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Associations between pretreatment physical performance tests and treatment complications in patients with non-small cell lung cancer: A systematic review

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ABSTRACT

This systematic review evaluated which outcome variables and cut-off values of pretreatment exercise tests are associated with treatment complications in patients with stage I-III non-small cell lung cancer (NSCLC). PRISMA and Cochrane guidelines were followed. A total of 38 studies with adult patients undergoing treatment for stage I-III NSCLC who completed pretreatment exercise tests, and of whom treatment-related complications were recorded were included. A lower oxygen uptake at peak exercise amongst several other variables on the cardiopulmonary exercise test and a lower performance on field tests, such as the incremental shuttle walk test, stair-climb test, and 6-minute walk test, were associated with a higher risk for postoperative complications and/or postoperative mortality. Cut-off values were reported in a limited number of studies and were inconsistent. Due to the variety in outcomes, further research is needed to evaluate which outcomes and cut-off values of physical exercise tests are most clinically relevant.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, in which non-small cell lung cancer (NSCLC) accounts for 85 % of all lung cancers (Netherlands Cancer Registry, 2016). For fit patients with early stage I, II, and – in some cases – IIIa NSCLC, lung resection is recommended according to European guidelines (Brunelli et al., 2009a). For patients with early stage disease who are considered inoperable, stereotactic radiotherapy is the preferred treatment (Postmus et al., 2017). For fit patients with stage III disease, chemoradiotherapy is the standard treatment with the option of adjuvant immunotherapy after non-progression (Eberhardt et al., 2015). Clinical trials have shown that intensive treatment results in considerably longer disease-free and overall survival in relatively fit patients (Auperin et al., 2010), but is often accompanied with a high incidence of treatment complications (Driessen et al., 2016). Patients with a higher risk for treatment complications are often characterized as aged ≥70 years, having tobacco-related comorbidity and/or cognitive impairment, being physically inactive and/or malnourished, and especially as having a low physiological reserve capacity (low aerobic fitness) (Janssen-Heijnen et al., 2004; Jemal et al., 2011).

When standard pulmonary function tests to verify resectability, such

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as the forced expiratory volume in 1 s (FEV_1) and carbon monoxide lung diffusion capacity (DLCO), fall below 80 % of predicted, a cardiopulmonary exercise test (CPET) is performed for surgical decision-making (Vansteenkiste et al., 2014). Oxygen uptake at peak exercise (VO_{2peak}) as measured during a CPET has been used most widely for preoperative risk stratification in lung surgery; however, current cut-off values are not based on solid evidence (Warner et al., 2016; Roman et al., 2014). Although the CPET is the gold standard to evaluate a patient's aerobic fitness, it is relatively expensive, time-consuming, and requires trained personnel (Granger et al., 2015; Jones et al., 2007). Hence, practical, cheap, easy to administer, and time efficient field exercise tests such as the incremental shuttle walk test (iSWT), stair-climb test (SCT), 6-minute walk test (6MWT), 12-minute walk test (12MWT), and steep ramp test might be less complicated tests to estimate a patient's preoperative aerobic fitness (Granger et al., 2015; Cavalheri et al., 2016). The use of field exercise tests for estimating aerobic fitness has previously been investigated in patients with cardiac and pulmonary disease (Ambrosino, 1999). Results demonstrated a moderate-to-strong correlation between CPET-derived variables of aerobic fitness and field exercise test outcomes (Holland et al., 2014). Nevertheless, systematic evidence on the association between pretreatment field exercise tests and treatment complications in patients with NSCLC is lacking, especially in patients who undergo chemoradiotherapy.

Due to the predictive value of pretreatment exercise tests for treatment complications, outcome variables of the CPET and field exercise tests might be used to identify high-risk patients who might benefit from lifestyle interventions before and during cancer treatment (prehabilitation and early rehabilitation, respectively). Lifestyle interventions might improve a patient's aerobic fitness, which in turn can improve treatment tolerance and effectiveness (Ni et al., 2017; Perrotta et al., 2019). The aim of this systematic review was to evaluate which outcome variables of pretreatment exercise tests are associated with treatment complications in patients with stage I-III NSCLC, as well as to identify cut-off values for clinical risk stratification.

2. Methods

A systematic review was performed with respect to outcome variables of pretreatment exercise tests and their association with treatment complications in patients with stage I-III NSCLC. The Cochrane guidelines for systematic reviews (Vainshelboim, 2019) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (David Moher et al., 2009) were followed.

2.1. Literature search

PubMed, Embase, and Cinahl databases were searched for eligible studies published up to December 2019. In addition, references from retrieved studies were screened. The search strategy contained a combination of controlled vocabulary (e.g., MeSH or EMTREE) and key word terms and phrases searched in titles, abstracts, and key word fields, as appropriate. Key terms included in the search strategy included non-small cell lung cancer and lung surgery, exercise test, walk test (6-minute walk test and incremental shuttle walk test), cardiopulmonary exercise test or CPET, anaerobic threshold, aerobic fitness, postoperative complications, overall treatment time and postoperative mortality. Combinations of text words of the literature search are shown in Table 1.

2.2. Study selection

Prospective and retrospective cohort studies with adult patients undergoing treatment for stage I-III NSCLC who completed pretreatment exercise tests, and of whom treatment-related complications were recorded were included. Studies primarily investigating the impact of prehabilitation or any structured exercise program on physical fitness before treatment, and studies that primarily described survival as outcome measure were excluded. Conference papers, case series, case reports, opinion studies (non-original research), systematic reviews, randomized clinical trials, and studies not published in English were also excluded. Two reviewers (M.V. and R.F.) independently screened titles and abstracts of studies obtained by the literature search. Assessment of

Table 1
Combinations of text words of the literature search according to the PECO-structure.

