on PPCs (relative risk ranged from 0.33 to 0.50).

4.4.4 HRQoL

Five systematic reviews (Cavalheri et al., 2019; Cavalheri et al., 2013a; J. Li et al., 2017; Rosero et al., 2019; Sommer et al., 2018) reported the effects on HRQoL (Table 5). Reviews of postoperative exercise studies reported no significant increase on overall HRQoL, mental, functional, or symptom components of HRQoL. Regarding the physical component of HRQoL, two reviews (Cavalheri et al., 2019; Sommer et al., 2018) found statistically significant increases in physical HRQoL, while one review (J. Li et al., 2017) reported no significant improvement after postoperative exercise interventions. The strongest evidence (low quality) comes from a high-quality meta-analysis which found 5.02 (95% CI: 2.30-7.73) points increases in physical component of SF-36. One review (Rosero et al., 2019) examined the impact on HRQoL and found no significant difference after preoperative exercise interventions.

4.4.5 Muscle strength

A high-quality meta-analysis (Cavalheri et al., 2019) found a significant improvement on quadriceps force (standardized mean difference = 0.75, 95% CI: 0.39-1.10) after postoperative exercise interventions, and the quality of the evidence was moderate (Table 6).

4.4.6 LOS

Two reviews examined the effects of preoperative exercise interventions on postoperative length of hospital stay (LOS) and reported statistically significant shorter LOS (Cavalheri & Granger, 2017; Rosero et al., 2019) (Table 6). The strongest evidence (low quality) comes from a high-quality meta-analysis which found significant 4.24 reduced days (95% CI: -5.43, -3.06) of hospital stay after preoperative exercise interventions.

4.4.7 Dyspnea

Two reviews reported the effects on dyspnea (Cavalheri et al., 2019; Rosero et al., 2019). A high-quality meta-analysis reported significantly less dyspnea after postoperative exercise interventions (standardized mean difference = -0.43, 95% CI: -0.81, -0.05), but the quality of evidence was assessed as very low (Cavalheri et al., 2019). Significantly less dyspnea was also found after preoperative exercise interventions (standardized mean difference =-0.30, 95% CI: -0.51, -0.10), and the quality of this meta-analysis is critically low (Rosero et al., 2019).

4.4.8 Fatigue

Two reviews examined the effects on fatigue (Cavalheri et al., 2019; Rosero et al., 2019), and no reviews found significant changes after postoperative (Cavalheri et al., 2019) or preoperative (Rosero et al., 2019) exercise interventions (Table 6).

5 DISCUSSIONS

5.1 Summary of the evidence

This overview appraised and summarized evidence from seven systematic reviews assessing the effects of postoperative/ preoperative exercise interventions on surgical lung cancer patients. To our knowledge, it is the first synthesis of systematic reviews to provide a broad perspective on evidence-based perioperative exercise interventions in lung cancer. The included systematic reviews covered the effects of both postoperative and preoperative interventions, and varied in inclusion criteria, methodological quality, and assessed outcomes.

Looking across both the methodological quality of reviews and the quality of evidence, there is high/moderate quality evidence supporting that postoperative exercise interventions increase exercise capacity and muscle strength. In addition, Low/very-low quality evidence suggests that postoperative exercise interventions may increase physical component of HRQoL and decrease dyspnea. These findings with low/very-low quality of evidence should be interpreted with caution until more evidence accumulates. With respect to the effects of preoperative exercise interventions, no robust conclusions could be drawn owing to the low quality of reviews and/or evidence. Low quality evidence suggests that preoperative exercise interventions may increase exercise capacity and pulmonary function, decrease risk of PPCs, LOS, and dyspnea. The differences in effectiveness between postoperative and preoperative exercise interventions could be a function of the duration of the exercise interventions

because the window of opportunity for preoperative excise training is much shorter than for postoperative exercise training.

It is important to identify whether the differences are clinically significant. We compared the significant mean differences of 6MWD, VO2 peak, FVC, and SF-36 to their minimal clinically important difference (MCID): (1) **6MWD.** The improvement in 6MWD after postoperative exercise interventions was 57.26 meters (Cavalheri et al., 2019), which exceeds the MCID of 42 meters for lung cancer patients (Granger, Holland, Gordon, & Denehy, 2015). However, the 18.23 meters increase in 6MWD after preoperative interventions does not meet the MCID. (2) **VO_2 peak.** The improvement in VO_2 peak (2.97 mL/kg/min) after postoperative exercise interventions may be clinically important, since 1 mL/kg/min increase in VO_2 peak is associated with a 4% reduction in all-cause mortality (Jones et al., 2010); (3) **FVC.** The improvement of 2.97% predict in FVC after preoperative exercise interventions may be clinical significant, since the MCIDs of FVC in other lung diseases are 2-6% (du Bois et al., 2011) and 3-5.3% (Kafaja et al., 2018); and (4) **SF-36.** The increase of 5.02 points in physical component of SF-36 (Cavalheri et al., 2019) after postoperative exercise interventions is considered to be clinically important as it exceeds the MCID of 3 to 5 points (Samsa, Edelman, Rothman, & Williams, 1999).

5.2 Implications for research

As shown in this overview, there exists a considerable body of evidence evaluating the effects of exercise interventions on surgical lung cancer patients. However, the quality of the evidence is low in terms of most outcomes due to risk of bias in primary studies and statistical heterogeneity in the meta-analyses. Some of the included systematic reviews have critical methodological limitations. Also, in reviews, outcomes are assessed regardless of the heterogeneity of exercise interventions, meaning that exercise interventions of different type and amount are combined to assess the outcomes. Rigorous RCTs and systematic reviews are needed to provide high-quality evidence for the specificity of exercise interventions, to more clearly delineate the specific effects of each type of exercise and to establish the appropriate volume for each type of exercise, with the goal of optimizing outcomes for surgical lung cancer patients.

5.3 Limitations

This overview of systematic review has several limitations. First, this overview did not include non-English or grey literatures; Second, there is overlap among reviews in terms of included RCTs, and some RCTs contribute to multiple systematic reviews. To interpret the results of this overview, we used figures to visualize the overlap; Third, we retrieved data from reviews instead of primary studies. The reviews could have several weaknesses in

methodological quality, which would affect the findings of this overview. Thus, we assessed the methodological quality of included reviews to show weaknesses. When interpreting the evidence, the methodological quality was considered.

