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Review Article

Evidence base for exercise prehabilitation suggests favourable outcomes for patients undergoing surgery for non-small cell lung cancer despite being of low therapeutic quality: a systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this systematic review was to evaluate whether exercise prehabilitation programs reduce postoperative complications, postoperative mortality, and length of hospital stay (LoS) in patients undergoing surgery for non-small cell lung cancer (NSCLC), thereby accounting for the quality of the physical exercise program.

Methods: Two reviewers independently selected randomized controlled trials (RCTs) and observational studies and assessed them for methodological quality and therapeutic quality of the exercise prehabilitation program (i-CONTENT tool). Eligible studies included patients with NSCLC performing exercise prehabilitation and reported the occurrence of 90-day postoperative complications, postoperative mortality, and LoS. Meta-analyses were performed and the certainty of the evidence was graded (Grading of Recommendations Assessment, Development and Evaluation (GRADE)) for each outcome.

Results: Sixteen studies, comprising 2,096 patients, were included. Pooled analyses of RCTs and observational studies showed that prehabilitation reduces postoperative pulmonary complications (OR 0.45), postoperative severe complications (OR 0.51), and LoS (mean difference −2.46 days), but not postoperative mortality (OR 1.11). The certainty of evidence was very low to moderate for all outcomes. Risk of ineffectiveness of the prehabilitation program was high in half of the studies due to an inadequate reporting of the dosage of the exercise program, inadequate type and timing of the outcome assessment, and low adherence.

Conclusion: Although risk of ineffectiveness was high for half of the prehabilitation programs and certainty of evidence was very low to moderate, prehabilitation seems to result in a reduction of postoperative pulmonary and severe complications, as well as LoS in patients undergoing surgery for NSCLC.

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1. Introduction

Lung cancer is the most common diagnosed cancer globally [1]. Surgery is advised for patients with resectable early stage non-small cell lung cancer (NSCLC) [2,3]. In the Netherlands, approximately 35% of all patients with NSCLC who underwent surgery in 2018, developed a postoperative complication, of which 20% within 30 days postoperatively [4]. The 30-day mortality rate is 2% [4]. Postoperative complications are most common in older patients (≥70 years) who have a low physical fitness [5,6], are physically inactive, malnourished, and have tobacco-related comorbidity [7–9]. Especially patients with a high risk for adverse postoperative outcomes might benefit from preoperative interventions such as exercise prehabilitation.

Exercise prehabilitation in patients undergoing lung resection aims to improve a patient's health, including aerobic fitness level in the period between diagnosis and surgery in order to postoperatively reduce the risk for complications and reduce the length of hospital stay (LoS) [10]. Recent systematic reviews in patients with NSCLC reported that exercise prehabilitation may be effective in reducing complications and LoS, but with inconsistent results [11–15]. A better assessment of the quality of prehabilitation programs could potentially contribute to the certainty of evidence regarding the merit of prehabilitation to reduce postoperative complications, postoperative mortality, and LoS in patients undergoing surgery for NSCLC. In addition, there are no guidelines concerning the optimal content of an exercise prehabilitation program for preoperatively improving physical fitness to subsequently improve postoperative outcomes in patients with NSCLC. Finally, observational studies are frequently left out of systematic reviews while these studies might actually provide an additional perspective to randomized controlled trials (RCTs) [16].

Therefore, the aim of this systematic review was to evaluate whether exercise prehabilitation programs reduce postoperative complications, postoperative mortality, and LoS in patients undergoing surgery for NSCLC, thereby accounting for the quality of the physical exercise program. To do so, we employed the international Consensus on Therapeutic Exercise aNd Training (i-CONTENT) tool in this systematic review to help understand, structure, and value the potential of preoperative physical exercises to improve the outcomes of NSCLC surgery [17].

2. Methods

A systematic review of the literature was performed according to the Cochrane guidelines for systematic reviews [18] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. The study protocol was registered at PROSPERO (CRD42021244223). Studies in which postoperative complications, postoperative mortality, and LoS after exercise prehabilitation was compared with usual care or between different frequencies of sessions in prehabilitation programs were selected.

2.1. Literature search

MEDLINE, Embase, and CINAHL databases were searched for eligible studies published up to December 2021. In addition, reference lists from retrieved studies were screened. The search strategy, which has been set up and optimized by the researchers and a librarian, contained a combination of controlled vocabulary (e.g., MeSH or EMTREE) and keyword terms and phrases searched in titles, abstracts, and key word fields, as appropriate. Key terms included in the search strategy are "non-small cell lung cancer" and "lung surgery", "prehabilitation", "postoperative complications", "postoperative mortality", and "length of hospital stay". Combinations of text words of the literature search are shown in supplementary file 1.

2.2. Study selection

RCTs and observational studies in patients aged ≥18 years, with ≥95% patients with NSCLC undergoing elective surgery were included. The exercise prehabilitation program could be unimodal or multimodal, but should at least include physical exercise training that aimed to preoperatively improve physical fitness. Usual care groups consisted of patients who either received no intervention (usual care) or a comparison intervention (e.g., a different preoperative physical exercise program). Outcome measures of the studies should at least include postoperative complications, postoperative mortality, and/or LoS. Physical exercise training was defined as a structured form of either aerobic, interval, and/or resistance exercises, based upon validated measurements describing training intensity (e.g., heart rate, rating of perceived exertion, work rate), eventually supplemented with breathing exercises. Studies only involving health promotion initiatives without a structured professional follow-up were excluded in this review. Conference papers, case series, case reports, opinion studies (non-original research), systematic reviews, and studies not published in English were also excluded. Two reviewers (M.V. and R.F.) independently screened titles and abstracts of retrieved records using Rayyan software [20] based on inclusion criteria and exclusion criteria. Thereafter, assessment of full-text articles according to eligibility criteria was performed by the two reviewers (M.V. and R.F.) independently. Any disagreements between reviewers were resolved through discussion and consensus. When no consensus was reached, a third party acted as an adjudicator (M.J.).

2.3. Data extraction

One reviewer (M.V.) extracted data from the included studies by using a standardized extraction form, after which another reviewer (R.F.) checked the extracted data. Extracted data included first author, publication year, number of participants, patient characteristics of the intervention group and control group, disease stage, age (mean; range), sex, type of surgery, and comorbidity. Items of the i-CONTENT tool were also described in terms of content. Characteristics of the physical exercise training program were extracted using the training frequency, training intensity, training time, training type, training volume, and training progression principles (FITT-VP) [21,22] of the prescribed physical exercises of the intervention group and control group. Differences in postoperative pulmonary complications, any complications (Clavien-Dindo grade I-IV), severe complications (Clavien-Dindo grade II-IV), and postoperative mortality (Clavien-Dindo grade V) within 90 days, and LoS between the intervention group and usual care group were evaluated.

2.4. Methodological quality

The two reviewers (M.V. and R.F.) independently assessed the methodological quality of included studies by means of the Cochrane risk of bias tool for randomized controlled trials II (RoB2) [18] and observational studies of interventions for observational studies (ROBINS-I) tool [23]. The RoB2 reviews six domains, and the ROBINS-I tool reviews seven domains. In the RoB2 tool, each item was rated as 'high', 'low', or 'some'. In the ROBINS-I tool, each item was rated as 'low', 'moderate', 'serious', 'critical', or 'no information'. Risk of bias of the included studies was assessed according to the outcomes postoperative complications, postoperative

mortality, and LoS. No global score was given, but the score per study was given based on the relevant outcomes for this systematic review. Discrepancies were resolved by consensus. If no consensus was reached, a third person acted as an adjudicator (M.J.).

2.5. Therapeutic quality

Therapeutic quality of the physical exercise training module of the prehabilitation programs was assessed independently by two reviewers (M.V. and R.F.) using the i-CONTENT tool [17]. Using the i-CONTENT tool, the following eight items were substantively described: 1) patient selection, 2) dosage of the exercise program, 3) type of the exercise program, 4) qualified supervisor, 5) type and timing of outcome assessment, 6) safety of the exercise program, and 7) adherence to the exercise program. To ensure a uniform assessment of the assessors, basic guidelines for the application and interpretation were composed for each item of the i-CONTENT (Table 1) by all authors. The original authors of the i-CONTENT did not provide an aggregated cut-off for which studies could be considered of low, some, or high risk for ineffectiveness. A rating scheme was arbitrarily developed for this study (see supplementary file 2) to determine low and high risk for ineffectiveness per study.

2.6. Data synthesis

The effects of prehabilitation versus usual care on postoperative complications, postoperative mortality, and LoS, were analysed using random-effects meta-analysis models. Meta-analyses were performed separately for RCTs and observational studies [18]. For postoperative complications and postoperative mortality, the odds ratios (OR) and 95% CI were calculated using a Mantel-Haenszel model. For LoS, the mean differences (MD) and 95% confidence intervals (CI) were taken from the original studies. Meta-analyses were conducted using Review Manager (version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A P-value <0.05 was considered statistically significant. Heterogeneity was evaluated using the I^2 statistic. Results were classified as follows: 0%–40% indicates low heterogeneity, 30%–60% indicates moderate heterogeneity, 50%–90% indicates substantial heterogeneity, and 75%–100% indicates considerable heterogeneity [24].