Databases [a]	Population	Exposure/comparator	Outcome
Embase, PubMed, Cinahl	("lung neoplasms"[MeSH Terms:NoExp] OR "Carcinoma, Non-Small-Cell Lung"[Mesh] OR lung-neoplasm*[tiab] OR lung-cancer*[tiab] OR pulmonary-cancer*[tiab] OR pulmonary-neoplasm*[tiab] OR cancer-of-the-lung*[tiab] OR cancers-of-the-lung*[tiab] OR non-small-cell-lung-carcinoma*[tiab] OR NSCLC[tiab] OR non-small-cell-lung-cancer*[tiab]) AND ("Chemoradiotherapy"[Mesh] OR "Radiotherapy"[MeSH] OR "Pulmonary Surgical Procedures"[MeSH] OR "Pneumonectomy"[Mesh] OR "Thoracic Surgical Procedures"[MeSH] OR radiation[tiab] OR radiotherap*[tiab] OR chemotherap*[tiab] OR radiochemotherapy[tiab] OR radiochemotherapies[tiab] OR radio-chemotherapy[tiab] OR radio-chemotherapies[tiab] OR CHRT[tiab] OR chemoradiation[tiab] OR chemo-radiation[tiab] OR pulmonary-surgical-procedure*[tiab] OR lung-operation*[tiab] OR lung-resection*[tiab] OR ((lobectomy[tiab] OR lobectomies[tiab] OR segmentectomy[tiab] OR segmentectomies[tiab] OR resection*[tiab] OR surgery[tiab] OR surgic*[tiab]) AND (pulmonary*[tiab] OR lung[tiab] OR pneumon*[tiab])) OR pneumonectomy[tiab] OR thoracic-surgical-procedure*[tiab] OR "Therapeutics"[Mesh] OR therapeutic*[tiab] OR treatment*[tiab]) OR operable[tiab]	"Walk Test"[MeSH] OR "Walking"[MeSH] OR field-test*[tiab] OR walk-test*[tiab] OR walking-test*[tiab] OR "exercise test"[MeSH] OR exercise-test*[tiab] OR 6-minute-walk-test*[tiab] OR 6-minute-walking-test*[tiab] OR 6MWT[tiab] OR 6MWD[tiab] OR 6-minute-walk-distance*[tiab] OR 6-minute-walking-distance*[tiab] OR six-minute-walk-test*[tiab] OR six-minute-walk[tiab] OR 6-minute-walk[tiab] OR six-minute-walking-test*[tiab] OR six-minute-walk-distance*[tiab] OR six-minute-walking-distance*[tiab] OR "stair climbing"[MeSH Terms] OR stair-climbing-test*[tiab] OR SCT[tiab] OR steep-ramp-test*[tiab] OR shuttle-walk-test*[tiab] OR shuttle-walk-distance[tiab] OR shuttle-walking-test*[tiab] OR ESWT[tiab] OR ISWT[tiab] OR ESWD[tiab] OR ISWD[tiab] OR SWT[tiab] OR SWD[tiab] OR "exercise test"[MeSH] OR "Ergometry"[Mesh] OR exercise-test*[tiab] OR cardiopulmonary-exercise-test*[tiab] OR VO_{2peak}-test*[tiab] OR VO2-max-test*[tiab] OR physical-fitness-test*[tiab] OR ergometry-test*[tiab] OR cycle-ergometr*[tiab] OR cardiopulmonary-exercise*[tiab] OR CPX[tiab] OR (CPET[tiab] NOT clostridium[tiab]) OR exercise-tolerance[tiab] OR Peak-oxygen-consumption[tiab] OR Peak-oxygen[tiab]	"postoperative complications"[MeSH] OR postoperative-complication*[tiab] OR associated-conditions[tiab] OR coexistent-disease[tiab] OR complication*[tiab] OR toxicity-of-side-effects[tiab] OR toxicit*[tiab] OR adverse-effects[tiab] OR side-effects[tiab] OR adverse-reaction*[tiab] OR adverse-events[tiab] OR "mortality"[MeSH] OR mortality[tiab] OR Mortalities[tiab] OR death[tiab] OR fatality[tiab] OR fatal*[tiab] OR "hospitalization"[MeSH] OR hospitalisation[tiab] OR hospitalization[tiab] OR length-of-stay[tiab] OR length-of-hospital-stay[tiab] OR patient -discharge [tiab] OR reduce-treatment-dose[tiab] OR overall-treatment-time[tiab] OR time-to-treatment[tiab] OR delay*[tiab] OR dose-modification*[tiab] OR completion-of-planned-treatment[tiab] OR toxicity-of-systematic-treatment[tiab] OR withdrawal[tiab] OR chemotherapy-toxicity[tiab] OR toxicity-systematic-treatment[tiab] OR postoperative-decrease[tiab] OR pulmonary function[tiab] OR health-outcomes[tiab] OR postoperative[tiab] OR post-operative[tiab] OR operative-risk[tiab] OR risk-stratification[tiab]

[a] : search presented for PubMed only: the search strategy has been adjusted for searching in the other databases.

full texts according to eligibility criteria was performed independently by these two reviewers. Any disagreements between reviewers were resolved through discussion and consensus. When no consensus was reached, a third party acted as an adjudicator (J.V.).

2.3. Data extraction

Two authors (M.V. and R.F.) independently extracted data from each of the included studies by using a standardized extraction form. Information collected included the name of the first author, year of publication, type of cohort, sample size, age and sex of participants, used pretreatment exercise test, used test protocol with steps, preselection method, follow-up period, type of cancer treatment, outcome variables of treatment complications, measures for associations between outcomes of pretreatment tests and treatment complications, and cut-off values of pretreatment exercise tests. Complications of treatment were reported as cardiac complications and pulmonary complications or as mortality when mortality was separately identified as a complication.

2.4. Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (David Moher et al., 2009). Studies scoring 3 or 4 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain were defined as good-quality studies. Studies scoring 2 stars in the selection domain, 1or 2 stars in comparability domain, and 2 or 3 stars in outcome/exposure domain were defined as fair-quality studies, and a score of 0–1 star in selection domain were classified as fair-quality studies. Studies scoring 0 stars in the comparability domain, or 0 or 1 stars in the outcome/exposure domain, were defined as low-quality studies (Wells et al., 2013). Two investigators (M.V. and R.F.) independently assessed the quality of included studies. Discrepancies were resolved by consensus. When consensus was not reached, a third person acted as an adjudicator (J.V.).

2.5. Data analyses

Associations between pretreatment exercise tests and treatment complications were interpreted as statistically significant when p-values were <0.05. Cut-off values for outcomes of exercise tests for an increased risk of treatment complications were presented when receiver operating characteristic (ROC) curves, including area under the curve (AUC), sensitivity and specificity, and/or odds ratios were determined in the included studies.

3. Results

3.1. Study characteristics

3.1.1. Study selection

Initially, the literature search identified 684 studies, of which 38 were eventually included. A flow diagram for the selection of studies is shown in Fig. 1. An overview of the characteristics of the 38 studies is shown in Table 2. Twenty-three studies were prospective observational, eleven studies were retrospective observational, and four studies had an unclear observational design. The oldest publications dated from 1984 (Smith et al., 1984; Bagg, 1984) and the most recent from 2018 (Kasikcioglu et al., 2018; Yakal et al., 2018; Miyazaki et al., 2018; Nakagawa et al., 2018). Median sample size was 110 patients (ranging from 12 to 287, with a total of 4191) and the mean age of the included patients ranged between 56 and 72 years. In nine studies (24 %), it was indicated which stages of NSCLC had been included (Kasikcioglu et al., 2018; Yakal et al., 2018; Brutsche et al., 2000; Fang et al., 2013;