6 CONCLUSIONS

This overview identified and summarized available evidence from seven systematic reviews about the effects of perioperative exercise interventions on lung cancer patients. There is high/moderate quality evidence that postoperative exercise interventions increase the exercise capacity and quadriceps force. Low/very-low quality evidence shows that postoperative exercise interventions may increase physical component of HRQoL and decease dyspnea. In addition, low quality evidence suggests that preoperative exercise interventions may increase exercise capacity and pulmonary function, decrease risk of PPCs, and reduce LOS. More high-quality research is required, to evaluate the effects of different types and amounts of exercises on health outcomes for surgical lung cancer patients.

7 RELEVANCE TO CLINICAL PRACTICE

This overview of systematic review synthesized evidence to inform practitioners and decision-makers about the effects of postoperative and preoperative exercise interventions for surgical lung cancer patients. The findings provide evidence to support the implementation of exercise interventions for surgical lung cancer patients.

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Table 1 Characteristics of included systematic reviews

Systematic reviews	Years searched	Primary studies (pre- or postoperative interventions)	Participants characteristics	Type of interventions	Synthesis method	Main conclusions
Cavalheri et al. 2013	Up to February 2013	3 RCTs (Postoperative)	178 NSCLC patients who had undergone resections of any type, with or without induction or adjuvant chemotherapy (mean age range 58~65 years)	Exercise training of any type (aerobic exercise, resistance exercise, respiratory muscle training or any combination) started within 12 months of lung resection	Meta-analysis	Exercise training could improve exercise capacity. No improvement is shown in HRQoL, lung function or strength of the leg muscles

Mainini et al. 2016	May 2013 to May 2016	6 RCTs (1 preoperative study + 5 postoperative studies)	Participants who underwent surgery for NSCLC: -preoperative trial: 40 participants (mean age 65 years) -postoperative trials: 374 participants (mean age 66 years)	Any supervised or unsupervised, inpatient or outpatient or home-based pulmonary rehabilitation exercise-training program	Narrative synthesis	Although results show improvement in exercise performance after preoperative pulmonary rehabilitation, it is not possible to identify the best preoperative intervention due to paucity of clinical trials in this area. Physical training programs differ in every postoperative study with conflicting results, so comparison is difficult. Current literature shows inconsistent results regarding preoperative or postoperative physical exercise in patients undergoing lung resection.
Cavalheri & Granger, 2017	Up to November 2016	5 RCTs (Preoperative)	167 patients who were scheduled to undergo lung resection for NSCLC (mean age ranged 54~72.5 years)	Preoperative exercise: a minimum of seven exercise sessions completed over a minimum of one week in the preoperative setting. The exercise sessions include aerobic, resistance or respiratory muscle training, or a combination.	Meta-analysis	Preoperative exercise training may reduce the risk of developing a postoperative pulmonary complication, the duration of intercostal catheter use, postoperative length of hospital stay and improve both post-intervention exercise capacity and lung function.
Li et al. 2017	Up to February 2017	6 RCTs (Postoperative)	438 patients with lung cancer who underwent lung resection	Various forms of exercise trainings, including endurance, resistance,	Meta-analysis	Insufficient evidence is available to support the efficacy of exercise training in patients with lung cancer after lung resection.

				strength, treadmill and walking		
Sommer et al. 2018	Up to February 2016	4 RCTs (Postoperative)	262 patients undergoing resection for NSCLC (mean age: over 60 years)	Postoperative exercise intervention (aerobic exercise, resistance exercise, ambulation or mobility exercise) initiated within 1 year after lung resection	Meta-analysis	Exercise has a small-to-moderate effect at short-term follow-up on exercise capacity and the physical component of health-related quality of life in patients operated for lung cancer. The long-term effects on exercise capacity are unknown. Early-initiated exercise programs (2 weeks post-operation) does not show an effect on exercise capacity.
Cavalheri et al. 2019	Up to February 2019	8 RCTs (Postoperative)	450 patients with NSCLC who underwent lung resection (mean age range 63~71 years)	Exercise training that included aerobic exercise, resistance exercise, or a combination of both, and started within 12 months of lung resection	Meta-analysis	Exercise interventions improve exercise capacity, physical HRQoL, capacity of the quadriceps muscle, and reduce dyspnea. The effects on the mental component of general HRQoL, disease-specific HRQoL, handgrip force, fatigue, and lung function are uncertain. There is insufficient evidence for improvements in the strength of breathing muscles or feelings of anxiety and depression.

Rosero et al. 2019	January 1970 to February 2018	10 RCTs (Preoperative)	676 patients with NSCLC underwent lung resection (mean age range 63~72.5 years)	Physical exercise intervention including aerobic exercise, strength training and inspiratory muscle training	meta-analysis	The results show intervention-induced improvement in walking endurance, peak exercise capacity, dyspnea, risk of hospitalization, and post-operative pulmonary complications.

Table 2 Summary of findings from the meta-analysis for the outcome of exercise capacity

Pre/postoperative group	Systematic reviews	Outcomes	Number of participants (studies)	Type of intervention	Anticipated absolute effects (95%CI)	Quality of evidence (GRADE)
Postoperative	Cavalheri et al. 2013	6MWD	139 (3 RCTs)	3(RT+AT)	**MD=50.4 [15.4, 85.2]m**	**Low**
	Li et al. 2017	6MWD	190 (4 RCTs)	3(RT+AT)+1(RMT)	No significant difference: WMD=23.50 [-22.04, 69.03]m	NR
	Cavalheri et al. 2019	6MWD	182 (5 RCTs)	5(RT+AT)	**MD=57.26 [34.34, 80.18]m**	**High**
		VO_2 peak	135 (4 RCTs)	2(RT+AT)+1(AT+RMT)+1(RT+AT+RMT)	**MD=2.97 [1.93, 4.02] mL/kg/min**	**Moderate**
	Sommer et al. 2018	6MWD (Follow-up 1 year)	56 (1 RCT)	1(RT+AT)	No significant difference: SMD=0.09 [-0.44, 0.61]	**Low**
		Exercise capacity (VO_2 peak and 6MWD, follow-up 12-20 weeks)	234 (4 RCTs)	3(RT+AT)+1(RT+AT+RMT)	**SMD=0.48 [0.04, 0.93]**	**Low**
Preoperative	Cavalheri & Granger, 2017	6MWD	81 (2 RCTs)	1(RT+AT+RMT)+1(AT+RMT)	**MD=18.23 [8.50, 27.96]m**	**Low**
	Rosero et al. 2019	6MWD	NR (6 RCTs)	3(AT+RMT)+2(RT+AT+RMT)+1(RT+AT)	**SMD=0.27 [0.11, 0.44]**	NR
		VO_2 peak	NR (3 RCTs)	1(AT)+1(RT+AT)+1(AT+RMT)	**SMD=0.78 [0.35,1.21]**	NR