2.7. Certainty of evidence

The two reviewers (M.V. and R.F.) independently rated the certainty of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [24]. In order to interpret the findings, a GRADE summary of findings table was created in which the following outcomes were included: 1) pulmonary complications, 2) any complications, 3) severe complications, 4) postoperative mortality, and 5) LoS. The certainty of evidence was assessed for each outcome by downgrading based on the GRADE criteria for RCTs and upgrading for observational studies. Furthermore, the current systematic review aimed to integrate the overall risk of ineffectiveness scores into the GRADE approach. Within the GRADE approach, risk of ineffectiveness of exercise prehabilitation programs was added under 'other considerations'. It was devised after consensus between the researchers that if at least 80% of the studies for a certain outcome measure had an overall risk of ineffectiveness of low or some, the GRADE level of certainty was upgraded by one level.

3. Results

3.1. Study characteristics

A total of 1,299 records were identified with the systematic search. After removing duplicates, 1,052 unique records were screened on title and abstract after which 47 full text articles were reviewed. Reasons for exclusion are described in Supplementary file 3. After full-text review, sixteen studies were included, of which twelve randomized controlled trials (RCTs) [25–37], three retrospective observational studies [26,38,39], and one prospective observational study [40]. The studies included a total of 2,094 patients with operable NSCLC with pathological stage I, II, III, or IV. The sample size of the studies ranged from 19 to 939 patients, with

Table 1
Basic guidelines for the application and interpretation of therapeutic quality of the physical exercise training module of prehabilitation programs for each item of the i-CONTENT tool [17].

	Low risk of ineffectiveness	High risk of ineffectiveness
1. Patient selection	A VO_{2peak} < 20 mL/kg/min and/or a predicted postoperative VO_{2peak} < 10 mL/kg/min or other selection criteria with clear rationale.	No preselection or selection (described).
2. Dosage of the training program	Intensity and duration of the exercise program must be clearly described and/or based on existing literature relevant to the target population of operable patients with NSCLC and/or an adequate exercise test (e.g., steep ramp test, CPET).	Not described where (the intensity of) the content of the exercise is based on and/or no physiological improvement can be expected due to low training dosage (frequency, intensity, time).
3. Type of the training program	At least aerobic exercise training with or without resistance exercise training.	An intervention inconsistent with the goal of physical exercise training for patients undergoing surgery for lung cancer.
4. Qualified supervisor (if applicable)	Guidance of a physical therapist who is specialized in supervising adult clinical populations.	Supervision is not reported or guidance was provided by a professional other than a physical therapist, or guidance is not described.
5. Type and timing of outcome assessment	- 30- to 90-day follow-up for postoperative complications, length of hospital stay, postoperative mortality. - To measure change in preoperative physical fitness, a pre- and post-prehabilitation exercise test must be performed preoperatively, with at least two weeks between the measurements.	Less than 30 days or more than 90 days postoperatively description of follow-up.
6. Safety of the training program	Adverse events related to the exercise program are described and acceptable as would be expected in the studied population.	Adverse events related to the exercise program are higher than would be expected in the studied population.
7. Adherence to the training program	Adherence was determined separately for training frequency and deemed good in case of ≥80%.	Adherence to the training frequency was <80%.

Abbreviations: CPET = cardiopulmonary exercise test, i-CONTENT = international Consensus on Therapeutic Training aNd Training, NSCLC = non-small cell lung cancer, VO_{2peak} = oxygen uptake at peak training.

a mean age-range between 56.2 and 74.4 years. Surgical procedures in the studies consisted of video-assisted thoracic surgery (n = 9), open thoracotomy (n = 5), lobectomy (n = 2), robot-assisted thoracic surgery (n = 2), pneumonectomy or bilobectomy (n = 1), pneumonectomy (n = 1), and segmentectomy (n = 1). Fifteen studies compared exercise prehabilitation with usual care [25–39]. One observational study [40] compared ≥3 prehabilitation sessions per week with <3 prehabilitation sessions per week. Postoperative complications and LoS were reported in all studies [25–40]. Seven publications [26,27,29,31,32,37,38] reported postoperative complications according to the Clavien-Dindo classification [41], in one study [33] the Melbourne group scale had been used, and in six studies no classification system for postoperative complications had been used [25,28,30,34–36,39,40]. Postoperative mortality was reported in seven studies [28–32,37,38]. General characteristics of the included studies are described in Table 2.

3.2. Exercise prehabilitation characteristics

Exercise prehabilitation consisted of aerobic exercises in fifteen studies [25–37,39,40] (94%), resistance exercises in nine studies [25,26,30,31,33,36,38–40] (56%), and breathing exercises in fourteen studies [25,26,28,29,31–40] (88%). In seven studies [25,26,28,29,34,36,37] (50%), breathing exercises consisted of inspiratory muscle strength training and in seven studies [31–33,35,38–40] (50%) of tidal volume training. Duration of prehabilitation programs varied between one and four weeks, with a training frequency between one and seven times per week. Training session duration (time) varied between 15 and 120 min per session. The exact content of the prehabilitation programs is reported in Table 3.

3.3. Methodological quality of the studies

Table 4 summarizes the risk of bias assessment. Of the included RCTs, two studies [30,37] had an overall low risk of bias, two studies [25,34] had some risk of bias, and eight studies [27–29,31–33,35,36] had a high risk of bias. High risk of bias was mainly caused by an unclear description of the randomization process (n = 5), unclear assignment to intended interventions (n = 6), and poor adherence to intended interventions (n = 7). Of the four included observational studies, two [38,39] showed a moderate risk of bias and two [26,40] a serious risk of bias. The latter was mainly caused by a high risk on the items confounding (n = 2), patient selection (n = 2), and a poor description of the intervention classification (n = 1).

3.4. Therapeutic quality of the exercise prehabilitation programs

Assessment of the risk of ineffectiveness based on the content of the exercise prehabilitation programs is described in Table 4. One physical exercise training program [34] (6%), was classified as having a low risk of ineffectiveness. In seven exercise prehabilitation programs [26,28,30,31,33,36,37] (44%) there was some risk of ineffectiveness, and eight programs [25,27,29,32,35,38–40] (50%) had a high risk of ineffectiveness. Main factors that increased the risk of ineffectiveness of exercise prehabilitation programs were inadequate patient selection (n = 10), inadequate dosage of the physical exercise training program (n = 10), inadequate description of type and timing of the outcome assessment (n = 6), and low adherence to the physical exercise training program (n = 5).

3.5. Effects of prehabilitation on postoperative complications, length of hospital stay, and postoperative mortality

3.5.1. Postoperative pulmonary complications

Postoperative pulmonary complications were assessed in eight RCTs [25,27–30,33–35] and two observational studies [32,39] (Fig. 1A). The pooled result of these studies showed a statistically significant lower incidence of postoperative pulmonary complications in the prehabilitation groups compared to the usual care groups in RCTs (OR 0.31, 95% CI 0.20 to 0.48; I^2 0%) and observational studies (OR 0.60, 95% CI 0.41 to 0.88; I^2 0%). Certainty of the evidence according to the GRADE approach was moderate and very low for RCTs and observational studies, respectively (see Table 5). The one observational study [40] which compared a different number of prehabilitation session with each other was not included in the meta-analysis reported that ≥3 prehabilitation sessions per week significantly reduced postoperative pulmonary complications compared to performing <3 sessions a week ($p < 0.01$).

3.5.2. Any postoperative complications

Incidence of any postoperative complication was assessed in eleven RCTs [25,27–31,33–37] and four observational studies [26,32,38,39] (Fig. 1B). The meta-analysis showed that the incidence of any complications was significantly lower in patients receiving prehabilitation compared to patients receiving usual care (OR 0.44, 95% CI 0.30 to 0.64; I^2 42%). The GRADE certainty of evidence was low based on RCTs and very low based on observational studies (see Table 5).

3.5.3. Severe postoperative complications

Four RCTs [27,29,31,37] and three observational studies [26,32,38] separately assessed severe complications (Fig. 1C). The pooled results showed that prehabilitation significantly reduced the risk of severe complications in RCTs (OR 0.36, 95% CI 0.20 to 0.68; I^2 0%) and observational studies (OR 0.56, 95% CI 0.29 to 1.06; I^2 32%). The GRADE certainty of evidence was moderate based on RCTs and low based on observational studies (see Table 5).

3.5.4. Postoperative mortality

The effect of prehabilitation on postoperative mortality was assessed in six RCTs [27,29–31,35,37] and two observational studies [32,39] (Fig. 1D). The effect of prehabilitation on postoperative mortality was not significant in both the RCTs and observational studies (RR 0.63, 95% CI 0.14 to 2.83; I^2 0% and RR 1.88, 95% CI 0.44 to 8.05; I^2 0%) with a very low certainty of evidence according to GRADE (see Table 5).