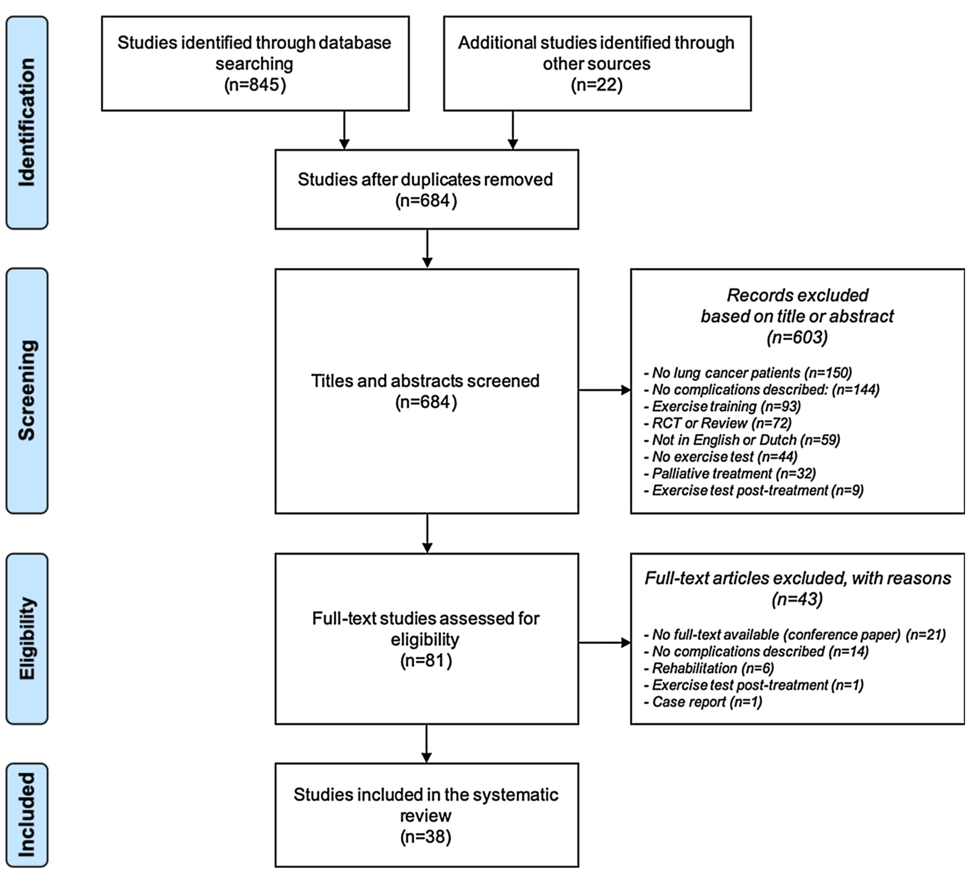

Fig. 1. PRISMA flow diagram displaying the selection of studies and reasons for exclusion.

Table 2
Study and characteristics of included studies that evaluated the association of preoperative exercise tests and postoperative complications.

First author	Type of cohort[a]	Sample size (n)	Age (years) mean ± SD (range)	Male (%)	Preselection	Preoperative exercise test	Protocol	Follow-up period (days)	Type of surgery
(Miyazaki et al., 2018)	Retrospective	209	72.4 ± 8.3	58	NR	CPET (cycle ergometer)	Ramp, 1 W/6 s	30, 90	L, S
(Rodrigues et al., 2016)	NR	54	64.7 ± 7.9 (46−80)	92	NR	CPET (cycle ergometer)	Ramp, NR	30	L
Shafiek et al., 2016)	Retrospective	51	65.4 ± 9.1	82	FEV_1 <30% [b] and DLCO < 40% [b]	CPET (cycle ergometer)	Incremental, NR	30, 365	P, L, S
(Vargas Fajardo Mdel et al., 2014)	Prospective	83	64.6 ± 9.5 (38−80)	82	FEV_1 and DLCO < 40% [b]	CPET (cycle ergometer)	Ramp, Wasserman	NR	P, L, S, B
(Fang et al., 2013)	Prospective	107	65.3 ± 7.0	97	FEV_1 <60% [b]	CPET (cycle ergometer)	Ramp, 10−20 Watt/min	30	P
(Licker et al., 2011)	Retrospective	243	NR	58	FEV_1 <80% [b]	CPET (cycle ergometer)	Ramp, 20 W/min	30	R
(Campione et al., 2010)	Retrospective	99	67.4 ± 8.1 (41−83)	81	FEV_1 ≤70% [b]	CPET (cycle ergometer)	Ramp, 10 W/min	30	P, L, S
(Varela et al., 2009)	Prospective	103	62.6 ± 13.5 (20−85)	NR	NR	CPET (cycle ergometer)	Incremental, 30 W/2 min	NR	P, L
(Brunelli et al., 2009b)	Prospective	204	66.5 ± 9.6	NR	FEV_1 <30% [b]	CPET (cycle ergometer)	Ramp, NR	30	P, L, S, WR
(Nagamatsu et al., 2004)	NR	211	65.9 ± 8.4	62	No preselection	CPET (cycle ergometer)	Ramp, 20 W/2 min	30	P, L, B
(Villani and Busia, 2004)	NR	150	57.1 ± 0.7	94	No preselection	CPET (cycle ergometer)	Incremental, 25 W/3 min	30	P
(Villani et al., 2003)	NR	150	57.1 ± 0.7 (33−79)	94	No preselection	CPET (cycle ergometer)	Incremental, 25 W/3 min	30	P
(Brutsche et al., 2000)	Prospective	125	63 ± 11 (20−80)	81	FEV_1 <1.6 L	CPET (cycle ergometer)	Ramp, 20 W/min	30	R
(Bechard and Wetstein, 1987)	Prospective	50	63.8 (47−76)	100	FEV_1 >0.9 L, FEV_1 WR > 1.2 L, $FEV_{1,}$ P > 1.7 L	CPET (cycle ergometer)	Incremental, 12.5 W/min	30	P, L, T
(Bolliger et al., 1995)	Prospective	25	62.8 ± 8.2 (47−77)	68	FEV_1 <2 L and DLCO < 50% [b]	CPET (cycle ergometer)	Ramp, 20 W/min	30	NR
(Richter Larsen et al., 1997)	Prospective	97	64.3 ± 8.9 (38−80)	69	FEV_1 >2.0 L	CPET (cycle ergometer)	Ramp, 10−15 Watt/min	30	P, L, S
(Epstein et al., 1993)	Prospective	42	62.7 ± 2.2	98	FEV_1 <70% [b]	CPET (cycle ergometer)	Ramp, Wasserman	30	P, WR
(Smith et al., 1984)	Prospective	22	55.7 ± 2.0	86	No preselection	CPET (cycle ergometer)	Incremental, 10 W/min	30	L, B, T
(Pate et al., 1996)	Prospective	12	63.6 ± 4.9	NR	FEV_1 <35% [b]	CPET (cycle ergometer), SCT, 12MWT	Incremental, 10 W/min	NR	T
(Holden et al., 1992)	Prospective	23	NR	NR	FEV_1 >2.0 L	CPET (cycle ergometer), SCT, 6MWT	Incremental, 15 W/min	30	P, L, T, WR
(Kasikcioglu et al., 2018)	Prospective	49	61 ± 9 (35−78)	90	NR	CPET (treadmill)	Naughton	NR	P, L, T, WR
(Yakal et al., 2018)	Prospective	123	63 ± 8 (44−85)	85	No preselection	CPET (treadmill)	Bruce	NR	P, L, WR
(Torchio et al., 2010)	Retrospective	145	64.2 ± 7.9 (41−82)	88	No preselection	CPET (cycle ergometer)	Balke	30	P, L, S, B
(Win et al., 2005)	Prospective	99	68.4 ± 8.0 (42−85)	60	No preselection	CPET (treadmill)	Steep	30	P, L
(Dales et al., 1993)	Retrospective	117	NR	62	NR	CPET (treadmill)	Multistage incremental	30	P, L, T, WR
(Fennelly et al., 2016)	Retrospective	101	65.5 ± 11.6 (19−85)	32	FEV_1 and DLCO < 80% [b]	iSWT	Singh	30	T
(Erdoğan et al., 2013)	Prospective	24	61.5 ± 8.6	96	NR	iSWT	Singh	30	P, L, B WR
(Win et al., 2004)	Prospective	111	69 (42−85)	36	NR	iSWT	Singh	NR	P, L, B, WR
(Dong et al., 2017)	Retrospective	171	65 ± 9	76	NR	SCT	Symptom-limited: as fast as they could without stopping to rest until they reached the highest floor possible	30	T
(Refai et al., 2014)	Prospective	287	66.5 ± 8.9	79	No preselection	SCT	Climb at a pace of their own choice, the maximum number of steps	30	P, L
(Nikolic et al., 2007)	Prospective	101	61.1 ± 8.4	81	FEV_1 <2.0 L	SCT	Climb the maximum number of steps, at a pace of their own choice	NR	P, K, T, B
(Toker et al., 2007)	Prospective	150	60.4 ± 10.6	85	NR	SCT	Do their best during 2-flat climbing exercises	NR	P, L

(continued on next page)

Table 2 (*continued*)