Note. Quality of evidence was extracted from the reviews; NR indicates the number of participants or quality of evidence (GRADE) was not reported in the reviews. Abbreviation: 6MWD (six-minute-walk distance); VO_2 peak (peak oxygen consumption); RT (resistance training); AT (aerobic training); RMT

(respiratory muscle training); CI (confidence interval); MD (mean difference); SMD (standardized mean difference); WMD (weighted mean difference).

Table 3 Summary of findings from the meta-analysis for the outcome of pulmonary function

Pre/postoperative group	Systematic reviews	Outcomes	Number of participants (studies)	Type of intervention	Anticipated absolute effects (95%CI)	Quality of evidence (GRADE)
Postoperative	Cavalheri et al. 2013	FEV1	89 (2 RCTs)	2(RT+AT)	No significant difference: MD=-0.13 [-0.36, 0.11]L	**Low**
	Li et al. 2017	FEV1	89 (2 RCTs)	2(RT+AT)	No significant difference: WMD=0.03 [-0.19, 0.26]L	NR
	Cavalheri et al. 2019	FEV1	166 (4 RCTs)	3(RT+AT)+1(RT+AT+RMT)	No significant difference: SMD=-0.06 [-0.37, 0.25]	NR
		FVC	83 (2 RCTs)	2(RT+AT)	No significant difference: MD=-0.06 [-0.26, 0.15]L	NR
Preoperative	Cavalheri & Granger, 2017	FEV1	NR (3 RCTs)	2(AT+RMT)+1(RT+AT+RMT)	None of the three studies reported between group difference in FEV1	NR
		FVC	84 (2 RCTs)	1(RT+AT+RMT)+1(AT+RMT)	**MD=2.97 [1.78, 4.16] %predicted**	NR
	Rosero et al. 2019	FEV1	NR (3 RCTs)	3(AT+RMT)	No significant difference: SMD=0.13 [-0.14, 0.39]	NR
		FVC	NR (2 RCTs)	2(AT+RMT)	No significant difference: SMD=-0.08	NR

					[-0.38, 0.22]	

Note. Quality of evidence was extracted from the reviews; NR indicates the number of participants or quality of evidence (GRADE) was not reported in the reviews. Abbreviation: FVC (forced vital capacity); FEV1 (forced expiratory volume); RT (resistance training); AT (aerobic training); RMT (respiratory muscle training); CI (confidence interval); MD (mean difference); SMD (standardized mean difference); WMD (weighted mean difference).

Table 4 Summary of findings from the meta-analysis for the outcome of PPCs

Pre/postoperative group	Systematic reviews	Outcomes	Number of participants (studies)	Type of intervention	Relative effects (95%CI)	Quality of evidence (GRADE)
Postoperative	Li et al. 2017	POCs	250 (3 RCTs)	2(RT+AT)+1(RMT)	No significant difference: RR=0.79 [0.41, 1.53]	NR
	Cavalheri et al. 2013	PPCs	61 (1 RCT)	1(RT+AT)	one study reported two complications following lung resection in the intervention group and three in the control group	NR
Preoperative	Cavalheri & Granger, 2017	PPCs	158 (4 RCTs)	2(RT+AT+RMT)+2(AT+RMT)	**RR=0.33 [0.17, 0.61]**	**Low**
	Rosero et al. 2019	PPCs	NR (8 RCTs)	4(AT+RMT)+2(RT+AT+RMT)	**RR=0.50 [0.39, 0.66]**	NR

				+1(AT)+1(RT+AT)		

Note. Quality of evidence was extracted from the reviews; NR indicates the number of participants or quality of evidence (GRADE) was not reported in the reviews. Abbreviation: POCs (postoperative complications); PPCs (postoperative pulmonary complications); RT (resistance training); AT (aerobic training); RMT (respiratory muscle training); CI (confidence interval); RR (relative risk).

Table 5 Summary of findings from the meta-analysis for the outcome of HRQoL

Pre/postoperative group	Systematic reviews	Outcomes	Number of participants (studies)	Type of intervention	Anticipated absolute effects (95%CI)	Quality of evidence (GRADE)

Pre/postoperative group	Systematic reviews	Outcomes	Number of participants (studies)	Type of intervention	Anticipated absolute effects (95%CI)	Quality of evidence (GRADE)
Postoperative	Cavalheri et al. 2013	HRQoL (EORTC-C30 and SF-36 and SGRQ)	147 (3 RCTs)	3(RT+AT)	No significant difference: MD=0.17 [-0.16, 0.49]	**Low**
	Li et al. 2017	HRQoL physical component (SF-36)	206 (3RCTs)	2(RT+AT)+1(RT+AT+RMT)	No significant difference: WMD=2.41 [-5.20, 10.02]	NR
		HRQoL mental component (SF-36)	139 (2RCTs)	1(RT+AT)+1(RT+AT+RMT)	No significant difference: WMD=0.46 [-20.52, 19.61]	NR
	Sommer et al. 2018	HRQoL physical component (SF-36 and EORTC QLQ-C30, follow-up 12-20 weeks)	145 (3 RCTs)	2(RT+AT)+1(RT+AT+RMT)	**SMD=0.50 [0.19, 0.82]**	**Low**
		HRQoL physical component (SF-36, follow-up 1 year)	58 (1 RCT)	1(RT+AT)	No significant difference: SMD=-0.27 [-0.78, 0.25]	**Low**
		HRQoL mental component (SF-36, follow-up 10-20 weeks)	97 (2 RCTs)	1(RT+AT)+1(RT+AT+RMT)	No significant difference: SMD=0.53 [-0.78, 1.83]	**Very low**
		HRQoL mental component (SF-36, follow-up 1 year)	58 (1 RCT)	1(RT+AT)	No significant difference: SMD=-0.48 [-1.01, 0.04]	**Low**
	Cavalheri et al. 2019	HRQoL physical component (SF-36)	208 (4 RCTs)	3(RT+AT)+1(RT+AT+RMT)	**MD= 5.02 [2.30, 7.73]**	**Low**
		HRQoL mental component (SF-36)	208 (4 RCTs)	3(RT+AT)+1(RT+AT+RMT)	No significant difference: MD=-2.32 [-11.26, 6.62]	**Low**
		HRQoL (EORTC QLQ-C30)	111 (4 RCTs)	3(RT+AT)+1(AT+RMT)	No significant difference: MD=-0.14 [-7.24, 6.96]	NR
		HRQoL functional scales (EORTC QLQ-C30)	60 (2 RCTs)	2(RT+AT)	No significant difference: MD=-0.82 [CI -8.81, 7.17]	NR
		HRQoL physical function (EORTC QLQ-C30)	51 (2 RCTs)	1(RT+AT)+1(AT+RMT)	No significant difference: MD=2.05 [-3.50, 7.59]	NR

