Value of Cardiopulmonary Exercise Testing in the Prognosis Assessment of Chronic Obstructive Pulmonary Disease Patients: A Retrospective, Multicentre Cohort Study

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Keywords

Chronic obstructive pulmonary disease · Lung function · Cardiopulmonary exercise testing · Prognosis · All-cause mortality

Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is one of the most common chronic diseases associated with high mortality. Previous studies suggested a prognostic role for peak oxygen uptake (VO₂peak) assessed during cardiopulmonary exercise testing (CPET) in patients with COPD. However, most of these studies had small sample sizes or short follow-up periods, and despite their relevance, CPET parameters are not included in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) tool for assessment of severity. **Objectives:** We therefore aimed to assess the prog-

nostic value of CPET parameters in a large cohort of outpatients with COPD. **Methods:** In this retrospective, multicentre cohort study, medical records of patients with COPD who underwent CPET during 2004–2017 were reviewed and demographics, smoking habits, GOLD grade and category, exacerbation frequency, dyspnoea score, lung function measurements, and CPET parameters were documented. Relationships with survival were evaluated using Kaplan-Meier analysis, Cox regression, and receiver operating characteristic (ROC) curves. **Results:** Of a total of 347 patients, 312 patients were included. Five-year and 10-year survival probability was 75% and 57%, respectively. VO₂peak significantly predicted survival (hazard ratio: 0.886 [95% confidence interval: 0.830; 0.946]). The optimal VO₂peak threshold for discrimination of 5-year survival was 14.6 mL/kg/min (area under ROC curve: 0.713). Five-year survival in patients with VO₂peak <14.6 mL/kg/min versus ≥ 14.6 mL/kg/min was 60% versus 86% in

GOLD categories A/B and 64% versus 90% in GOLD categories C/D. **Conclusions:** We confirm that $\text{VO}_{2\text{peak}}$ is a highly significant predictor of survival in COPD patients and recommend the incorporation of $\text{VO}_{2\text{peak}}$ into the assessment of COPD severity.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic diseases worldwide, affecting 105 million men and 70 million women [1]. The severity of COPD is graded based on airflow limitation (measured as forced expiratory volume in 1 s [FEV_1]) [2], but prognosis in COPD is not determined by lung function limitations alone. Compared with the general population, patients with COPD have higher rates of comorbidity, especially cardiac disease, diabetes mellitus, lung cancer, and depression [3, 4]. These comorbidities significantly influence mortality [5, 6] as well as cardiorespiratory fitness and physical activity [7]. Physical activity in turn significantly influences the course of COPD (decline of lung function) [8] and survival in patients with COPD [9]. Cardiopulmonary exercise testing (CPET) has prov-

en to be an important non-invasive tool for assessing patients with various pulmonary diseases, such as COPD, interstitial lung disease, or cystic fibrosis [10–16].

In patients with COPD, multidimensional indices have been established for the evaluation of prognosis [17]. Some of these indices include parameters of cardiorespiratory fitness, such as the 6-min walking distance or peak oxygen uptake ($\text{VO}_{2\text{peak}}$) assessed during CPET [18]. The prognostic value of CPET parameters in patients with COPD has been reported in several studies [19–24], but most of these studies had small sample sizes and only a few had an observation time exceeding 5 years [21–23], and despite their relevance only few CPET parameters were currently included. Further, CPET variables were not included in key algorithms for assessment of COPD severity [2, 25]. The aim of this multicentre, retrospective, observational study was to assess the long-term prognostic value of CPET-derived parameters in a large cohort of outpatients with COPD.

Patients/Methods

Patients

Patients with COPD of all grades who had undergone CPET during the period January 2004–December 2017 were retrospec-

Fig. 1. Patient flow. COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; FEV_1 , forced expiratory volume in 1 s.

tively included from different pulmonary specialist practices in Germany. Exclusion criteria were coincident other airway or pulmonary diseases, chronic hypercapnic respiratory insufficiency with arterial partial pressure of carbon dioxide >50 mm Hg at rest, acute COPD exacerbations, necessary change of long-term medication in the 6 weeks prior to inclusion, unstable coronary disease necessitating intervention in the previous 6 months, impaired left ventricular pump function (ejection fraction <50%) measured by echocardiogram, clinical signs of right heart overload, and uncontrolled comorbidities. Enrolled patients were excluded from the analysis if their observation period was <6 months or if they did not have a post-bronchodilatation FEV₁ value recorded.