First author	Type of cohort[a]	Sample size (n)	Age (years) mean ± SD (range)	Male (%)	Preselection	Preoperative exercise test	Protocol	Follow-up period (days)	Type of surgery
(Brunelli et al., 2001)	Prospective	115	66.5 ± 9.5	77	No preselection	SCT	Symptom-limited: as fast as they could until they reached the highest floor possible	30	P, L
(Nakagawa et al., 2018)	Retrospective	121	71.4 ± 7.0	89	FEV_1 and DLCO < 60% [b]	6MWT	Walking as rapidly as possible	90	L, WR
(Irie et al., 2015)	Prospective	188	71 (64−77) [c]	62	Tumor ≤6 cm and FEV_1 >600 m L	6MWT	ATS statement	NR	L
(Marjanski et al., 2015)	Retrospective	253	63	59	FEV_1 and DLCO < 80% [b]	6MWT	ATS statement	30, 90	L
(Ha et al., 2013)	Retrospective	96	65.6 ± 9.6	52	NR	6MWT	ATS statement	30	P, S, WR
(Bagg (1984)	Prospective	30	NR	NR	NR	12MWT	Cooper	28	T

Abbreviations: B=bilobectomy resection; CPET=cardiopulmonary exercise test; iSWT=incremental shuttle walk test; L=lobectomy; NR=not reported; P=pneumonectomy; SCT=stair-climb test; ; S=segmentectomy, T=thoracotomy; WR=wedge resection; 12MWT=12-minute walk test; 6MWT=6-minute walk test.
[a] :all studies were observational.[b]:values are expressed as a percentage of predicted.[c]:median (interquartile range).

Nagamatsu et al., 2004; Richter Larsen et al., 1997; Ha et al., 2013; Irie et al., 2015; Marjanski et al., 2015), of which five studies (14 %) also reported stage distribution among patients (Campione et al., 2010; Pate et al., 1996; Shafiek et al., 2016; Erdoğan et al., 2013; Win et al., 2004). No study was found in which patients underwent any other NSCLC treatment than surgery, such as chemoradiotherapy. One or more of the following surgical techniques were used in the included studies: pneumonectomy, lobectomy, segmentectomy, bilobectomy, wedge resection, and thoracotomy. Although the initial search strategy captured CPET as well as field exercise tests, the resultant outcomes of the CPET and field exercise tests are presented separately. Preselection of participants by means of FEV_1 or DLCO was used in 22 studies (58 %).

3.1.2. Treatment complications

In all included studies, surgical resection for NSCLC was performed. Neoadjuvant chemotherapy and/or adjuvant chemotherapy were included in five studies (13 %) (Rodrigues et al., 2016; Brunelli et al., 2009b; Villani and Busia, 2004; Villani et al., 2003; Toker et al., 2007). An association between outcome variables of pretreatment exercise tests and postoperative cardiac and pulmonary complications and/or postoperative mortality was found in 33 of the 38 studies (87 %). The included studies do not provide information about which complications occur most frequently stratified by type of surgery. The most frequently reported complications were pneumonia (in 88 % of the studies), lobar atelectasis (bronchoscopy required) (78 %), symptomatic cardiac arrhythmias requiring treatment (61 %), myocardial infarction (60 %), mortality (65 %), pulmonary embolism (57 %), long-term mechanical ventilation (>48 h) (51 %), infiltration on chest radiography (27 %), and purulent sputum (19 %). In two studies (5%), complications were not categorized, and in 15 studies (39 %), postoperative mortality was reported separately.

3.1.3. Quality assessment

The results of the quality assessment are depicted in Table 3. In seven studies there was no consensus, because one of the domains was interpreted differently between the reviewers. These discrepancies were resolved by discussion between the two reviewers. In 26 studies (68 %), there was a poor methodological quality, five studies (13 %) were ranked with a fair quality, and seven studies (19 %) had a good quality. A poor score on the Newcastle-Ottawa quality assessment scale was often the result of the lack of: 1) an accurate description of the representativeness of the exposed cohort (23/38, 61 %), 2) a clear description of the outcome of interest at start of the study (34/38, 89 %), 3) a clear description on the comparability of cases in the cohorts (21/38, 55 %), and 4) complete description of complications and/or mortality (24/38, 63 %). In addition, length of follow-up and adequacy of follow-up of the missing cases were poorly or not described (15/38, 39 %).

3.2. Pretreatment exercise tests

Associations between pretreatment exercise tests and postoperative complications are presented in Table 4.

3.2.1. Cardiopulmonary exercise test

In 20 (80 %) of the 25 studies where the CPET was used preoperatively, one or more outcomes were statistically significant associated with postoperative complications. Cycle ergometry was used in 20 studies (80 %) (Smith et al., 1984; Miyazaki et al., 2018; Brutsche et al., 2000; Fang et al., 2013; Nagamatsu et al., 2004; Richter Larsen et al., 1997; Campione et al., 2010; Pate et al., 1996; Shafiek et al., 2016; Rodrigues et al., 2016; Vargas Fajardo Mdel et al., 2014; Licker et al., 2011; Varela et al., 2009; Brunelli et al., 2009b; Villani and Busia, 2004; Villani et al., 2003; Bechard and Wetstein, 1987; Bolliger et al., 1995; Epstein et al., 1993; Holden et al., 1992), of which 16 (80 %) reported that preoperative CPET variables were associated with postoperative complications. Different CPET protocols were used, with ten different workload increment protocols. A total of 24 different CPET variables were associated with one or more types of complications after surgery. Fifteen studies (Smith et al., 1984; Miyazaki et al., 2018; Brutsche et al., 2000; Nagamatsu et al., 2004; Richter Larsen et al., 1997; Pate et al., 1996; Shafiek et al., 2016; Rodrigues et al., 2016; Licker et al., 2011; Brunelli et al., 2009b; Villani and Busia, 2004; Villani et al., 2003; Bechard and Wetstein, 1987; Epstein et al., 1993) reported that VO_{2peak} (both absolute values and values normalized for body mass) was associated with cardiac and pulmonary complications or mortality after surgery, whereas two studies merely reported an association with postoperative pulmonary complications (Fang et al., 2013; Villani et al., 2003). Predicted VO_{2peak} was associated with postoperative cardiac and pulmonary complications (Smith et al., 1984; Brutsche et al., 2000; Fang et al., 2013; Rodrigues et al., 2016; Licker et al., 2011; Villani and Busia, 2004; Villani et al., 2003), pulmonary complications (Brunelli et al., 2009b), and postoperative mortality (Richter Larsen et al., 1997; Brunelli et al., 2009b). Oxygen pulse at peak exercise was found to be associated with postoperative cardiac and pulmonary complications (Fang et al., 2013; Campione et al., 2010; Epstein et al., 1993), as well as with postoperative mortality (Fang et al., 2013). Oxygen uptake at the ventilatory anaerobic threshold normalized for body mass was associated with cardiac and pulmonary complications (Bechard and Wetstein, 1987; Nagamatsu et al., 2015) and postoperative mortality (Fang et al., 2013). The slope describing the relation between minute ventilation and carbon dioxide production (VE/VCO_2-slope) was also associated with cardiac and pulmonary complications (Miyazaki et al., 2018; Shafiek et al., 2016) and postoperative mortality (Miyazaki et al., 2018). For all associations, a better preoperative score on the respective CPET variable with cycle ergometry was associated with a lower risk of postoperative complications, with the exception of four studies in which no association

Table 3
Quality assessment based on the Newcastle-Ottawa Scale for cohort studies[a].