Pre/postoperative group	Systematic reviews	Outcomes	Number of participants (studies)	Type of intervention	Anticipated absolute effects (95%CI)	Quality of evidence (GRADE)
		HRQoL symptoms scales (EORTC QLQ-C30)	60 (2 RCTs)	2(RT+AT)	No significant difference: MD=-3.05 [-10.58, 4.47]	NR
Preoperative	Rosero et al. 2019	HRQoL	NR (4 RCTs)	3(AT+RMT)+1(RT+AT+RMT)	No significant difference: SMD = 0.20 [-0.02, 0.41]	NR

Note. Quality of evidence was extracted from the reviews; NR indicates the number of participants or quality of evidence (GRADE) was not reported in the reviews. Abbreviation: HRQoL (health-related quality of life); EORTC QLQ-C30 (The European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core Questionnaire 30); SF-36 (36-item Short Form Health Survey); SGRQ (Saint George Respiratory Questionnaire); RT (resistance training); AT (aerobic training); RMT (respiratory muscle training); MD (mean difference); SMD (standardized mean difference); WMD (weighted mean difference).

Table 6 Summary of findings from the meta-analysis for the outcome of muscle strength, LOS, dyspnea, and fatigue

Pre/postoperative group	Systematic reviews	Number of participants (studies)	Type of intervention	Anticipated absolute effects (95%CI)	Quality of evidence (GRADE)
Outcome: Muscle strength (Quadriceps force)					
Postoperative	Cavalheri et al. 2013	61 (1 RCT)	1(RT+AT)	one study demonstrated no between group difference in Quadriceps force	NR
	Cavalheri et al. 2019	133 (4 RCTs)	3(RT+AT)+1(RT+AT+RMT)	**SMD=0.75 [0.39, 1.10]**	**Moderate**
Outcome: Postoperative LOS					
Preoperative	Cavalheri & Granger, 2017	158 (4 RCTs)	2(RT+AT+RMT)+2(AT+RMT)	**MD=-4.24 [-5.43, -3.06] days**	**Low**

	Rosero et al. 2019	NR (6 RCTs)	4(AT+RMT)+`1(RT+AT+RMT)+1(RT+AT)	**SMD=-0.58 [-0.97, -0.20]**	NR
Outcome: Dyspnea					
Postoperative	Cavalheri et al. 2019	110 (3 RCTs)	1(RT+AT)+1(AT+RMT)+1(RT+AT+RMT)	**SMD=-0.43 [-0.81, -0.05]**	**Very low**
Preoperative	Rosero et al. 2019	NR (4 RCTs)	4(AT+RMT)	**SMD=-0.30 [-0.51, -0.10]**	NR
Outcome: Fatigue					
Postoperative	Cavalheri et al. 2019	68 (3 RCTs)	2(RT+AT)+1(AT+RMT)	No significant difference: SMD=-0.05 [-0.52, 0.43]	NR
Preoperative	Rosero et al. 2019	NR (2 RCTs)	2(AT+RMT)	No significant difference: SMD=-0.11 [-0.37, 0.15]	NR

Note. Quality of evidence was extracted from the reviews; NR indicates the number of participants or quality of evidence (GRADE) was not reported in the reviews. Abbreviation: RT (resistance training); AT (aerobic training); RMT (respiratory muscle training); MD (mean difference); SMD (standardized mean difference).

Figure 1 Flow diagram of study selection

Note. Brocki et al. 2010 and Brocki 2014 are duplicate publications; Cavalheri et al. 2015 and Cavalheri et al. 2017 are duplicate publications; Abbreviation: RT-resistance training; AT-aerobic training; RMT-respiratory muscle training.

Figure 2 Citation matrix of RCTs included in the systematic reviews (**postoperative group**)

Note. Morano et al 2013 and Morano et al 2014 shared the same intervention design but reported different outcomes; Abbreviation: RT-resistance training; AT-aerobic training; RMT-respiratory muscle training.

Figure 3 Citation matrix of RCTs included in the systematic reviews (**preoperative group**)

Appendix 1: Search Strategy

PubMed

1. Exercise[Mesh]
2. Exercise therapy[Mesh]
3. Physical therapy modalities[Mesh]
4. Rehabilitation[Mesh]
5. exercise*[Title/Abstract]
6. physical training[Title/Abstract]
7. aerobic training[Title/Abstract]
8. resistance training[Title/Abstract]
9. strength training[Title/Abstract]
10. endurance training[Title/Abstract]
11. muscle training[Title/Abstract]
12. respiratory training[Title/Abstract]
13. respiration training[Title/Abstract]
14. inspiratory training[Title/Abstract]
15. balance training[Title/Abstract]
16. high-intensity interval training[Title/Abstract]
17. high intensity interval training[Title/Abstract]
18. high-intensity training[Title/Abstract]
19. HIIT[Title/Abstract]
20. physical activit*[Title/Abstract]
21. physical therap*[Title/Abstract]
22. physical education[Title/Abstract]
23. physical condition*[Title/Abstract]
24. physiotherap*[Title/Abstract]
25. rehabilitat*[Title/Abstract]
26. prehabilitat*[Title/Abstract]
27. walk*[Title/Abstract]
28. climb*[Title/Abstract]
29. bicycl*[Title/Abstract]
30. treadmill[Title/Abstract]
31. yoga[Title/Abstract]
32. Tai Chi[Title/Abstract]
33. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32