Data Collection

The following information was collected from the medical records of participating patients: gender, age, body mass index (BMI), smoking history, number of exacerbations in the year preceding lung function testing and CPET, lung function parameters, and CPET data. Lung function parameters were calculated relative to reference values as described previously [26–28]. CPET parameters were obtained using a modified Jones protocol (3 min rest, 1 min unloaded cycling, stepwise increase in workload of 16 Watt/min, starting with unloaded cycling plus the ergometer-related permanent load, 5 min recovery) on a braked cycle ergometer, as described previously [29]. All technical staff in the participating centres underwent specific CPET training, and the evaluation of CPET data was performed centrally by few experienced physicians. If a patient had undergone CPET multiple times during the study period, only the first CPET was included for analysis. The severity grading of COPD followed the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades I–IV and GOLD categories A–D [2] as well as the modified BMI, airflow obstruction, dyspnoea, and exercise capacity (mBODE) index [18], the age, dyspnoea, and airflow obstruction index [30], and the dyspnoea, airflow obstruction, current smoking status, and exacerbations index [31]. The degree of dyspnoea was assessed by the modified MRC scale.

The participating patients were followed until June 30, 2018. Survival was determined by contacting the patient or their local physician. Patients who could not be contacted were classed as lost to follow-up.

Statistical Analyses

Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA); $p < 0.05$ was considered statistically significant. No sample size calculation was performed; all patients with available data who underwent CPET at participating centres were included. Differences between groups were analysed by the Wilcoxon test. The analysis of survival data followed the Kaplan-Meier method. To identify predictors of survival, models were determined using Cox regression with elimination of variables by selection procedures using a cut-off p value of 0.05. For selected parameters, optimal cut-offs for prediction of survival were identified using receiver operating characteristic (ROC) curves and the Youden index.

Analysis of Literature

We searched PubMed for observational studies of the prognostic value of CPET parameters in COPD published up to Dec 10, 2020, with the following terms in the title/abstract: (cardiopulmo-

Table 1. Patient characteristics

	Patients with COPD (<i>n</i> = 312)
Female	81 (26.0)
Age at time of CPET, years	65±9
BMI, kg/m ²	26.9±5.2
Time since COPD diagnosis, years (<i>n</i> = 171)	8±7
Smoking status (<i>n</i> = 299)	
Never-smoker	36 (12.0)
Smoker	112 (37.5)
Ex-smoker	151 (50.5)
Pack years available	
Smoker (<i>n</i> = 84)	38±14
Ex-smoker (<i>n</i> = 150)	38±21
COPD grade (GOLD)	
I	9 (2.9)
II	86 (27.6)
III	170 (54.5)
IV	47 (15.1)
COPD category (<i>n</i> = 242)	
A	15 (6.2)
B	49 (20.2)
C	16 (6.6)
D	162 (66.9)
Dyspnoea scale (mMRC; <i>n</i> = 275)	
1	33 (12.0)
2	98 (35.6)
3	128 (46.5)
4	16 (5.8)
Exacerbations in previous year (<i>n</i> = 223), <i>n</i>	
0–1	153 (68.6)
>1	70 (31.4)
mBODE index (<i>n</i> = 275)	4.79 (2.25)
0	5 (1.8)
1	22 (8.0)
2	24 (8.7)
3	28 (10.2)
4	39 (14.2)
5	42 (15.3)
6	48 (17.5)
7	41 (14.9)
8	14 (5.1)
9	8 (2.9)
10	4 (1.5)
ADO index (<i>n</i> = 275)	4.66 (1.51)
0	1 (0.4)
1	9 (3.3)
2	14 (5.1)
3	35 (12.7)
4	52 (18.9)
5	78 (28.4)
6	61 (22.2)
7	23 (8.4)
8	2 (0.7)
DOSE index (<i>n</i> = 196)	3.09 (1.47)
0	6 (3.1)
1	29 (14.8)
2	27 (13.8)
3	55 (28.1)
4	47 (24.0)
5	24 (12.2)
6	6 (3.1)
7	2 (1.0)