First author	Selection				Comparability	Outcome			
	Representativeness exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest present at start of the study	Comparability of cohorts on the basis of the design of analysis	Assessment of outcome	Follow-up time	Adequacy of follow-up of cohort	Quality [b]
(Miyazaki et al., 2018)	–	A⋆	A⋆	B	A⋆	B⋆	A⋆	D	Fair
(Rodrigues et al., 2016)	D	A⋆	A⋆	B	–	B⋆	A⋆	A⋆	Poor
(Shafiek et al., 2016)	B⋆	A⋆	A⋆	B	A⋆	D	A⋆	D	Poor
(Vargas Fajardo Mdel et al., 2014)	D	A⋆	A⋆	B	–	B⋆	B	A⋆	Poor
(Fang et al., 2013)	B⋆	A⋆	A⋆	B	A⋆	D	A⋆	A⋆	Good
(Licker et al., 2011)	D	A⋆	A⋆	B	A⋆	B⋆	A⋆	A⋆	Fair
(Campione et al., 2010)	A⋆	A⋆	A⋆	B	A⋆	D	A⋆	A⋆	Good
(Varela et al., 2009)	D	A⋆	A⋆	B	A⋆	D	B	D	Poor
(Brunelli et al., 2009b)	D	A⋆	A⋆	B	A⋆, B	D	A⋆	D	Poor
(Nagamatsu et al., 2004)	A⋆	A⋆	A⋆	B	A⋆	D	A⋆	A⋆	Good
(Villani and Busia, 2004)	D	A⋆	A⋆	A⋆	–	D	A⋆	A⋆	Poor
(Villani et al., 2003)	D	A⋆	A⋆	B	–	D	A⋆	D	Poor
(Brutsche et al., 2000)	B⋆	A⋆	A⋆	B	–	D	A⋆	A⋆	Poor
(Bechard and Wetstein, 1987)	D	A⋆	A⋆	B	–	D	A⋆	A⋆	Poor
(Bolliger et al., 1995)	D	A⋆	A⋆	B	–	D	A⋆	B	Poor
(Richter Larsen et al., 1997)	B⋆	A⋆	A⋆	B	–	D	A⋆	A⋆	Poor
(Epstein et al., 1993)	D	A⋆	A⋆	B	A⋆	B⋆	A⋆	A⋆	Fair
(Smith et al., 1984)	D	A⋆	A⋆	B	–	D	A⋆	A⋆	Poor
(Pate et al., 1996)	B⋆	A⋆	A⋆	B	–	A⋆	A⋆	A⋆	Poor
(Holden et al., 1992)	D	A⋆	A⋆	B	–	D	A⋆	A⋆	Poor
(Kasikcioglu et al., 2018)	A⋆	A⋆	A⋆	B	–	D	B	A⋆	Poor
(Yakal et al., 2018)	A⋆	A⋆	A⋆	B	–	D	B	A⋆	Poor
(Torchio et al., 2010)	D	A⋆	A⋆	B	A⋆	D	A⋆	A⋆	Fair
(Win et al., 2005)	A⋆	A⋆	A⋆	B	A⋆	B⋆	A⋆	A⋆	Good
(Dales et al., 1993)	D	A⋆	A⋆	B	–	B⋆	A⋆	A⋆	Poor
(Fennelly et al., 2016)	D	A⋆	A⋆	A⋆	A⋆	B⋆	A⋆	A⋆	Good
(Erdoğan et al., 2013)	A⋆	A⋆	A⋆	B	–	D	A⋆	A⋆	Poor
(Win et al., 2004)	B⋆	A⋆	A⋆	B	–	D	B	D	Poor
(Dong et al., 2017)	D	A⋆	A⋆	B	A⋆	D	A⋆	B	Poor
(Refai et al., 2014)	D	A⋆	A⋆	B	–	D	A⋆	A⋆	Poor
(Nikolic et al., 2007)	D	A⋆	A⋆	B	A⋆	B⋆	A⋆	A⋆	Poor
(Toker et al., 2007)	D	A⋆	A⋆	B	A⋆	D	B	D	Poor
	D	A⋆	A⋆	B	A⋆, B	D	A⋆	A⋆	Fair

(continued on next page)

Table 3 (*continued*)

First author	Selection				Comparability	Outcome			
	Representativeness exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest present at start of the study	Comparability of cohorts on the basis of the design of analysis	Assessment of outcome	Follow-up time	Adequacy of follow-up of cohort	Quality [b]
(Brunelli et al., 2001)									
(Nakagawa et al., 2018)	D	A⋆	A⋆	A⋆	–	B⋆	A⋆	B	Poor
(Irie et al., 2015)	B⋆	A⋆	A⋆	A⋆	–	B⋆	B	A⋆	Good
(Marjanski et al., 2015)	B⋆	A⋆	A⋆	B	A⋆	B⋆	A⋆	A⋆	Good
(Ha et al., 2013)	A⋆	A⋆	A⋆	B	–	B⋆	A⋆	A⋆	Poor
(Bagg (1984)	D	A⋆	A⋆	B	–	D	A⋆	D	Poor

[a] stars (⋆) are awarded on the basis of answers (A, B, C, or D) provided for each item.
[b] thresholds for converting the Newcastle-Ottawa scale scores to AHRQ standards (good, fair, and poor): good quality = 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; fair quality = 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; poor quality = 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain.

was reported (20 %) (Vargas Fajardo Mdel et al., 2014; Varela et al., 2009; Bolliger et al., 1995; Holden et al., 1992). In five studies (20 %) (Kasikcioglu et al., 2018; Yakal et al., 2018; Torchio et al., 2010; Win et al., 2005; Dales et al., 1993) treadmill ergometry was performed. In these studies, a total of seven different CPET outcomes were associated with one or more types of postoperative complications and/or postoperative mortality. Absolute VO_{2peak} was associated with postoperative cardiac and pulmonary complications (Kasikcioglu et al., 2018; Yakal et al., 2018; Torchio et al., 2010) with pulmonary complications (Dales et al., 1993), and postoperative mortality (Yakal et al., 2018; Torchio et al., 2010). Predicted VO_{2peak} was associated with postoperative complications (Win et al., 2005). The oxygen uptake efficiency slope (Kasikcioglu et al., 2018; Yakal et al., 2018) and the VE/VCO_2-slope were associated with cardiac and pulmonary complications after surgery (Torchio et al., 2010).

3.2.2. Incremental shuttle walk test

Three studies (Erdoğan et al., 2013; Win et al., 2004; Fennelly et al., 2016) investigated the association between preoperative iSWT performance and postoperative complications. One study reported that oxygen desaturation ≥4% during the iSWT, and distance walked <400 m were associated with a higher risk of postoperative complications (Fennelly et al., 2016). In two studies, no associations were found between outcomes of the preoperative iSWT and postoperative complications (Erdoğan et al., 2013; Win et al., 2004).