34. General Surgery[Mesh]
35. Surgical Procedures, Operative[Mesh]
36. surgery[Subheading]
37. Thoracic Surgery[Mesh]
38. Thoracic Surgery, Video-Assisted[Mesh]
39. surg*[Title/Abstract]
40. presurg*[Title/Abstract]
41. postsurg*[Title/Abstract]
42. operati*[Title/Abstract]
43. operable[Title/Abstract]
44. operated[Title/Abstract]
45. preoperat*[Title/Abstract]
46. postoperat*[Title/Abstract]
47. perioperat*[Title/Abstract]
48. resect*[Title/Abstract]
49. lobectom*[Title/Abstract]
50. bilobectom*[Title/Abstract]
51. segmentectom*[Title/Abstract]
52. pneumonectom*[Title/Abstract]
53. thoracotom*[Title/Abstract]
54. VATS*[Title/Abstract]
55. #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54
56. Lung Neoplasms[Mesh]
57. lung cancer*[Title/Abstract]
58. pulmonary cancer*[Title/Abstract]
59. lung neoplasm*[Title/Abstract]
60. pulmonary neoplasm*[Title/Abstract]
61. NSCLC[Title/Abstract]
62. non-small cell[Title/Abstract]
63. non small cell[Title/Abstract]
64. nonsmall cell[Title/Abstract]
65. non-small-cell[Title/Abstract]
66. lung carcinoma*[Title/Abstract]
67. lung tumor*[Title/Abstract]
68. lung tumour*[Title/Abstract]
69. lung malignancy[Title/Abstract]
70. #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR

#67 OR #68 OR #69

71. #33 AND #55 AND #70

72. Filters: Article Types: Meta-analysis, Systematic Reviews

CINHAL

1. MH "Exercise+"
2. MH "Physical Activity"
3. MH "Exercise Physiology+"
4. MH "Rehabilitation+"
5. TI AB exercise*
6. TI AB physical training
7. TI AB aerobic training
8. TI AB resistance training
9. TI AB strength training
10. TI AB endurance training
11. TI AB muscle training
12. TI AB respiratory training
13. TI AB respiration training
14. TI AB inspiratory training
15. TI AB balance training
16. TI AB high-intensity interval training
17. TI AB high intensity interval training
18. TI AB high-intensity training
19. TI AB HIIT
20. TI AB physical activit*
21. TI AB physical therap*
22. TI AB physical education
23. TI AB physical condition*
24. TI AB physiotherap*
25. TI AB rehabilitat*
26. TI AB prehabilitat*
27. TI AB walk*
28. TI AB climb*
29. TI AB bicycl*
30. TI AB treadmill
31. TI AB yoga
32. TI AB Tai Chi
33. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32

34. MH "Surgery, Operative+"
35. TI AB surg*
36. TI AB presurg*
37. TI AB postsurg*
38. TI AB operati*
39. TI AB operable
40. TI AB operated
41. TI AB preoperat*
42. TI AB postoperat*
43. TI AB perioperat*
44. TI AB resect*
45. TI AB lobectom*
46. TI AB bilobectom*
47. TI AB segmentectom*
48. TI AB pneumonectom*
49. TI AB thoracotom*
50. TI AB VATS*
51. #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50
52. MH "Lung Neoplasms+"
53. TI AB lung cancer*
54. TI AB pulmonary cancer*
55. TI AB lung neoplasm
56. TI AB pulmonary neoplasm*
57. TI AB NSCLC
58. TI AB non-small cell
59. TI AB non small cell
60. TI AB nonsmall cell
61. TI AB non-small-cell
62. TI AB lung carcinoma*
63. TI AB lung tumor*
64. TI AB lung tumour*
65. TI AB lung malignancy
66. #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65
67. #33 AND #51 AND #66

68. Filters: Publication Type: Meta Analysis, Meta Synthesis, Systematic Review

Embase

1. exercise exp
2. physical activity exp
3. kinesiotherapy exp
4. physiotherapy exp
5. training exp
6. rehabilitation exp
7. exercis* ti,ab,kw
8. physical training ti,ab,kw
9. aerobic training ti,ab,kw
10. resistance training ti,ab,kw
11. strength training ti,ab,kw
12. endurance training ti,ab,kw
13. muscle training ti,ab,kw
14. respiratory training ti,ab,kw
15. respiration training ti,ab,kw
16. inspiratory training ti,ab,kw
17. balance training ti,ab,kw
18. high-intensity interval training ti,ab,kw
19. high intensity interval training ti,ab,kw
20. high-intensity training ti,ab,kw
21. hiit ti,ab,kw
22. physical activit* ti,ab,kw
23. physical therap* ti,ab,kw
24. physical education ti,ab,kw
25. physical condition* ti,ab,kw
26. physiotherap* ti,ab,kw
27. rehabilitat* ti,ab,kw
28. prehabilitat* ti,ab,kw
29. walk* ti,ab,kw
30. climb* ti,ab,kw
31. bicycl* ti,ab,kw
32. treadmill ti,ab,kw
33. yoga ti,ab,kw
34. tai chi ti,ab,kw
35. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34

36. surgery exp
37. surg* ti,ab,kw
38. presurg* ti,ab,kw
39. postsurg* ti,ab,kw
40. operati* ti,ab,kw
41. operable ti,ab,kw
42. operated ti,ab,kw
43. preoperat* ti,ab,kw
44. postoperat* ti,ab,kw
45. perioperat* ti,ab,kw
46. resect* ti,ab,kw
47. lobectom* ti,ab,kw
48. bilobectom* ti,ab,kw
49. segmentectom* ti,ab,kw
50. pneumonectom* ti,ab,kw
51. thoracotom* ti,ab,kw
52. vats ti,ab,kw
53. #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52
54. lung cancer exp
55. lung cancer* ti,ab,kw
56. pulmonary cancer* ti,ab,kw
57. lung neoplasm* ti,ab,kw
58. pulmonary neoplasm* ti,ab,kw
59. nsclc ti,ab,kw
60. non-small cell ti,ab,kw
61. nonsmall cell ti,ab,kw
62. non small cell ti,ab,kw
63. lung carcinoma* ti,ab,kw
64. lung tumor* ti,ab,kw
65. lung tumour* ti,ab,kw
66. lung malignancy ti,ab,kw
67. #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66
68. #35 AND #53 AND #67 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