3.5.5. Length of hospital stay

LoS was assessed in seven RCTs [25,27,28,34–37] and three observational studies [32,38,39] (Fig. 1E). LoS was shorter in the prehabilitation groups compared to usual care in RCTs (mean difference (MD) −3.02 days, 95% CI −4.82 to −1.22; I^2 85%) with a very low certainty according to the GRADE approach (see Table 5). In observational studies, no significant differences were found between prehabilitation and usual care (MD -0.60 days, 95% CI -3.95 to 2.75; I^2 54%) with a very low certainty according to the GRADE approach. The one study that was not included in the meta-analysis [40] found a significant reduction (3.5 days) of LoS in the group that performed ≥3 prehabilitation sessions a week compared to the prehabilitation group that performed <3 sessions a week.

4. Discussion

The aim of this systematic review was to evaluate whether exercise prehabilitation programs reduce postoperative

Table 2
General characteristics of the included studies.

First author, year	- Number of participants, n - Study design - Intervention	- NSCLC stage of disease, n - Inclusion/participation of patients, n	Age, year, ±SD (range)	Comorbidity, n (%)	Type of surgery, n	Postoperative outcomes
Benzo, [25] 2011	- Prehab: 9, UC: 8 - RCT - Aerobic exercises, resistance exercises, breathing exercises	- NR - NR	Prehab: 70.2 ± 8.6, UC: 72.0 ± 6.7, p = 0.71	- Coronary artery disease: Prehab: 1 (10.0), UC: 3 (33.3), p = 0.31 - Diabetes: Prehab: 3 (30.0), UC: 3 (33.3), p = 0.88	- VATS, NR - Open thoracotomy, NR	- Postoperative complications[a] - LoS
Boujibar, [26] 2018	- Prehab: 19, UC: 15 - Observational study - Aerobic exercises, resistance exercises, breathing exercises, education, smoking cessation	- I-IIIa - NR	Prehab: 69 (56–73), UC: 65 (59–71), p = 0.61	- COPD: Prehab: 9 (47.3), UC: 10 (66.7), p = 0.49	- VATS: Prehab: 15, UC: 13 - RATS: Prehab: 4, UC: 2	- 30-day post-operative complications (Clavien-Dindo classification) - LoS
Huang, [37] 2017	- Prehab: 30, UC: 30 - RCT - Aerobic exercises, breathing exercises, psychological education	- I: Prehab: 16, UC: 17 II: Prehab: 10, UC: 11 III: Prehab: 4, UC: 2 - NR	Prehab: 63.0 ± 8.7 UC: 63.6 ± 6.5 p = 0.75	- ASA score >3: Prehab: 3, UC: 2 p = 1.00 - COPD: Prehab: 5, UC: 6, p = 0.73	- VATS: Prehab: 17, UC:19 - Open thoracotomy: Prehab: 13, UC: 11	- 30-day post-operative pulmonary complications (Clavien-Dindo classification) - 30-day post-operative mortality - LoS
Lai, [27] 2016	- Prehab: 30, UC: 30 - RCT - Aerobic exercises	- I: Prehab: 16, UC: 18 II: Prehab: 10, UC: 10 III: Prehab: 3, UC: 2 IV: Prehab: 1, UC: 0 - 67: did not meet the inclusive criteria, 38: refused to participate, 22: other reasons	Prehab: 72.5, ±3.4, UC: 71.6, ±1.9, p = 0.23	- ASA score: Prehab: 3 (10.0) UC: 3 (10.0), p = 1.00 - COPD Prehab: 5 (17.0) UC: 4 (13), p = 1.00	- VATS: Prehab: 21, UC: 20 - Open surgery: Prehab: 9, UC: 10	- 30-day post-operative pulmonary complications (Clavien-Dindo classification) - 30-day post-operative mortality - LoS
Lai, [28] 2017	- Prehab: 51, UC: 50 - RCT - Aerobic exercises, breathing exercises	- I: Prehab: 30, UC: 20 II: Prehab: 14, UC: 25 III: Prehab: 6, UC: 5 IV: Prehab: 1, UC: 0 - 24: refuse to participate	Prehab: 63.8 ± 8.2, UC: 64.6 ± 6.6, p = 0.58	- Charlson comorbidity index 0–2: Prehab: 32 (63%), UC: 43 (86%), p = 1.00 - Charlson comorbidity index ≥3: Prehab 18 (35%), UC: 7 (14%), p = 1.00	- VATS: Prehab: 32, UC: 34 - Open surgery: Prehab: 19, UC: 16	- 30-day post-operative complications - LoS
Lai, [29] 2019	- Prehab: 34, UC: 34 - RCT - Aerobic exercises, breathing exercises	- I: Prehab: NR, UC: NR - 22: refuse to participate	Prehab: 64.2 ± 6.8, UC: 63.4 ± 8.2, p = 0.67	- Hypertension: Prehab: 8 (25%), UC: 3 (9%), p = 1.00 - Diabetes: Prehab: 3 (9%), UC: 1 (3%), p = 0.61 - COPD: Prehab: 9 (28%), UC: 11 (34%), p = 0.61	- VATS: 64	- 30-day post-operative complications (Clavien-Dindo classification) - 30-day post-operative mortality - LoS
Licker, [30] 2017	- Prehab: 74, UC: 77 - RCT - Aerobic exercises, resistance exercises	- I: Prehab: 33, UC: 40 II: Prehab: 28, UC: 27 III: Prehab: 13, UC: 10 - 12: not meeting the criteria, 8: refuse to participate, 5: short delay	Prehab: 64 ± 10 UC: 64 ± 13, p = 0.74	- Hypertension: Prehab: 33 (45%), UC: 32 (42%), p = 0.74 - Diabetes: Prehab: 10 (14%), UC: 11 (14%), p = 0.89 - Cardiac arrhythmia: Prehab: 3 (4%), UC: 5 (7%), p = 0.72 - COPD: Prehab: 30 (41%), UC: 27 (35%), p = 0.51 - Coronary artery disease: Prehab: 10 (14%), UC: 8 (10%), p = 0.62 - Heart failure: Prehab: 8 (11%), UC 8 (10%), p = 0.98	- Pneumonectomy or bilobectomy: Prehab: 13, UC: 17 - Lobectomy: Prehab: 49, UC: 46 - Segmentectomy: Prehab: 1, UC: 15	- 30-day post-operative complications - 30-day post-operative mortality - LoS

(*continued on next page*)

Table 2 (*continued*)