3.2.3. Stair-climb test

A preoperative SCT was performed in seven studies (Pate et al., 1996; Holden et al., 1992; Dong et al., 2017; Refai et al., 2014; Nikolic et al., 2007; Toker et al., 2007; Brunelli et al., 2001), in which different SCT protocols were used. Patients were asked 1) to climb the maximum number of steps at a pace of their own choice (Pate et al., 1996; Holden et al., 1992; Refai et al., 2014; Nikolic et al., 2007; Brunelli et al., 2001), 2) to climb five stairs with 20 steps as fast as they could without stopping to rest (Dong et al., 2017), or 3) to do their best during 2 stair-climbing exercises in which each flight of stairs was composed of 20 steps and climbing time was recorded (Toker et al., 2007). There were also differences between studies concerning test duration, step height, and number of steps. The total number of steps that were taken was associated with postoperative complications (Pate et al., 1996; Brunelli et al., 2009b; Holden et al., 1992; Nikolic et al., 2007) and postoperative mortality (Nikolic et al., 2007). There was an association between the height of climbing in meters, exercise oxygen desaturation, and the change in heart rate from start to finish on the one hand and cardiac and pulmonary complications after surgery on the other hand (Dong et al., 2017). Test duration, speed, heart rate, and oxygen saturation during exercise were associated with postoperative complications and postoperative mortality (Nikolic et al., 2007). Oxygen saturation at the end of the SCT, and the change in oxygen saturation during the SCT were associated with postoperative complications (Toker et al., 2007). In all studies where the preoperative SCT was used, better scores on the test variables were associated with a lower risk of postoperative complications, with the exception of one study that reported no association (Pate et al., 1996).

3.2.4. Six- and twelve-minute walk test

Five studies (Nakagawa et al., 2018; Ha et al., 2013; Irie et al., 2015; Marjanski et al., 2015; Holden et al., 1992) assessed the ability of the preoperative 6MWT to predict the risk of postoperative complications and postoperative mortality. Distance walked as a percentage of predicted was associated with cardiac and pulmonary complications (Ha et al., 2013). Other studies reported an association between shorter walked distances and a higher risk of postoperative complications (Irie et al., 2015; Marjanski et al., 2015; Pate et al., 1996; Holden et al., 1992), and postoperative mortality (Holden et al., 1992). All studies using the preoperative 6MWT showed that a poor performance was associated with a higher risk for postoperative complications. Two studies (Bagg, 1984; Pate et al., 1996) used the 12MWT during the preoperative assessment. Both studies reported no association between the distance walked and postoperative complications. One small study (Pate et al., 1996) described a relation between the walked distance in meters and complications, in which a better performance on the 12MWT was associated with a lower risk on postoperative complications.

3.2.5. Cut-off values

Cut-off values of outcomes of pretreatment exercise tests associated with an increased risk of postoperative complications and postoperative mortality are presented in Table 5. A limited number of studies reported a cut-off value of outcomes of pretreatment exercise tests for a higher risk for postoperative complications; however, the accuracy of these cut-off values was usually moderate. A study using the CPET on a cycle ergometer reported VO_{2peak} cut-off values of <12.8 mL/kg/min and <58 % of predicted to be optimal cut-off values for a higher risk for postoperative cardiac complications (Licker et al., 2011). In the same study, optimal cut-off values indicating a higher risk for postoperative pulmonary complications were a VO_{2peak} <13.6 mL/kg/min or a predicted

Table 4
Association between preoperative exercise tests and postoperative complications.

First author	Mean age of patients without /with complications (years)	Variables associated with cardiac and/or pulmonary complications				Variables associated with postoperative mortality			
Cardiopulmonary exercise test, cycle ergometer		**VO_{2peak}**	**VE/ VCO_2-slope**	**VO_{2peak} (% of predicted)**	**Other**	**VO_{2peak}**	**VE/ VCO_2-slope**	**VO_{2peak} (% of predicted)**	**Other**
(Miyazaki et al., 2018)	NR	Y	Y	–	–	–	Y	–	–
(Rodrigues et al., 2016)	65.0/64.1	Y	–	Y	–	N	–	–	–
(Shafiek et al., 2016)	64.0/67.1	Y	Y		WR_{peak}	–	–	–	–
(Vargas Fajardo Mdel et al., 2014)	63.8/69.0	N	–	N	–	–	–		–
(Fang et al., 2013)	64.7/66.9	Y	–	Y	O_2 $pulse_{peak}$ ΔSpO_2 VAT	–	–	–	–
(Licker et al., 2011)	62/66	Y	–	Y	–	–	–	–	–
(Campione et al., 2010)	67.2/68.3	N	–	–	O_2 $pulse_{peak}$	–	–	–	–
(Varela et al., 2009)	NR	–	–	–	–	–	–	–	–
(Brunelli et al., 2009b)	66.3/67.6	Y	–	Y [b]	–	Y	–	Y	O_2 $pulse_{peak}$
(Nagamatsu et al., 2004)	NR	Y	–	–	VAT	–	–	–	–
(Villani and Busia, 2004)	57.2/57.1	Y	–	Y	WR_{peak}	–	–	–	–
(Villani et al., 2003)	57.2/57.1	Y	–	Y	WR_{peak}	–	–	–	–
(Brutsche et al., 2000)	63/64	Y	–	Y	–	–	–	–	–
(Bechard and Wetstein, 1987)	63.6/66.6	Y	–	–	VAT	–	–	–	–
(Bolliger et al., 1995)	NR	N	–	N	–	–	–	–	–
(Richter Larsen et al., 1997)	NR	Y	–	–	WR_{peak} VE_{peak}	–	–	Y	WR_{peak}
(Epstein et al., 1993)	63/62	Y	–	–	O_2 $pulse_{peak}$	Y	–	–	–
(Smith et al., 1984)	51.8/59.6	Y	–	Y	–	–	–	–	–
(Pate et al., 1996)	64.2/63.1	Y	–	–	–	–	–	–	–
(Holden et al., 1992)	67.0/70.1	N	–	–	–	N	–	–	–
Cardioulmonary exercise test, treadmill		**VO_{2peak}**	**VE/ VCO_2-slope**	**VO_{2peak} (% of predicted)**	**Other**	**VO_{2peak}**	**VE/ VCO_2-slope**	**VO_{2peak} (% of predicted)**	**Other**
(Kasikcioglu et al., 2018)	NR	Y	–	–	OUES	–	–	–	–
(Yakal et al., 2018)	NR	Y	–	–	OUES VE_{peak} HR at the VAT	Y	–	–	OUES VE_{peak}
(Torchio et al., 2010)	63.7/67.1	Y	Y	N	–	Y	Y	N	–
(Win et al., 2005)	NR	N	–	Y	–	N	–	N	–
(Dales et al., 1993)	NR	Y [b]	–	N	VE_{peak} [b]	–	–	–	–
Incremental shuttle walk test		**Distance**							
(Fennelly et al., 2016)	64.0/70.7	Y	–	–	–	–	–	–	–
(Erdoğan et al., 2013)	NR	N	–	–	–	–	–	–	–
(Win et al., 2004)	NR	N	–	–	–	–	–		–
Stair-climb test		**Height of climbing**	**Steps**		**Other**	**Height of climbing**	**Steps**		**Other**
(Dong et al., 2017)	NR	Y	–	–	Predicted exercise SpO_2 ΔHR	–	–	–	–
(Refai et al., 2014)	65.5/69.7	N	–	–	–	–	–	–	–
(Nikolic et al., 2007)	58.2/67.1	–	Y	–		–	Y	–	SpO_2 during

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Table 4 (*continued*)