Cochrane Library

1. MeSH descriptor: [Exercise] explode all trees
2. MeSH descriptor: [Exercise Therapy] explode all trees
3. MeSH descriptor: [Physical Therapy Modalities] explode all trees
4. MeSH descriptor: [Rehabilitation] explode all trees
7. exercis* ti,ab,kw
8. physical training ti,ab,kw
9. aerobic training ti,ab,kw
10. resistance training ti,ab,kw
11. strength training ti,ab,kw
12. endurance training ti,ab,kw
13. muscle training ti,ab,kw
14. respiratory training ti,ab,kw
15. respiration training ti,ab,kw
16. inspiratory training ti,ab,kw
17. balance training ti,ab,kw
18. high-intensity interval training ti,ab,kw
19. high intensity interval training ti,ab,kw
20. high-intensity training ti,ab,kw
21. HIIT ti,ab,kw
22. physical activit* ti,ab,kw
23. physical therap* ti,ab,kw
24. physical education ti,ab,kw
25. physical condition* ti,ab,kw
26. physiotherap* ti,ab,kw
27. rehabilitat* ti,ab,kw
28. prehabilitat* ti,ab,kw
29. walk* ti,ab,kw
30. climb* ti,ab,kw
31. bicycl* ti,ab,kw
32. treadmill ti,ab,kw
33. yoga ti,ab,kw
34. Tai Chi ti,ab,kw
35. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34
36. MeSH descriptor: [General Surgery] explode all trees

37. MeSH descriptor: [Thoracic Surgery] explode all trees
38. MeSH descriptor: [Thoracic Surgery, Video-Assisted] explode all trees
39. surg* ti,ab,kw
40. presurg* ti,ab,kw
41. postsurg* ti,ab,kw
42. operati* ti,ab,kw
43. operable ti,ab,kw
44. operated ti,ab,kw
45. preoperat* ti,ab,kw
46. postoperat* ti,ab,kw
47. perioperat* ti,ab,kw
48. resect* ti,ab,kw
49. lobectom* ti,ab,kw
50. bilobectom* ti,ab,kw
51. segmentectom* ti,ab,kw
52. pneumonectom* ti,ab,kw
53. thoracotom* ti,ab,kw
54. VATS ti,ab,kw
55. #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54
56. MeSH descriptor: [Lung Neoplasms] explode all trees
57. lung cancer* ti,ab,kw
58. pulmonary cancer* ti,ab,kw
59. lung neoplasm* ti,ab,kw
60. pulmonary neoplasm* ti,ab,kw
61. nsclc ti,ab,kw
62. non-small cell ti,ab,kw
63. nonsmall cell ti,ab,kw
64. non small cell ti,ab,kw
65. lung carcinoma* ti,ab,kw
66. lung tumor* ti,ab,kw
67. lung tumour* ti,ab,kw
68. lung malignancy ti,ab,kw
69. #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68
70. #35 AND #55 AND #69
71. Filter: Cochrane Reviews

SPORTDiscus

1. DE REHABILITATION
2. DE EXERCISE
3. DE EXERCISE physiology
4. DE EXERCISE & psychology
5. DE EXERCISE therapy
6. DE CLINICAL exercise physiology
7. DE TREADMILL exercise
8. DE HIGH-intensity interval training
9. DE YOGA
10. DE RESISTANCE training
11. DE PHYSICAL training & conditioning
12. DE AEROBIC exercises
13. DE PHYSICAL therapy
14. DE PHYSICAL activity
15. DE CYCLING
16. TI AB KW exercise*
17. TI AB KW physical training
18. TI AB KW aerobic training
19. TI AB KW resistance training
20. TI AB KW strength training
21. TI AB KW endurance training
22. TI AB KW muscle training
23. TI AB KW respiratory training
24. TI AB KW respiration training
25. TI AB KW inspiratory training
26. TI AB KW balance training
27. TI AB KW high-intensity interval training
28. TI AB KW high intensity interval training
29. TI AB KW high-intensity training
30. TI AB KW HIIT
31. TI AB KW physical activit*
32. TI AB KW physical therap*
33. TI AB KW physical education
34. TI AB KW physical condition*
35. TI AB physiotherap*
36. TI AB KW rehabilitat*
37. TI AB KW prehabilitat*

38. TI AB KW walk*

39. TI AB KW climb*

40. TI AB KW bicycl*

41. TI AB KW treadmill

42. TI AB KW yoga

43. TI AB KW Tai Chi

44. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43

45. DE SURGERY

46. TI AB KW surg*

47. TI AB KW presurg*

48. TI AB KW postsurg*

49. TI AB KW operati*

50. TI AB KW operable

51. TI AB KW operated

52. TI AB KW preoperat*

53. TI AB KW postoperat*

54. TI AB KW perioperat*

55. TI AB KW resect*

56. TI AB KW lobectom*

57. TI AB KW bilobectom*

58. TI AB KW segmentectom*

59. TI AB KW pneumonectom*

60. TI AB KW thoracotom*

61. TI AB KW VATS*

62. #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61

63. DE LUNG cancer

64. TI AB KW lung cancer*

65. TI AB KW pulmonary cancer*

66. TI AB KW lung neoplasm

67. TI AB KW pulmonary neoplasm*

68. TI AB KW NSCLC

69. TI AB KW non-small cell

70. TI AB KW non small cell

71. TI AB KW nonsmall cell

72. TI AB KW non-small-cell

73. TI AB KW lung carcinoma*

74. TI AB KW lung tumor*

75. TI AB KW lung tumour*

76. TI AB KW lung malignancy

77. #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76

78. #44 AND #62 AND #77

PEDro

Filters: Title/abstract: lung cancer; Method: systematic review

Appendix 2 Excluded articles

Author, year	Title	Reasons for exclusion
Archer et al., 2019	The effectiveness of preoperative pulmonary rehabilitation in reducing postoperative pulmonary complications in lung cancer: a systematic review and meta-analysis	Poster presentation abstract, not full-text article
Batarseh et al., 2019	Preoperative respiratory muscle training for lung cancer patients scheduled for surgical resection (meta-analysis)	Electronic poster, not full-text article
Crandall et al., 2014	Exercise intervention for patients surgically treated for Non-Small Cell Lung Cancer (NSCLC): a systematic review	Included non-RCTs
Driessen et al., 2017	Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: A systematic review	Included studies that involves participants who didn't undergo surgery (chemotherapy or radiation)
Faithfull et al., 2019	Prehabilitation for adults diagnosed with cancer: a systematic review of long-term physical function,	Included studies that involves participants