First author, year	- Number of participants, n - Study design - Intervention	- NSCLC stage of disease, n - Inclusion/participation of patients, n	Age, year, ±SD (range)	Comorbidity, n (%)	Type of surgery, n	Postoperative outcomes
				- History of stroke: Prehab: 6 (8%), UC: 1 (1%), p = 0.06		
Liu, [31] 2019	- Prehab: 37, UC: 36 - RCT - Aerobic exercises, resistance exercises, breathing exercises, nutritional counselling, psychological adjustment, conventional guidance	- I-III - 6: ASA grade III, 4: stage IV, 5: neoadjuvant therapy, 2: declined to participate, 2: contraindications for 6 MWT distance, 1: severe renal insufficiency	Prehab: 56.2 ± 10.3, UC: 56.2 ± 8.7, p = NR	- Hypertension: Prehab: 8 (22%), UC: 11 (31%) - Diabetes: Prehab: 4 (11%), UC: 5 (14%) - Ischemic heart disease: Prehab: 3 (8%), UC: 2 (6%) - Cardiac arrhythmia: Prehab: 4 (11%), UC: 5 (14%) - Cerebral infarction: Prehab 2 (5%), UC: 3 (8%) - COPD: Prehab: 0 (0%), UC: 1 (3%) - Asthma: Prehab: 5 (14%), UC: 2 (6%)	- VATS: 73	- 30-day postoperative complications (Clavien-Dindo classification) - 30-day postoperative mortality - LoS
Morano, [34] 2013	- Prehab: 12, UC: 12 - RCT - Aerobic exercises, breathing exercises	- I/II: Prehab: 11, UC: 9 IIIA: Prehab: 1, UC: 3 - UC: 3: inoperable cancer	Prehab: 64.8 ± 8, UC: 68.8 ± 7.3, p = 0.33	- COPD: Prehab: 9 (75%), UC: 9 (75%), p = 0.62	- VATS: NR - Open thoracotomy: NR	- 30-day postoperative complications (Clavien-Dindo classification) - LoS
Pehlivan, [35] 2011	- Prehab: 30, UC: 30 - RCT - Aerobic exercises, breathing exercises	- IA to IIIB - NR	Prehab 54.1 ± 8.5 UC 54.8 ± 8.5, p = 0.70	- NR	- Lobectomy: Prehab: 19, UC 2 - Pneumonectomy: Prehab: 11, UC: 6, p = 0.30	- Postoperative complications - LoS
Rispoli, [40] 2020	- Prehab1: 13, Prehab2: 46 - Observational study - Aerobic exercises, resistance exercises, breathing exercises, stretching and relaxation, smoking cessation, ≥3 sessions a week prehabilitation is Prehab1, <3 sessions a week prehabilitation is Prehab2	- I: Prehab1: 8, Prehab2: 32, p = 0.48 II: Prehab1: 4, Prehab2: 10, p = 0.61 III: Prehab1: 1, Prehab2: 4, p = 0.90 - 3: refused to participate, 1: underwent bilobectomy instead of planned lobectomy	Prehab 1: 69.3 ± 1.4, Prehab2: 69.7 ± 3.5, p = 0.74	- Charlson comorbidity index: Prehab1: mean 2.8 ± 0.3, Prehab2: mean 2.77 ± 0.3, p = 0.69	- VATS: Prehab1: 12, Prehab2: 38 - Open surgery: Prehab1: 1, Prehab2: 8, p = 0.98	- Postoperative complications[a] - LoS
Saito, [39] 2017	- Prehab: 51, UC: 65 - Observational study - Aerobic exercises, resistance exercises	- I: Prehab: 31, UC: 40 II: Prehab: 10, UC: 12 IIIa: Prehab: 10, UC: 13, p = 0.52 - 189: other type of surgery, 471: non-COPD	Prehab: 74.4 ± 7.7, UC: 68.2 ± 8.6, **p < 0.01**	- COPD GOLD I: Prehab: 26 (51%), UC: 54 (83%) - COPD GOLD II: Prehab: 25 (49%), 11 (17%) in UC **p < 0.01**	- VATS: Prehab: 18, UC: 28 - Open surgery: Prehab: 33, UC: 37	- 90-day postoperative complications - LoS
Saito, [38] 2021	- Prehab: 51, UC: 93 - Observational study - Resistance exercises, breathing exercises	- I: Prehab: 33, UC: 67 II: 10, UC: 14 III: Prehab: 7, UC: 12 IV: 1, UC: 0 - 2: superior sulcus tumour, 1: exploratory thoracotomy, 1: lack of preoperative lung function	Prehab: 73.0 ± 6.0 UC: 71.3 ± 7.3, p = 0.15	Charlson comorbidity index - 0: Prehab: 15 (29%), UC: 33 (36%) - 1–2: Prehab: 27 (53%), UC: 45 (48%) - 3–4: Prehab: 7 (14%), UC: 14 (15%) - ≥5: Prehab: 2 (4%), UC: 1 (1%) **p = 0.08**	- Open thoracotomy: Prehab: 1, UC: 4 - VATS: Prehab: 39, UC: 66 - RATS: Prehab: 11, UC: 23, p = 0.37	- 90-day postoperative complications - 90-day postoperative mortality - LoS
Sebio Garcia, [33] 2016	- Prehab: 10, UC: 12 - RCT - Aerobic exercises, resistance exercises, breathing exercises	- NR - Prehab: 2 referred to preoperative physical therapy, 2: not evaluated, 1: reconversion to thoracotomy, 1: not surgery, 1: not malignant disease. UC: 2: not malignant disease, 1: neoadjuvant therapy, 2 abandoned intervention, 2: surgery re-scheduled, 1 irresectable tumour, 1 excluded by the investigators, 1: other	Prehab: 70.9 ± 6.1 UC: 69.0 ± 4.4, p = NR	- Colinet comorbidity score: Prehab: mean 9.3 ± 4.3, UC: mean 8.7 ± 4.2, p = NR	- VATS: Prehab: 10, UC: 12	- 90-day postoperative complications - LoS
Tenconi, [36] 2021	- Prehab: 70, UC: 70 - RCT	- I-II - NR	Prehab: 66.0 ± 10.6 UC:	- NR	- VATS - RATS	- 30-day postoperative complications - LoS

Table 2 (*continued*)

First author, year	- Number of participants, n - Study design - Intervention	- NSCLC stage of disease, n - Inclusion/participation of patients, n	Age, year, ±SD (range)	Comorbidity, n (%)	Type of surgery, n	Postoperative outcomes
	- Aerobic exercises, resistance exercises, breathing exercises, therapeutic education		67.7 ± 10.8, p = NR			
Zhou [32] 2017	- Prehab: 197, UC: 742 - Observational study - Aerobic exercises, breathing exercises	-I: Prehab: 16, UC: 18 II: Prehab: 10, UC: 10 III: Prehab: 3, UC: 2 IV: Prehab: 1, UC: 0 -NR	Prehab: 58.5 ± 9.6, UC: 58.8 ± 9.3, p = 0.56	- Hypertension or/and coronary disease: Prehab 10 (5%), UC: 37 (5%), p = 0.63 - COPD: Prehab: 22 (11%), UC: 92 (12%), p = 0.64 - Diabetes Prehab: 13 (7%), UC: 49 (7%), p = 0.99	- VATS: Prehab: 122, UC: 489, p = 0.30 - Open surgery: Prehab 75, UC: 253	- 30-day postoperative complications (Clavien-Dindo classification) - 30-day postoperative mortality - LoS

Bold = considered significant with $p < 0.10$.
Abbreviations: 6 MWT = 6-min walk test, ASA = American Society of Anesthesiologists score, COPD = chronic obstructive pulmonary disease, LoS = length of hospital stay, NR = not reported, NSCLC = non-small cell lung cancer, Prehab = prehabilitation group, RATS = robot-assisted thoracic surgery, RCT = randomized controlled trial, SD = standard deviation, UC = usual care group, VATS = video-assisted thoracic surgery.
[a] Follow-up time is not described.

complications, postoperative mortality and LoS in patients undergoing surgery for NSCLC, thereby accounting for the quality of the physical exercise programs. The pooled estimates of the RCTs show that prehabilitation results in a reduction of postoperative pulmonary complications, severe postoperative complications, and postoperative LoS. Pooled estimates of the included observational studies also indicate that exercise prehabilitation may reduce postoperative complications and LoS. However, the GRADE certainty of evidence of each outcome was very low to moderate.

Results of the current review are in line with previous research, as several systematic reviews have shown that exercise prehabilitation might be an effective intervention for reducing postoperative complications and LoS in NSCLC/lung resection [11–14]. Furthermore, in a recently published systematic review [15], the certainty of evidence was described. However, the certainty of evidence was described without an explanation to which content it was assessed on, which is a major limitation. Nevertheless, previous reviews neither described nor assessed the quality of the content of the physical exercise training module of included prehabilitation studies. Although prehabilitation seems effective, it remains unclear how an optimally effective exercise prehabilitation program should be designed.

The finding that prehabilitation improved most postoperative outcomes, despite the fact that half of the included studies in this systematic review had a high risk of ineffectiveness, might suggest that the full potential of prehabilitation might not have been unlocked. Main concerns with regard to the risk of ineffectiveness were that most included studies (63%) did not specially select patients with a higher risk for postoperative complications and even seemed to exclude them [25,27,29–31,35,36,38–40]. Because especially patients who are at a high risk for complications and functional decline after surgery might benefit most from prehabilitation [49], patient selection should start preoperatively with an adequate assessment of treatment-associated risk factors for a personalized approach [50–52].

The description of the dosage of prehabilitation programs was unclear in 63% of the included articles [25,27–29,32,35,37–40]. Full reporting of the prescription and adherence to of exercise prehabilitation is eminent for adequate estimation of the risk of ineffectiveness, and thereby the quality of the exercise program. Merely three studies offered a personalized physical exercise prescription based on outcomes of the cardiopulmonary exercise test of any other formal exercise test [26,33,53]. In addition, the progression principle was applied in only three studies [34,36,37]. Both personalization, as well as adequate progression of exercises are of major importance to allow for sufficient overload to improve physical fitness [54]. Previous research in patients undergoing elective surgery for abdominal cancer recommends personalized and well-controlled high-intensity interval training to achieve the greatest improvements in physical fitness in the short preoperative time period [55]. Overall, prehabilitation programs of the included studies were safe, as no serious adverse events were reported and there were no relevant dropouts due to the nature of the programs.

4.1. Strength and limitations

A strength of this systematic review was the inclusion of both RCTs and observational studies. RCTs often have high internal validity but limited generalizability due to the strict inclusion criteria, while observational studies are more generalizable due to the use of real-life data. Another strength was the detailed assessment and description of the content of prehabilitation programs, thereby indicating shortcomings in the development and reporting of prehabilitation programs so that they can receive attention in future studies. This will contribute to further improve the content and effectiveness of the programs, as well as the reproducibility of studies. A limitation of this systematic review involves the choice to only include studies with prehabilitation programs that met a certain minimum set of requirements (i.e., at least a physical exercise module). However, this is considered the cornerstone of an effective (multimodal) prehabilitation program, especially in unfit (high-risk) patients. A second limitation was that the two reviewers did not independently extracted data from each of the included studies. The extraction has been carefully checked by another reviewer and therefore no bias is expected. A third imitation was that the included studies included different types of surgery without specifying how many postoperative complications occurred per type of surgery, making stratification impossible. The risk of ineffectiveness of the prehabilitation programs was moderate to high, and therefore a meta-analysis could not be stratified by risk of ineffectiveness (i.e., low, moderate, or high) of the prehabilitation programs. The latter also precluded a comparison between different training types (e.g., aerobic exercises, resistance exercises, breathing exercises).

Table 3
Content of exercise prehabilitation according to the items of therapeutic quality on the i-CONTENT tool.