First author	Mean age of patients without /with complications (years)	Variables associated with cardiac and/or pulmonary complications				Variables associated with postoperative mortality			
(Toker et al., 2007)	60.7/59.3	–	–	–	SpO_2 during exercise HR_{max} SpO_2 at start SpO_2 at the end SpO_2 change during exercise	–	–	–	exercise HR_{max}
(Brunelli et al., 2001)	NR	–	Y	–	VO_{2peak}	–	–	–	–
(Pate et al., 1996)	64.2/63.1	Y	Y	–	Number of flights	–	–	–	–
(Holden et al., 1992)	67.0/70.1	–	Y	–	VO_{2peak}	–	Y	–	VO_{2peak}
6-minute walk test/12-minute walk test		**Distance**	**ΔSpO_2**		**Other**	**Distance**	**ΔSpO_2**		**Other**
(Nakagawa et al., 2018)	65.3/69.2	–	Y	–	SpO_2	–	Y	–	SpO_2
(Irie et al., 2015)	NR	Y	–		–	–	–	–	–
(Marjanski et al., 2015)	NR	Y	–	–	–	N	–	–	–
(Ha et al., 2013)	64.8/66.7	N	N	–	HRR Distance % of predicted	–	–	–	HRR
(Holden et al., 1992)	67.0/70.1	Y	–	–	–	Y	–	–	–
(Pate et al., 1996)	64.2/63.1	Y	–	–	–	–	–	–	–
(Bagg, 1984)	NR	N	–		–	–	–	–	–

Abbreviations: ATS=American Thoracic Society; DLCO=carbon monoxide lung diffusion capacity; FEV_1=forced expiratory volume in 1 s; HR=heart rate; HRR=heart rate reserve; N=no, not statistically significant; NR=not reported; OUES=oxygen uptake efficiency slope; O_2 $pulse_{peak}$=oxygen pulse (VO_2/HR) at peak exercise; P=pneumonectomy; SpO_2=transcutaneous pulse oxygen; VAT=ventilatory anaerobic threshold; VE_{peak}=minute ventilation at peak exercise; VE/VCO_2-slope=slope describing the relationship between the minute ventilation and carbon dioxide production; VO_{2peak}=oxygen uptake at peak exercise; WR=wedge resection; WR_{peak}=work rate at peak exercise; Y=yes, statistically significant; ΔHR=difference between heart rate at start and end of exercise; ΔSpO_2=transcutaneous pulse oxygen saturation difference during load exercise.
[a]% of predicted.
[b]Only pulmonary complications.

VO_{2peak} <53 % of predicted, whereas a VO_{2peak} <12.3 mL/kg/min and a predicted VO_{2peak} <37 % were optimal cut-off values for postoperative mortality (Licker et al., 2011). In another study, a VO_{2peak} cut-off value of ≤500 mL/min was reported to indicate a higher risk for postoperative cardiac and pulmonary complications (Epstein et al., 1993). In another study, most optimal VE/VCO_2-slope cut-off values for an increased risk for postoperative complications were >35 (Shafiek et al., 2016), while a VE/VCO_2-slope >40 was reported as a cut-off value for an increased risk for postoperative mortality (Miyazaki et al., 2018). A VO_{2peak} <19.1 mL/kg/min, measured by means of a CPET on a treadmill, was a cut-off value for an increased risk for postoperative complications (Kasikcioglu et al., 2018), whereas a VE/VCO_2-slope ≥34 reflected an increased risk for postoperative mortality (Torchio et al., 2010). Participants who walked a distance <500 m at the iSWT had an increased risk for cardiac and pulmonary postoperative complications (Fennelly et al., 2016). When using the preoperative 6MWT, a distance walked <400 m (Irie et al., 2015) and <500 m (Marjanski et al., 2015) were cut-off values for an increased risk for postoperative complications.

4. Discussion

This systematic review aimed to evaluate which outcome variables of pretreatment exercise tests are associated with treatment complications in patients with stage I-III NSCLC, as well as to identify cut-off values that can be used for clinical risk stratification. Results demonstrate that a wide variety of outcome variables of different preoperative exercise tests seem to be associated with postoperative complications and/or postoperative mortality. However, used exercise protocols varied widely between the studies. In addition, only a limited number of cut-off values with a moderate accuracy were provided. Publications on other treatment strategies than surgery were lacking.

The CPET is the most frequently used preoperative exercise test and mandatory in guidelines as a risk assessment tool when lung function tests values are <80 % of predicted. VO_{2peak} was associated with postoperative complications and/or postoperative mortality in 18 of the 25 studies (72 %), in which a higher aerobic fitness reflected a reduced risk. Lower preoperative aerobic fitness has been shown to be associated with an increased risk for short-term and long-term postoperative complications in several other surgical populations as well (Moran et al., 2016; West et al., 2014; Moyes et al., 2013; Lee et al., 2018). Although the CPET seems to be a valuable test that is associated with postoperative complications in patients with NSCLC, accurate and consistent cut-off values to identify patients with a higher risk for complications are lacking. This means that the best method for pretreatment risk assessment based on CPET is still unclear, given the wide variety of associated outcomes and study characteristics. In the current systematic review, VO_{2peak} cut-off values for an increased risk for postoperative complications ranged between <12.8 mL/kg/min and <19.1 mL/kg/min (Kasikcioglu et al., 2018; Licker et al., 2011). One study (Licker et al., 2011) reported a VO_{2peak} cut-off value of <58 % of predicted to reflect a higher risk for cardiac complications. A VO_{2peak} cut-off value of <53 % of predicted was reported in the same study for a higher risk for postoperative pulmonary complications, and <37 % of predicted for a higher risk for postoperative mortality (Licker et al., 2011). Interpretation of these cut-off values is debatable, because of uncertainty concerning the used VO_{2peak} references values and the poor methodological quality of studies. Several international guidelines have described a large range of VO_{2peak} cut-off values between <16 mL/kg/min and <20 mL/kg/min,

Table 5
Cut-off values at pretreatment exercise tests for an increased risk for postoperative complications and postoperative mortality.

First author, year	Variable	Cut-off value for an increased risk for postoperative complications	
Cardiopulmonary exercise test, cycle ergometer			
(Licker et al., 2011)	**VO_{2peak}**	<12.8 mL/kg/min [a]	AUC 0.717 (95 % CI of 0.651−0.777), sensitivity 51%, specificity 85%
		<13.6 mL/kg/min [b]	AUC 0.708 (95 % CI of 0.640−0.771), sensitivity 63%, specificity 72%
		<12.3 mL/kg/min [c]	AUC 0.723 (95 % CI of 0.654−0.784), sensitivity 51%, specificity 85%
(Epstein et al., 1993)	**VO_{2peak}**	>500 mL/min	1.0 (reference category)
		≤500 mL/min [a, b]	OR 6.0 (95 % CI of 1.4−26.0)
		≥500 mL/min	1.0 (reference category)
		<500 mL/min [a]	OR 6.2 (95 % CI of 1.36−28.5
(Rodrigues et al., 2016)	**VO_{2peak} % of predicted**	>61 %	1.0 (reference category)
		≤61 % [a, b]	OR 5.1 (95 % CI of 1.5−17.8)
(Licker et al., 2011)	**VO_{2peak} % of predicted**	<58 % [a]	AUC 0.657 (95 % CI of 0.589−0.722), sensitivity 75%, specificity 48%
		<53 % [b]	AUC 0.633 (95 % CI of 0.562−0.700), sensitivity 64%, specificity 61%
		<37 % [c]	AUC 0.616 (95 % CI of 0.544−0.684), sensitivity 30%, specificity 95%
(Miyazaki et al., 2018)	**VE/VCO_2-slope**	<40	1.0 (reference category)
		≥40 [c]	OR 1.05 (95 % CI of 1.0−1.1)
(Shafiek et al., 2016)	**VE/VCO_2-slope**	≤35	1.0 (reference category)
		>35 [a, b, c]	OR 5.3 (95 % CI of 1.3−20.8)
(Richter Larsen et al., 1997)	**WR_{peak}**	<70 W [a, b]	Sensitivity 39 %, specificity 83 %
Cardiopulmonary exercise test, treadmill			
(Kasikcioglu et al., 2018)	**VO_{2peak}**	19.1 mL/kg/min	AUC 0.81
(Torchio et al., 2010)	**VE/VCO_2-slope**	≥34 [c]	AUC 0.871 (95 % CI 0.70−1.01)
Incremental shuttle walk test			
(Fennelly et al., 2016)	**Distance**	≥400 m	1.0 (reference category)
		<400 m [a, b]	OR 4.3 (95 % CI of 1.4−15.9)
6-minute walk test			
(Irie et al., 2015)	**Distance**	≥400 m	1.0 (reference category)
		<400 m [a, b]	OR 4.0 (95 % CI of 1.6−10.2)
(Marjanski et al., 2015)	**Distance**	≥500 m	1.0 (reference category)
		<500 m [a, b]	OR 2.6 (95 % CI of 1.4−4.9), sensitivity 36%, specificity 81.9%