Author, year	Title	Reasons for exclusion
	nutrition and patient-reported outcomes	without lung cancer
García et al., 2013	Effect of pre-operative pulmonary rehabilitation in lung cancer patients	Non-English review
Granger et al., 2011	Exercise intervention to improve exercise capacity and health related quality of life for patients with Non-small cell lung cancer: a systematic review	Included studies that involves participants who didn't undergo surgery
Harman et al., 2018	Effects of an Exercise Intervention on Lung Cancer Patients Who Have Undergone a Lobectomy	Abstract, not full-text article
Heywood et al., 2017	Safety and feasibility of exercise interventions in patients with advanced cancer: a systematic review	Included studies that involves participants who didn't undergo surgery or without lung cancer
Jones et al., 2013	A review of enhanced recovery for thoracic anaesthesia and surgery	Included studies with other than exercise intervention
Li et al., 2019	Impact of preoperative exercise therapy on surgical outcomes in lung cancer patients with or without COPD: a systematic review and meta-analysis	Included non-RCTs
Liu et al., 2013	Breathing exercises improve post-operative pulmonary function and quality of life in patients with lung cancer: A meta-analysis	Included non-RCTs
Liu et al., 2019	Effects of Breathing Exercises on Patients with Lung Cancer	Included studies that involves participants who didn't undergo surgery
Makwana et al., 2016	Effect of exercise training on subjective and objective outcome in lung cancer	Included studies that involves participants who didn't undergo surgery
Nan et al., 2018	The Impact of Preoperative Exercise Therapy on the Surgical Outcomes of Patients with Lung Cancer and COPD: A Systematic Review and Meta-Analysis	Abstract, not full-text article
Ni et al., 2017	Exercise Training for Patients Pre- and Postsurgically Treated for Non-Small Cell Lung Cancer: A Systematic Review and Meta-analysis	Included non-RCTs
Piraux et al, 2018	Effects of preoperative combined aerobic and resistance exercise training in cancer patients undergoing tumour resection surgery: A systematic review of randomised trials	Included studies that involves participants without lung cancer
Pouwels et al.,	Preoperative exercise therapy in lung surgery patients:	Included non-RCTs

Author, year	Title	Reasons for exclusion
2015	A systematic review	
Rodrigues-Larrad et al., 2014	Perioperative physiotherapy in patients undergoing lung cancer resection	Included studies with other than exercise intervention
Schmidt-Hansen et al., 2013	The effect of preoperative smoking cessation or preoperative pulmonary rehabilitation on outcomes after lung cancer surgery: a systematic review	Included studies with other than exercise intervention
Sebio Garcia et al., 2016	Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: A systematic review and meta-analysis	Included non-RCTs
Skinner et al., 2017	Intensive preoperative rehabilitation improves functional capacity and postoperative hospital length of stay in elderly patients with lung cancer	Abstract, not full-text article
Steffens et al., 2018	Preoperative exercise halves the postoperative complication rate in patients with lung cancer: a systematic review of the effect of exercise on complications, length of stay and quality of life in patients with cancer	Included studies that involves participants without lung cancer
Wang et al., 2019	Impact of breathing exercises in subjects with lung cancer undergoing surgical resection: a systematic review and meta-analysis	Included studies with other than exercise intervention

Appendix 3 Outcomes reported in the systematic reviews

Systematic reviews	Exercise capacity	Pulmonary function	HRQoL	PPCs	Muscle strength	LOS	Dyspnea	Fatigue	The duration of intercostal catheter use	Postoperative mortality	Adverse event	Feelings of anxiety and depression
Cavalheri et al. 2013	✔	✔	✔	✔	✔							
Mainini et al. 2016	✔	✔	✔									
Cavalheri & Granger, 2017	✔	✔		✔		✔			✔	✔		
Li et al. 2017	✔	✔	✔	✔								
Sommer et al. 2018	✔		✔									
Cavalheri et al. 2019	✔	✔	✔		✔		✔	✔			✔	✔
Rosero et al. 2019	✔	✔	✔	✔		✔	✔	✔				

Note: HRQoL (health-related quality of life); PPCs (postoperative pulmonary complications); LOS (length of hospital stay)

Appendix 4 Methodological quality of systematic reviews assessed by AMSTAR 2

Systematic reviews	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall rating
Cavalheri et al. 2013	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Mainini et al. 2016	No	No	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	No	N/A	Yes	Low
Cavalheri & Granger, 2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Li et al. 2017	Yes	No	No	Partial yes	No	Yes	No	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Sommer et al. 2018	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Cavalheri et al. 2019	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Rosero et al. 2019	No	No	No	Partial yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Critically low

Q1. Did the research questions and inclusion criteria for the review include the components of PICO? Q2. 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? Q3. Did the review authors explain their selection of the study designs for inclusion in the review? Q4. Did the review authors use a comprehensive literature search strategy? Q5. Did the review authors perform study selection in duplicate? Q6. Did the review authors perform data extraction in duplicate? Q7. Did the review authors provide a list of excluded studies and justify the exclusions? Q8. Did the review authors describe the included studies in adequate detail? Q9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Q10. Did the review authors report on the sources of funding for the studies included in the review? Q11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? Q12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Q13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review? Q14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Q15. 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? Q16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