First author, year	Patient selection Eligible if:	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)	Qualified supervisor	Type and timing of outcome assessment	Safety dropouts and adherence, n (%) (range)
Benzo, [25] 2011	Low-risk group[a]: Moderate to severe COPD and FEV_1 <80%	- Based on: NR - Program duration: 1 week - **Aerobic exercises**: **F**: 2/day, **I**: NR, **T**: 20 min, **T**: treadmill or cross-trainer (Nu-Step) and arm-R-size exercises or arm-ergometer **Resistance exercises**: **F**: 2/day, **I**: at least light intensity on the Borg scale, **T**: 2 × 10–12 repetitions, **T**: Thera band **Breathing exercises**: **F**: 1/day, **I**: perceived exertion of somewhat hard on the Borg scale, **T**: 15–20 repetitions, **T**: Threshold Inspiratory Muscle Trainer or P-Flex valve	Physical therapist	- Postoperative complications[b] - Postoperative mortality[b] - LoS	- Safety: no adverse events - Dropouts: none - Exercise adherence: all participants completed all sessions
Boujibar, [26] 2018	High-risk group[a]: ≥18 years and $VO_{2peak} \leq 20$ mL/kg/min	- Based on: international recommendations [42] - Program duration: NR - **Aerobic exercises**: **F**: 3–5/week, **I**: tailored to the ventilatory threshold (VT1) on the CPET, **T**: 45 min, **T**: cycling **Resistance exercises**: **F**: 3–5/week, **I**: 70% of 1RM, **T**: 3 × 12 repetitions, **T**: NR, **Breathing exercises**: **F**: 3–5/week, **I**: 30% of maximum inspiratory pressure, **T**: NR, **T**: Threshold Inspiratory Muscle Trainer	Physical therapists	- 30-day post-operative complications - LoS	- Safety: no adverse events - No dropouts - Exercise adherence: mean number of exercise sessions was 17 (14–20). 10 (52%): received >17 exercise sessions, 9 (47%): received ≤17 exercise sessions
Huang, [37] 2017	High-risk group[a]: Age >70 years, BMI >30, COPD with heavy smoking history (≥20 pack-years) FEV_1 ≤70%, or prior thoracic surgery	- Based on: NR - Program duration: 1 week - **Aerobic exercises**: **F**: 7/week, **I**: own speed and power, progressively increased the resistance range, **T**: 20 min, **T**: cross-trainer (NuStep) **Breathing exercises**: **F**: 2–3/day, **I**: NR, **T**: 15–20, **T**: Threshold Inspiratory Muscle Trainer	Aerobic exercises in hospital with a physical therapist, breathing exercises with trained nurses.	- 30-day post-operative complications - 30-day post-operative mortality - LoS	- Safety: NR - Dropouts: Prehab: 1 (3%): acute COPD exacerbation, 2 (7%): knee pain - Exercise adherence: NR
Lai, [27] 2016	Low-risk group[a]: ≥70 years	- Based on: NR - Program duration: 1 week - **Aerobic exercises**: **F**: 1/day, **I**: self-preferred speed and power, **T**: 30 min, **T**: cross-trainer (Nu-Step)	Aerobic exercises supervised by a physical therapist	- 30-day post-operative complications - 30-day post-operative mortality - LoS	- Safety: NR - Dropouts: Prehab: 4 (13%) could not endure the high-intensive regimen, 1 (3%): perceived lack of benefit, 1 (3%): knee pain - Exercise adherence: NR
Lai, [28] 2017	High-risk group[a]: >75 years and >20 pack-year smoking history and BMI >30 kg/m^2 and $ppoFEV_1$ <60% and ppoDLCO <60% and COPD	- Based on: NR - Program duration: 1 week - **Aerobic exercises**: **F**: 1/day, **I**: not clearly reported, **T**: 30 min, **T**: cross-trainer (Nu-Step) **Breathing exercises**: **F**: 2–3/day, **I**: NR, **T**: 15–20 min, **T**: Threshold Inspiratory Muscle Trainer and manual deep breathing exercises	Physical therapist dedicated to thoracic surgery patients	- 30-day post-operative complications - LoS	- Safety: no adverse events - Dropouts: Prehab: 6 (12%): not completion - Exercise adherence: NR
Lai, [29] 2019	Low-risk group[a]: 45–80 years and $ppoFEV_1$ <60%,	- Based on: NR - Program duration: 1 week - **Aerobic exercises**: **F**: 7/week, **I**: NR, **T**: 30 min, **T**: cross-trainer (Nu-Step) **Breathing exercises**: **F**: 3/day, **I**: NR, **T**: 20 breaths/session, **T**: Threshold Inspiratory Muscle Trainer	Aerobic exercises supervised by a physical therapist, respiratory exercises supervised by a trained nurse	- 30-day post-operative complications - 30-day post-operative mortality - LoS	- Safety: no adverse events - Dropouts: Prehab: 2 (6%): exercise intensity to high - Exercise adherence: NR
Licker, [30] 2017	Low-risk group[a]: All patients	- Based on: [43] - Program duration: NR - **Aerobic exercises**: **F**: 2–3/week, **I**: 80–100% of peak work-rate near-maximal heart rates toward the end of each series of sprints based on the individual's	Physical therapist specialized in rehabilitation	- 30-day post-operative complications - 30-day post-operative mortality - LoS	- Safety: no adverse events - Dropouts: Prehab: 3 (4%): patient withdrawal, 3 (4%): operation cancelled, UC: 5 (7%): patient withdrawal, 2 (3%): operation cancelled

Table 3 (*continued*)

First author, year	Patient selection Eligible if:	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)	Qualified supervisor	Type and timing of outcome assessment	Safety dropouts and adherence, n (%) (range)
		exercise response, **T**: 2 series of 10 min with 15-sec work-interval and 15 s rest-interval with 4-min rest between series, **T**: cycling **Resistance training**: **F**: 2–3/week, **I**: NR, **T**: NR, **T**: leg press, leg extension, back extension, seat row, biceps curls, or chest and shoulder press			- Exercise adherence: to the prescribed exercise sessions: 87% ± 18%, median 8 sessions
Liu, [31] 2019	Low-risk group[a]: <70 years	- Based on: [44] - Program duration: 2 weeks - **Aerobic exercises**: **F**: 3/week, **I**: based on Borg-score 13–16 and 70% of heart rate reserve, **T**: 30 min, **T**: jogging or walking or cycling **Resistance exercises**: **F**: 2/week, **I**: Borg-score moderate to high (13–16), **T**: 3 x 3–12 repetitions, **T**: major muscle groups with Thera band **Breathing exercises**: **F**: 2/day, **I**: NR, **T**: 10 min, **T**: 1) A Tri-Ball Respiratory Training (Leventon S.A., Barcelona, Spain) for breathing exercises; 2) cough exercises; 3) blowing up a small balloon in 1 breath and holding for >5 s	Home-based, instruction and resistance exercises supported by a physical therapist	- 30-day post-operative complications - 30-day post-operative mortality - LoS	- Safety: no adverse events - Dropouts: Prehab: 2 (6%) did not receive surgery, UC: 2 (6%) did not receive surgery - Exercise adherence: NR
Morano, [34] 2013	High-risk group[a]: Previous pulmonary disease, interstitial lung disease, COPD with impaired spirometry function	- Based on: NR - Program duration: 4 weeks - **Aerobic exercises**: **F**: 5/week, **I**: 80% on the maximum work rate achieved during a treadmill incremental test, **T**: 10 min in the first week with increments of 10 min every week, **T**: walking on a treadmill **Breathing exercises**: **F**: 1/day, **I**: 20% on the maximal inspiratory pressure (MIP), increased 5–10% each session, to reach 60% of their MIP, **T**: 10–30 min, **T**: Threshold Inspiratory Muscle Trainer	NR	- Postoperative complications[b] - LoS	- Safety: NR - Dropouts: UC: 3 (3%) inoperable cancer - Exercise adherence: NR
Pehlivan, [35] 2011	Low-risk group[a]: ASA I-II	- Based on: NR - Program duration: 1 week - **Aerobic exercises**: **F**: 3/day, **I**: according to patient's tolerance to training speed and time, **T**: NR, **T**: walking on a treadmill **Breathing exercises**: - **F**: 2/day, **I**: NR, **T**: NR, **T**: incentive spirometry	Physical therapist	- Postoperative complications[b] - LoS	- Safety: NR - No dropouts - Exercise adherence: NR
Rispoli, [40] 2020	Low-risk group[a]: COPD stage I	- Based on: [45, 46] - Program duration: 4 weeks - **Aerobic exercises**: **F**: ≥3/week, **I**: at least 15 min or dyspnoea-limited, **T**: 30 min, **T**: walking outside or treadmill **Resistance exercises**: **F**: ≥3/week, **I**: NR, **T**: NR, **T**: abdominal exercises, lower limbs exercises **Breathing exercises**: **F**: NR, **I**: NR, **T**: NR, **T**: incentive spirometry	Home-based instruction and weekly phone calls supported by a physical therapist	- Postoperative complications[b] - LoS	- Safety: NR - Dropouts: no - Exercise adherence: Prehab1: 13 (22%) performed <3 sessions per week, Prehab2: 46 (78%) performed ≥3 sessions per week
Saito, [39] 2017	Low-risk group[a]: COPD gold ≥ II and FEV_1 <100% and ECOG ≥2	- Based on: NR - Program duration: 2–4 weeks - **Aerobic exercises**: **F**: 5/week, **I**: NR, **T**: 30 min, **T**: cycling **Resistance exercises**: **F**: 5/week, **I**: NR, **T**: NR, **T**: bronchodilator, training for chest expansion, shoulder girdle mobilization	Aerobic exercises supervised by a physical therapist	- 90-day post-operative complications - LoS	- Safety: NR - Dropouts: NR - Exercise adherence: NR