Data are presented as mean±standard deviation or *n* (%). BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; GOLD, global initiative for chronic obstructive lung disease; mMRC, modified medical research council; mBODE, modified BMI, airflow obstruction, dyspnoea, and exercise capacity; ADO, age, dyspnoea, and airflow obstruction; DOSE, dyspnoea, airflow obstruction, current smoking status, and exacerbations.

nary exercise test OR cardiopulmonary exercise tests OR cardiopulmonary exercise testing OR CPET OR pulmonary exercise test OR pulmonary exercise tests OR pulmonary exercise testing OR oxygen uptake OR O₂ uptake OR oxygen consumption OR O₂ consumption OR VO₂ OR VO₂max) AND (mortality OR survival OR prognosis OR prognostic OR death OR deaths) AND (chronic obstructive pulmonary disease OR COPD). Studies focusing on a specific comorbidity associated with COPD were excluded. The identified studies suggested a prognostic role for VO₂peak and other variables assessed during CPET in patients with COPD. However, CPET parameters have not yet been included in the GOLD tool for assessment of COPD severity or prognosis.

Results

Patients

In total, 347 patients with COPD were enrolled (Fig. 1). We excluded 18/347 patients because their observation period was <6 months, and 17/347 patients because the post-bronchodilatation FEV₁ value was missing. The remaining 312 patients (mean ± standard deviation [SD] observation time: 67 ± 44 months [range: 6–170 months]) were included in the analysis. By the end of the study (June 30, 2018), 43/347 patients could not be contacted and were therefore lost to follow-up.

Patient characteristics are shown in Table 1. The mean age of the patients at the time of inclusion into the study was 65 ± 9 years, and the majority were male (74%). Most patients (54%) had COPD in GOLD grade III, indicating severe airflow limitation.

Lung function values and CPET results are summarized in Table 2. The mean FEV₁ value indicated severe airflow limitation. Pulmonary exercise limitation (ratio of minute ventilation [V_E] to maximum voluntary ventilation >80%) was detected in 48% of the patients. Impaired ventilatory efficiency was detected in 45% of the patients when defined as a V_E/carbon dioxide output (VCO₂) slope of >34, and in 58% of the patients when defined as a V_E/VCO₂ nadir >34.

Survival

After 3, 5, and 10 years, the survival probability was 83%, 75%, and 57%, respectively. Patient characteristics, lung function parameters, and CPET results were compared between those who had died and those who were still alive at each of the 3 follow-up time points (Tables 3–5). In all 3 comparisons, the deceased patients were significantly older at study entry and had significantly lower global diffusion capacity, cardiopulmonary capacity (maximum power, VO₂peak, and VO₂@AT), end-tidal pressure of carbon dioxide @AT (petCO₂@AT), ventila-

Table 2. Pulmonary function and CPET parameters

	Patients with COPD (n = 312)
Pulmonary function	
FEV ₁ /FVC, % (n = 308)	55.2±14.0
FEV ₁ , % predicted	45.6±16.4
VC, % predicted (n = 308)	68.4±17.2
RV, % predicted (n = 264)	206.8±66.0
RV/TLC, % (n = 262)	162.7±29.2
TLC, % predicted (n = 264)	117.9±23.0
DLCO, % predicted (n = 149)	39.4±15.9
KCO, % predicted (n = 152)	53.1±20.4
CPET	
Maximum power, % predicted* (n = 311)	53.0±16.9
VO ₂ peak, % predicted*	58.3±17.0
VO ₂ @AT, % predicted* (n = 265)	71.4±18.0
VO ₂ peak/HRpeak, % predicted* (n = 309)	72.0±18.9
V _E peak, % predicted* (n = 310)	64.1±17.9
V _E /MVV, % (n = 308)	79.9±19.4
Proportion of patients with V _E /MVV >80%	149 (48.4)
BFpeak, breaths/min (n = 310)	32±7
V _E /VCO ₂ slope (n = 300)	35±10
Proportion of patients with V _E /VCO ₂ slope >34	135 (45.0)
petCO ₂ @AT, mm Hg (n = 260)	34.0±6.1
Proportion of patients with petCO ₂ @AT >33, mm Hg	134 (51.5)
V _E /VCO ₂ nadir (n = 270)	36.7±7.7
Proportion of patients with V _E /VCO ₂ @AT >34	157 (58.1)