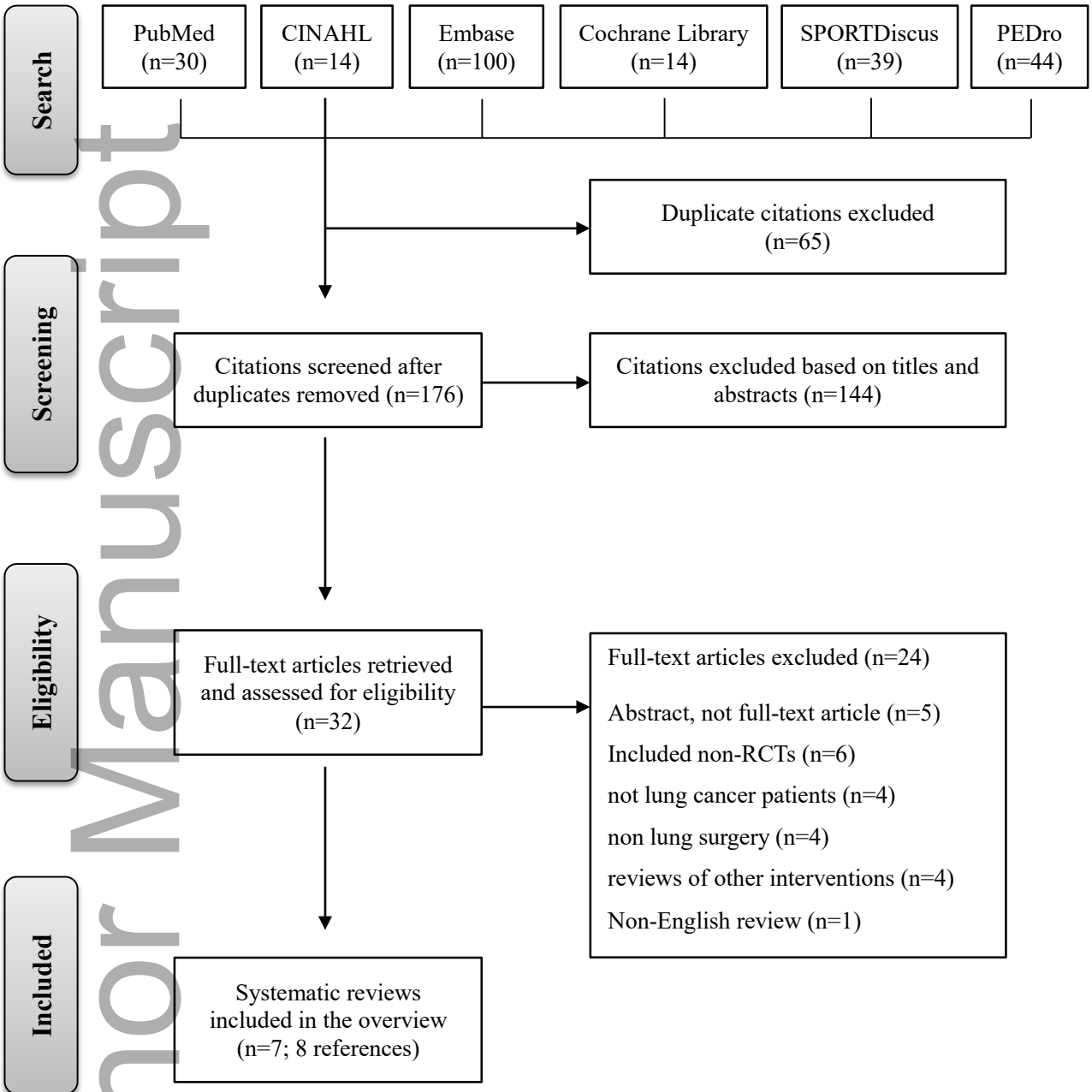

Figure 1 Flow diagram of study selection

Systematic reviews	Reported search range	Brocki et al. 2010	Arbane et al. 2011	Stigt et al. 2013	Arbane at al. 2014	Brocki et al. 2014	Brocki et al., 2016	Salhi et al. 2015	Edvardsen et al. 2015	Cavalheri et al. 2015	Hoffman et al. 2016	Cavalheri et al. 2017	Massaggi-Sartor et al. 2018
Cavalheri et al. 2013	Up to February 2013	RT+AT	RT+AT	RT+AT									
Mainini et al. 2016	May 2013 to May 2016				RT+AT	RT+AT			RT+AT+RMT	RT+AT	AT		
Li et al. 2017	Up to February 2017	RT+AT	RT+AT	RT+AT	RT+AT		RMT		RT+AT+RMT				
Sommer et al. 2018	Up to February 2016		RT+AT			RT+AT		RT+AT	RT+AT+RMT				
Cavalheri et al. 2019	Up to February 2019		RT+AT	RT+AT	RT+AT	RT+AT		RT+AT	RT+AT+RMT			RT+AT	AT+RMT

Note. Brocki et al. 2010 and Brocki 2014 are duplicate publications; Cavalheri et al. 2015 and Cavalheri et al. 2017 are duplicate publications; Abbreviation: RT-resistance training; AT-aerobic training; RMT-respiratory muscle training.

Figure 2 Citation matrix of RCTs included in the systematic reviews (**postoperative group**)

Systematic reviews	Reported search range	Benzo et al., 2011	Pehlivan et al. 2011	Stefanelli et al. 2013	Morano et al.2013	Morano et al. 2014	Lai et al. 2016	Lai et al. 2017	Sebio Garcia et al. 2017	Karenovics et al. 2017	Licker et al. 2017	Huang et al. 2017	Lai, Huang, et al. 2017	Lai Su et al. 2017
Mainini et al. 2016	May 2013 to May 2016			AT+RMT										
Cavalheri & Granger, 2017	Up to November 2016	RT+AT+ RMT	AT+RMT	AT+RMT	RT+AT+ RMT			AT+RMT						
Rosero et al. 2019	January 1970 to February 2018	RT+AT+ RMT		AT+RMT		RT+AT+ RMT	AT+RMT		RT+AT+ RMT	AT	RT+AT	AT+RMT	AT+RMT	AT+RMT

Note. Morano et al 2013 and Morano et al 2014 shared the same intervention design but reported different outcomes; Abbreviation: RT-resistance training; AT-aerobic training; RMT-respiratory muscle training.

Figure 3 Citation matrix of RCTs included in the systematic reviews (**preoperative group**)