Abbreviations: VE/VCO_2-slope=slope describing the relationship between the minute ventilation and carbon dioxide production; VO_{2peak}=oxygen uptake at peak exercise; AUC=area under the curve; CI=confidence interval; WR_{peak}=work rate at peak exercise; ROC=receiver operating characteristic.
[a] : cardiac complications.
[b] : pulmonary complications.
[c] : postoperative mortality.

and a VO_{2peak} between <35 % and <40 % of predicted to identify patients undergoing lung resection for cancer with an increased risk for postoperative complications (Brunelli et al., 2013; Lim et al., 2010). A broad range in used cut-off values was also seen in the current review, possibly as a result of poor methodological quality and inadequate sample size of studies. VO_{2peak} is a measure of aerobic fitness that requires a maximal effort of the patient, whereas the oxygen uptake at the ventilatory anaerobic threshold is a submaximal indicator of aerobic fitness that has been consistently reported to be an independent predictor of morbidity, mortality, and length of stay following major abdominal surgery (Moran et al., 2016). Nevertheless, only a limited number of studies (Fang et al., 2013; Nagamatsu et al., 2004; Bechard and Wetstein, 1987) addressed the prognostic value of the preoperative oxygen uptake at the ventilatory anaerobic threshold for postoperative outcomes in patients undergoing lung surgery. Therefore, more research is needed.

Field tests require little equipment and training prior to use (Fotheringham et al., 2015). In comparison, the CPET requires well-trained staff and relatively expensive equipment. The CPET provides a more in-depth assessment of cardiopulmonary function and gas exchange and, as described above, has been reported to predict outcome following lung cancer surgery. Unfortunately, the CPET may not always be available; making field tests an attractive alternative. However, there is only limited evidence to justify their use in the preoperative setting. Intuitively, the preoperative iSWT is more demanding than submaximal field tests and may therefore be a superior method of estimating aerobic fitness when the CPET is unavailable. Nevertheless, associations between the iSWT and postoperative complications are not covered sufficiently by study results; in only one of three studies a statistically significant association was found. Therefore, currently using the iSWT for risk-stratification seems not to be recommended. Similar to a study in abdominal surgery (Reddy et al., 2016), this systematic review demonstrated that a better performance on the preoperative SCT was associated with a lower risk for postoperative complications following lung surgery. This is in line with a previous publication, in which stair-climbing seemed to be predictive for postoperative outcomes after abdominal surgery (Reddy et al., 2016). In the current systematic review, also an association between a lower distance walked on the preoperative 6MWT and a higher risk for postoperative complications was shown. In two studies (Irie et al., 2015; Marjanski et al., 2015), 6MWT distance cut-off values of respectively <400 m and <500 m were associated with postoperative complications. A difference of 100 m in cut-off values is rather large. This is possibly a reflection of the small number of included patients. In addition, the 6MWT is susceptible to biased results, as patients can regulate their physical effort during the test which may underestimate or overestimate the results (Dourado et al., 2011). No study was found that investigated the association between the preoperative steep ramp test and postoperative complications or postoperative mortality. A previous study in adult cancer survivors demonstrated a strong correlation between steep ramp test performance and aerobic fitness (VO_{2peak}) as objectively measured during the CPET (De Backer et al., 2007). Furthermore, another study in hepatic surgery demonstrated that a lower aerobic fitness, as estimated with the steep ramp test, was associated with postoperative complications (Van Beijsterveld et al., 2019). This easy-to-use short-time maximal exercise test (Bongers and Takken, 2014) might therefore also be used for preoperative risk assessment in patients with lung cancer; however, evidence is currently lacking.

To correctly interpret the results, it is essential to know that there are limitations in the included studies. A poor score on the Newcastle-Ottawa Scale was particularly found in articles older than ten years. This is mainly due to the non-description or incomplete description of the population, as well as the representativeness of the exposed cohort, the assessment of the outcome, and the follow-up time. There was considerable variation between the studies in the type of surgery, the used outcome variables of exercise tests, and the incomplete description of postoperative complications. This variation could have influenced the associations between the outcome of the exercise test, and postoperative complications or mortality. The physiological impact and risks of a segmentectomy are expected to be less than those of a pneumonectomy; therefore, in different surgical procedures it would intuitively be expected to use different relative VO_{2peak} thresholds for preoperative risk stratification, depending on the extent of the surgical trauma (Licker et al., 2011).

Although studies have shown that preoperative exercise tests are associated with postoperative complications, more attention needs to be paid to which outcome variables and cut-off values of the CPET are clinically relevant, as well as to the possibility of supplementing the CPET with field tests. In an optimal situation there is a possibility of identifying high-risk patients before the start of the treatment, after which the physical performance status might be improved by prehabilitation in order to reduce a patient's risk for complications during and/or after treatment (Licker et al., 2017; Stefanelli et al., 2013).

Only surgical patients were included in this systematic review. More attention should be paid to the potential of exercise tests to predict treatment complications in patients with NSCLC who undergo other intensive treatments, such as chemoradiotherapy. Efforts should be made internationally to reach consensus on standardizing pretreatment exercise tests for accurate cut-off values in pretreatment risk stratification. In future studies, the description of postoperative complications and postoperative mortality should be used according to a standardized protocol, and consensus should be reached to use the same follow-up time regarding complications and mortality to enable pooling of study results. Currently, the evidence of field tests to predict treatment complications is weaker than for the CPET. In addition, research regarding the prognostic values of pretreatment field tests for treatment complications is of poor quality, which underlines the need for high-quality research using standardized field exercise test protocols.

5. Conclusion

A better performance of patients on preoperative exercise tests, especially a higher aerobic fitness as measured by the CPET, is associated with a lower risk for postoperative complications in patients with NSCLC. However, it is difficult to provide recommendations for pretreatment exercise tests to predict the risk of treatment complications due to a lack of accurate test-specific cut-off values. Additionally, recommendations for the use of field tests are difficult due to heterogeneity in tests, protocols, and used outcome measures in the current literature. Therefore, standardizing pretreatment exercise test protocols is eminent and more attention needs to be paid to which outcome variables and cut-off values of pretreatment exercise tests are clinically relevant. In addition, further research is needed concerning the ability of pretreatment exercise tests to accurately identify patients who have an increased risk for treatment complications across all curative NSCLC treatment options. This is important, as especially these high-risk patients might benefit from interventions to improve their physical performance status before treatment initiation.

Author contributions

The responsibility for the content of the manuscript is taken by MV. Both MV and RF have made substantial contributions to the acquisition of data, analysis and interpretation. All authors contributed to the interpretation and critical revision of the contents of the manuscript, provided approval for the current manuscript version, and agreed to be accountable for all aspects of the work and remaining questions.

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Declaration of Competing Interest

The authors report no declarations of interest.

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