(*continued on next page*)

Table 3 (*continued*)

First author, year	Patient selection Eligible if:	Type and dosage of the preoperative exercise program (F: Frequency, I: intensity, T: Time, T: Type)	Qualified supervisor	Type and timing of outcome assessment	Safety dropouts and adherence, n (%) (range)
Saito, [38] 2021	Low-risk group[a]: All patients	- Based on: NR - Program duration: 2–4 weeks preoperative - **Resistance exercises**: **F**: 7/week, **I**: 15 repetitions, **T**: NR, **T**: abdominal crunch **Breathing exercises**: **F**: 7/week, **I**: NR, **T**: based on vital capacity 50–100 breaths/session, **T**: incentive spirometry coach2	Physical therapist at the first instance of home-based exercises	- 90-day post-operative complications - 90-day post-operative mortality - LoS	- Safety: NR - Dropouts: NR - Exercise adherence: NR
Sebio Garcia [33], 2016	High-risk group[a]: FEV1 ⩽80%, BMI ⩾30; (c) age ⩾75 years or two or more co-morbidities identified in the Colinet Comorbidity Score.	- Based on: [47] - Program duration: NR - **Aerobic exercises**: **F**: 3–5/week, **I**: interval training (1 min at high intensity (80% of WR_{peak}) plus 4 min of active rest (performed at 50% of WR_{peak}) measured with the CPET, **T**: 30 min, **T**: cycling **Resistance exercises**: **F**: 3–5/week, **I**: 25 repetition maximum test, **T**: 3 × 15 repetitions, **T**: six training using Thera band and body mass for the large muscle groups **Breathing exercises**: **F**: 2/day, **I**: 80% of vital capacity, **T**: 6 cycles of 5 repetitions, **T**: incentive spirometry coach2	Physical therapist	- 90-day post-operative complications - LoS	- Safety: no adverse events - Dropouts: Prehab: 2 (17%): lost to follow up, UC: 1 (10%): clinical deterioration - Exercise adherence: NR
Tenconi, [36] 2021	Low-risk group[a]: All patients	- Based on: [48] - Program duration: 2–3 weeks - **Aerobic exercises**: **F**: 2–3/week, **I**: 60–80% peak workload previously determined with shuttle walking test and adapted to the patient's tolerance, **T**: 30–40 min, **T**: outpatient clinic cycling, home-based: walking **Resistance exercises**: **F**: 2–3/week, **I**: maximal load (previously determined with the 10-repetition maximum test), **T**: 2–3x 10 repetitions, **T**: lower limbs (extensor muscle group), upper limbs (biceps, triceps, deltoids, latissimus dorsi, pectoralis) and abdominal wall **Breathing exercises**: **F**: 1/day, **I**: ⩾30% of maximal predicted inspiratory pressure and adapted to the patient's tolerance, **T**: 15–30 min, **T**: Threshold Inspiratory Muscle Trainer	Physical therapist	- 30-day post-operative complications - LoS	- Safety: Adverse events: Prehab: 2 (7%): mild, 17 (55%): moderate, 11 (37%): severe, UC: 2 (4%): mild, 37 (69%): moderate, 15 (28%): severe - Dropouts: Prehab: 6 (9%): adjuvant treatment, 5 (7%): disease progression, 5 (7%): non-primary lung neoplasm, 8 (11%): lost to follow-up, 1 (1%): other, UC: 15 (21%): adjuvant treatment, 2 (3%): disease progression, 3 (4%): non-primary lung neoplasm, 9 (13%): lost to follow-up, 1 (1%): other - Exercise adherence: 90% of the patients had accomplished 80% session adherence
Zhou, [32] 2017	High-risk group[a]: ⩾50 years and ⩾20 pack-year smoking history and BMI ⩾28 kg/m^2 and FEV_1 ⩽60% and COPD, asthma or airway hyper reactivity	- Based on: NR - Program duration: 1 week - **Aerobic exercises**: **F**: 1/day. **I**: according to own speed and power, then increasing progressively, **T**: 30 min, **T**: cross-trainer (Nu-Step) **Breathing exercises:** **F**: 2–3/day: **I**: NR, **T**: 15–20 min, **T**: Volume training: abdominal breathing and inspiratory training with the Voldyne 2500	Education and teaching supported by a nursed specialized in lung cancer, aerobic exercise supervised by a physical therapist	- 30-day post-operative complications - 30-day post-operative mortality	- Safety: NR - Dropouts: Prehab: 7 (19%): required for advancing the surgery, 9 (24%): perceived lack of benefit, 11 (30%): could not endure the high-intensive regimen, 7 (19%): considered time/expense cost and suspended, 3 (8%): other reasons - Exercise adherence: NR

Abbreviations: 1RM = one repetition maximum, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CPET = cardiopulmonary exercise test, DLCO = carbon monoxide lung diffusion capacity, ECOG = Eastern cooperative oncology group, FEV_1 = forced expiratory volume in 1 s, i-CONTENT = international Consensus on Therapeutic Training aNd Training, min = minute, LoS = length of hospital stay, NR = not reported, ppoDLCO = predicted postoperative carbon monoxide lung diffusion capacity, ppoFEV_1 = predicted postoperative forced expiratory volume in 1 s, Prehab = prehabilitation group, UC = usual care group, VO_{2peak} = oxygen uptake at peak training, WR_{peak} = work rate at peak exercise.

[a] Including a low, moderate, or high-risk group was interpreted according to the patient selection in the included studies and the score on the i-CONTENT tool.

[b] Follow-up time was not described.

Table 4
Results of methodological quality according to the Cochrane risk of bias tool and the Robins-1 tool, and therapeutic quality according to the i-CONTENT tool.

Methodological quality for randomized controlled trials on the Cochrane risk of bias tool 2

	Risk assessed for outcome[a]	Randomization process	Assignment to intended interventions	Adherence to intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias	Direction of bias of the study outcome
Benzo [25]	Primary	Some	Low	Low	Low	Low	Low	**Some**	Unpredictable
Huang [37]	Primary	Low	Low	Low	Low	Low	Low	**Low**	Unpredictable
Lai [27]	Primary	Some	Low	High	Low	Low	Low	**High**	Favours comparator
Lai [28]	Secondary	Low	High	High	Low	Low	Low	**High**	Unpredictable
Lai [29]	Secondary	Some	Some	High	Low	Low	Low	**High**	Favours comparator
Licker [30]	Primary	Low	Low	Low	Low	Low	Low	**Low**	Not applicable
Liu [31]	Secondary	Low	High	High	Low	Low	Low	**High**	Unpredictable
Morano [34]	Primary	Some	Low	Low	Low	Low	Low	**Some**	Favours experimental
Pehlivan [35]	Primary	Low	Low	High	Low	Some	Low	**High**	Unpredictable
Sebio Garcia [33]	Side issue	Some	High	Low	High	Low	Low	**High**	Favours comparator
Tenconi [36]	Secondary	Some	Some	Some	Low	Low	Some	**High**	Unpredictable

Methodological quality for observational studies on the Robins-1 tool[a]

First author		Confounding	Selection	Intervention classification	Deviation from interventions	Missing outcome data	Measurement of outcome	Selection of reported results	Overall risk of bias	
Boujibar [26]	Secondary	Serious	No information	Low	Low	Low	Low	Low	**Serious**	Favours comparator
Rispoli [40]	Secondary	Moderate	Serious	Moderate	Low	Low	Low	Moderate	**Serious**	Favours experimental
Saito [39]	Primary	Moderate	Low	Moderate	Low	Low	Low	Low	**Moderate**	Unpredictable
Saito [38]	Primary	Moderate	Low	Moderate	Low	Low	Low	Low	**Moderate**	Unpredictable
Zhou [32]	Primary	Moderate	Low	Moderate	Serious	Low	Low	Low	**Serious**	Favours comparator

Therapeutic quality

First author	1. Patient selection	2. Dosage of the exercise program	3. Type of the exercise program	4. Qualified supervisor (if applicable)	5. Type and timing of outcome assessment	6. Safety of the exercise program	7. Adherence to the exercise program	Overall risk of ineffectiveness[b]
Benzo [25]	High	High	Low	Low	High	Low	Low	High
Boujibar [26]	Low	Low	Low	Low	Low	Low	High	Some
Huang [37]	Low	High	Low	Low	Low	Low	Low	Some
Lai [27]	High	High	Low	Low	High	Low	Low	High
Lai [28]	Low	High	Low	Low	High	Low	Low	Some
Lai [29]	High	High	Low	Low	High	Low	Low	High
Licker [30]	High	Low	Low	Low	Low	Low	Low	Some
Liu [31]	High	Low	Low	Low (home)	Low	Low	Low	Some
Morano [34]	Low	Low	Low	High	Low	Low	Low	Low
Pehlivan [35]	High	High	High	Low	Low	Low	Low	High
Rispoli [40]	High	High	Low	Low (home)	Low	Low	Low	High
Saito [39]	High	High	Low	Low	High	Low	High	High
Saito [38]	High	High	Low	Low (home)	Low	Low	High	High
Sebio Garcia [33]	Low	Low	Low	Low (home)	Low	Low	High	Some
Tenconi [36]	High	Low	Low	Low (home)	Low	Low	Low	Some
Zhou [32]	Low	High	Low	Low	High	Low	High	High

Methodological quality: low=low risk of bias, some= some concerns; high=high risk of bias, moderate=moderate risk of bias, serious=serious risk of bias.
Therapeutic quality: low=low risk of ineffectiveness; high=high risk of ineffectiveness.
[a]: Risk of bias was assessed in each study based on the relevant outcomes for this systematic review.
[b]: Overall risk of ineffectiveness:

- *Low risk of ineffectiveness*= Item 1, 2, 3, AND 7 scored a "low risk of ineffectiveness" AND ≥2 of the items 4, 5, 6 scored a "low risk of ineffectiveness"
- *Some risk of ineffectiveness*= Item 1, 2, 3, AND 7 scored a "low risk of ineffectiveness" AND 1 of the items 4, 5, 6 scored a "low risk of ineffectiveness" OR 3 of the items 1, 2, 3, and 7 scored a "low risk of ineffectiveness" AND ≥1 of the items 4, 5, 6 scored a "low risk of ineffectiveness"
- *High risk of ineffectiveness*= ≤2 of the items 1, 2, 3, and 7 scored a "low risk of ineffectiveness"

4.2. Future studies

The description of the FITT-VP principles of the exercise prehabilitation programs was incomplete in the included studies, making it difficult to truly assess the risk of ineffectiveness by means of the i-CONTENT scale. Therefore, it is recommended to use the i-CONTENT tool not only to evaluate exercise prehabilitation programs but also to improve the quality and description of prehabilitation programs already at the stage of study design. Gaining more insight into which content of exercise prehabilitation is most effective could be applied in a RCT with a large sample size, in which different exercise programs (e.g., high-intensity interval training, resistance exercises, and breathing exercises) individually and/or in combination are performed.

5. Conclusion

Based on the results of the current review, exercise prehabilitation effectively reduces the occurrence of postoperative pulmonary complications, postoperative severe complications, and reduce LoS in patients undergoing surgery for NSCLC, despite the high risk of ineffectiveness. However, results should be interpreted with caution as the certainty of evidence is very low to moderate for all outcomes. Future research should focus on the quality and reporting of prehabilitation programs, which is expected to improve postoperative outcomes through exercise prehabilitation with higher certainty.

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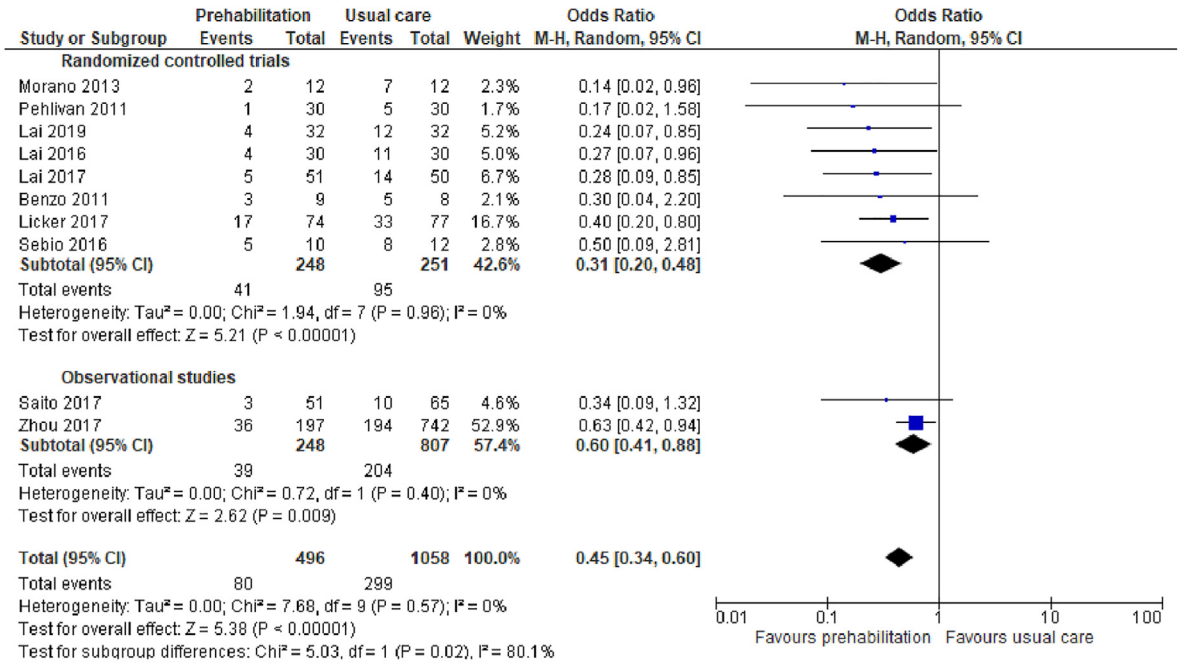
Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

CRediT authorship contribution statement

M.J.J. Voorn: Formal analysis, Conceptualization, Data curation,

A



B

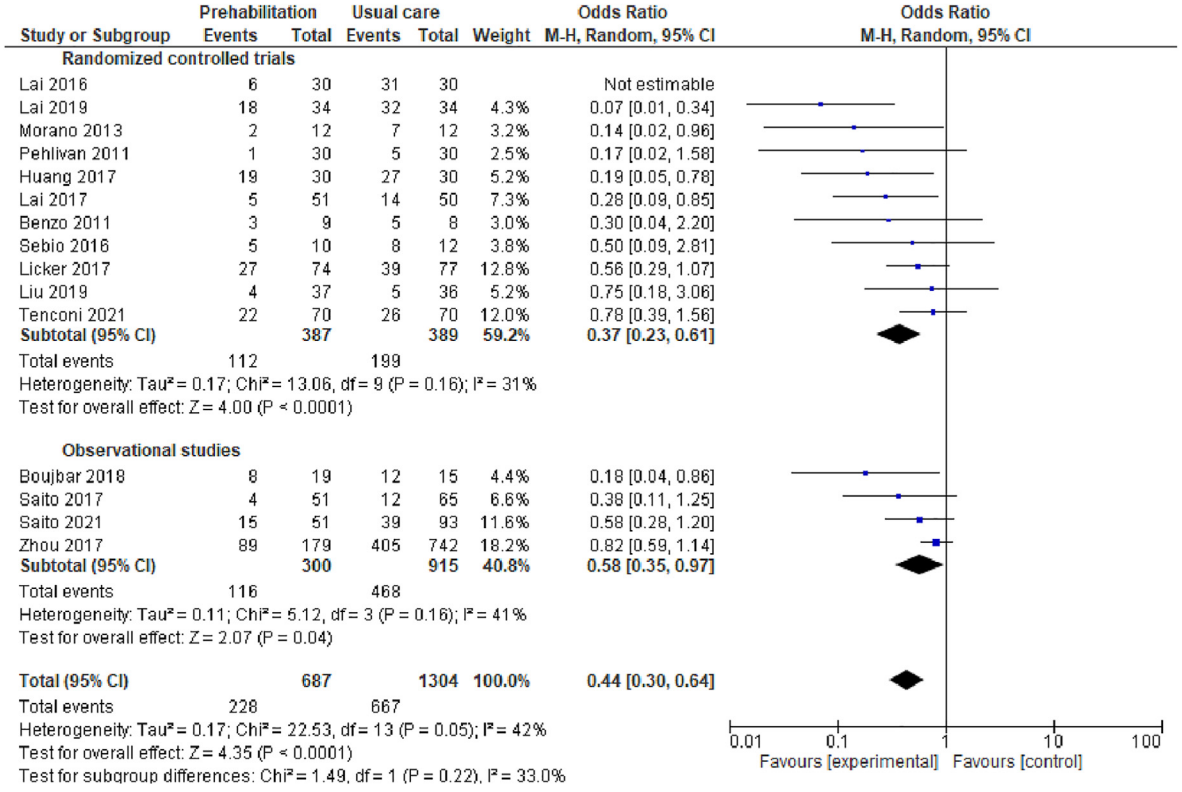
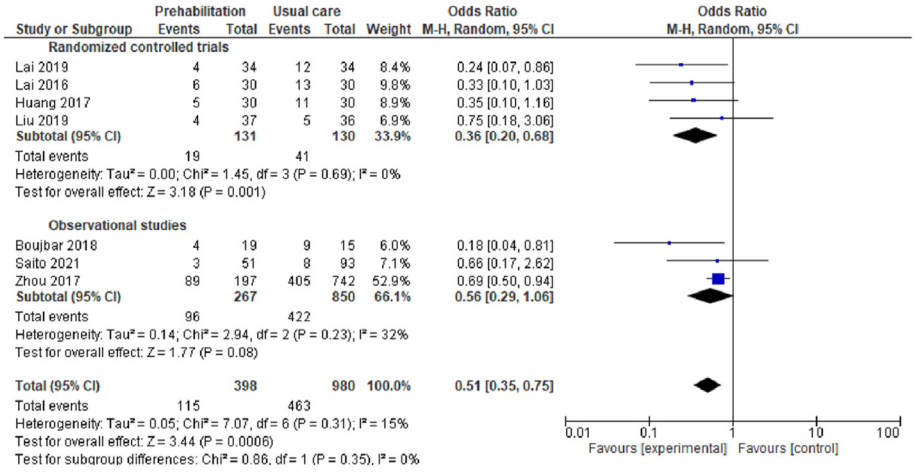
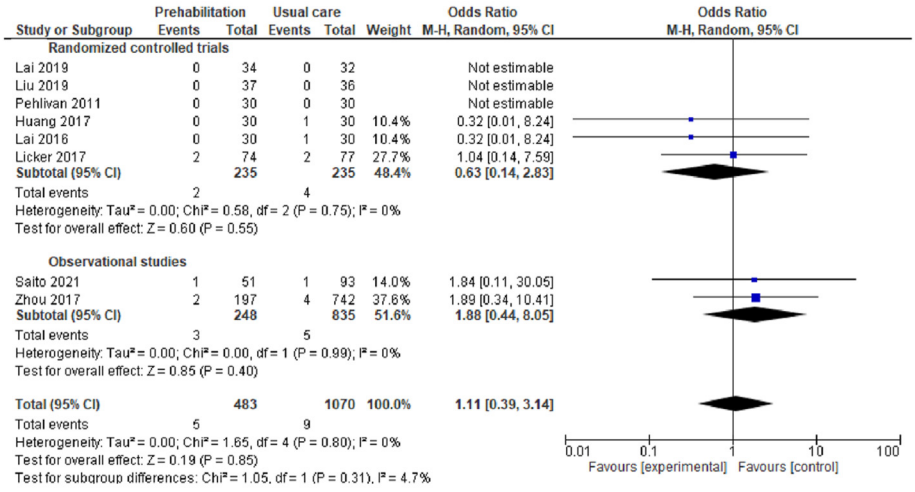


Fig. 1. The effect of exercise prehabilitation compared to usual care on postoperative pulmonary complications (A), any postoperative complications (B), any postoperative severe complications (C) postoperative mortality (D), and length of hospital stay (E).

C



D



E

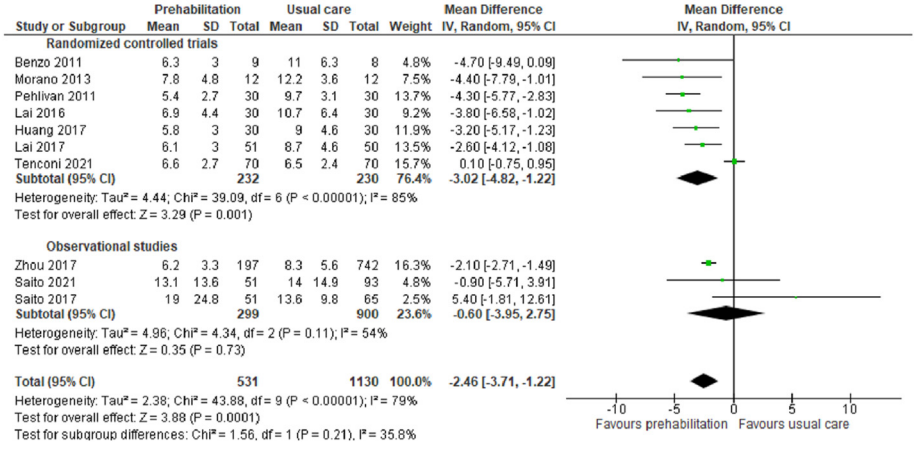


Fig. 1. (*continued*).

Table 5
Summary of findings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Certainty assessment							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	1. Publications bias[a] 2. Residual confounding 3. Dose-response gradient 4. Risk of ineffectiveness	Exercise prehabilitation with event/ total	Usual care with event/ total	Relative (95% CI)	absolute (95% CI)	
Postoperative pulmonary complications (follow up: 90 days)											
8	Randomized controlled trials	Serious[a,b]	Not serious	Not serious	Not serious	1. Publication bias 2. Strongly suspected 3. Strong association[a] 4. <80%	41/248 (16.5%)	95/251 (37.8%)	**OR 0.31** (0.20 −0.48)	**220 fewer per 1.000** (from 270 less to 152 less)	⨁⨁⨁◯ Moderate
Postoperative pulmonary complications (follow up: 90 days)											
2	Observational studies	Very serious[a,c]	Not serious	Not serious	Not serious	1. Publication bias 2. Strongly suspected 4. <80%	39/248 (15.7%)	204/807 (25.3%)	**OR 0.60** (0.41 −0.88)	**84 fewer per 1.000** (from 131 less to 23 less)	⨁◯◯◯ Very low
Postoperative any complications (follow up: 90 days)											
11	Randomized controlled trials	Very serious[a,b]	Not serious	Not serious[b]	Not serious	1. Publication bias 2. Strongly suspected 3. Strong association[a] 4. <80%	112/387 (28.9%)	116/300 (38.7%)	**OR 0.37** (0.23 −0.61)	**198 fewer per 1.000** (from 260 less to 109 less)	⨁⨁◯◯ Low
Postoperative any complications (follow up: 90 days)											
4	Observational studies	Very serious[a,c]	Not serious	Not serious	Serious	1. Publication bias 2. Strongly suspected 4. <80%	116/300 (38.7%)	468/915 (51.1%)	**OR 0.58** (0.35 −0.97)	**134 fewer per 1.000** (from 243 less to 8 less)	⨁◯◯◯ Very low
Postoperative severe complications (follow up: 90 days)											
4	Randomized controlled trials	Very serious[a,b]	Not serious	Not serious	Not serious	3. Strong association 4. <80%	19/131 (14.5%)	41/130 (31.5%)	**OR 0.36** (0.20 −0.68)	**173 fewer per 1.000** (from 231 less to 77 less)	⨁⨁⨁◯ Moderate
Postoperative severe complications (follow up: 90 days)											
3	Observational studies	Very serious[a,c]	Not serious	Not serious	Not serious	2. All plausible residual confounding would suggest spurious effect, while no effect was observed 4. <80%	96/267 (36.0%)	422/850 (49.6%)	**OR 0.56** (0.29 −1.06)	**141 fewer per 1.000** (from 274 less to 15 less)	⨁⨁◯◯ Low
Postoperative mortality (follow up: 90 days)											
6	Randomized controlled trials	Very serious[a,b]	Not serious	Not serious	extremely serious[f]	1. Publication bias 2. Strongly suspected 4. <80%	2/235 (0.9%)	4/235 (1.7%)	**OR 0.63** (0.14 −2.83)	**28 fewer per 1.000** (from 15 less to 30 more)	⨁◯◯◯ Very low
Postoperative mortality (follow up: 90 days)											
2	Observational studies	Very serious[a,c]	Not serious	Not serious	extremely serious[f]	1. Publication bias 2. Strongly suspected 4. <80%	3/248 (1.2%)	5/835 (0.6%)	**OR 1.11** (0.39 −3.14)	**1 more per 1.000** (from 4 less to 13 more)	⨁◯◯◯ Very low
Length of hospital stay											
15	Randomized controlled trials	Very serious[a,b]	Serious[c]	Not serious	Not serious	1. Publication bias 2. Strongly suspected 3. Strong association[a] 4. <80%	232	230	–	MD **3.02 lower** (4.82 less to 1.22 less)	⨁◯◯◯ Very low
Length of hospital stay											
3	Observational studies	Very serious[a,c]	Serious[d]	Not serious	Serious[d,e]	1. Publication bias 2. Strongly suspected 4. <80%	299	900	–	MD **0.6 lower** (3.95 lower to 2.75 higher)	⨁◯◯◯ Very low

Abbreviations: CI = confidence interval, OR = odds radio.
*: Funnel pots have been added in supplementary file 4.
[a] Most studies showed a high risk of bias favouring the usual care group.
[b] Unclear process and no description of the assignment, and undescribed exercise adherence to the intended interventions.
[c] High risk on confounding and classification of intervention status can be affected by knowledge of the outcome or risk of the outcome.
[d] Wide pooled effects of the confidence intervals.
[e] Small minimal important difference.
[f] Very imprecise estimate due to the low rate of such event in this small sample size.

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Declaration of competing interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.01.024.

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