Data are presented as mean ± standard deviation or n (%). BFpeak, peak breathing frequency; CPET, cardiopulmonary exercise testing; COPD, chronic obstructive pulmonary disease; DLCO, diffusion capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; KCO, Krogh factor (diffusion capacity of the lung for carbon monoxide per alveolar volume); PetCO₂@AT, end-tidal pressure of carbon dioxide at anaerobic threshold; RV, residual volume; TLC, total lung capacity; VC, vital capacity; V_E/MVV, ratio of ventilation to maximum voluntary ventilation; V_Epeak, peak ventilation; V_E/VCO₂ nadir, ratio of ventilation to carbon dioxide output; V_E/VCO₂ slope, slope of the relation between ventilation and carbon dioxide output; VO₂@AT, oxygen uptake at anaerobic threshold; VO₂peak, peak oxygen uptake; VO₂peak/HRpeak, ratio of peak oxygen uptake to peak heart rate. * Reference values were calculated as described [29] (see online suppl. Table 1 for details).

tory efficiency (V_E/VCO₂ slope and V_E/VCO₂ nadir), oxygen pulse (VO₂peak/peak heart rate [HRpeak]), and maximum ventilation (V_Epeak) compared with the surviving patients. In the comparisons at 5 and 10 years (but not 3 years) of follow-up, those who had died had a lower BMI, FEV₁, and FEV₁/forced vital capacity ratio than those who were still alive. In addition, volume-adapted diffusion capacity was significantly lower in those who had died compared with those who were still alive at 5 years, and vital capacity was significantly lower and V_E/maximum voluntary ventilation was significantly higher in those who had died compared with those who were still alive at 10 years.

Patients with COPD in GOLD grade I had 100% survival at 10 years (Fig. 2). Survival at 3, 5, and 10 years was 80%, 74%, and 66%, respectively, in patients with grade II COPD, 86%, 79%, and 51%, respectively, in patients with grade III COPD, and 74%, 56%, and 40%, respectively, in

Table 3. Characteristics, pulmonary function, and CPET parameters of patients stratified by survival status at 3 years

	Alive (n = 209)		Deceased (n = 46)		p value
	n	mean ± SD	n	mean ± SD	
Age at time of CPET, years	209	64±10	46	68±8	0.018
BMI, kg/m ²	209	27.4±4.9	46	25.7±5.7	0.054
Time since COPD diagnosis, years	126	9±7	25	11±8	0.25
Pulmonary function					
FEV ₁ /FVC, %	205	56.5±13.4	46	53.0±13.7	0.16
FEV ₁ , % predicted	209	46.6±16.2	46	42.0±14.0	0.11
VC, % predicted	205	68.3±17.4	46	65.6±16.3	0.50
RV, % predicted	168	210.9±58.0	41	195.6±79.0	0.16
RV/TLC, %	167	166.0±27.1	41	157.0±33.6	0.14
TLC, % predicted	168	119.3±20.5	41	111.6±27.6	0.10
DLCO, % predicted	91	40.6±16.5	23	32.6±12.1	0.019
KCO, % predicted	93	54.8±20.9	23	46.5±17.1	0.082
CPET					
Maximum power, % predicted*	208	55.2±17.0	46	47.2±17.7	0.021
VO ₂ peak, % predicted*	209	61.9±16.5	46	50.3±16.5	<0.0001
VO ₂ @AT, % predicted*	177	75.4±17.6	39	64.6±16.1	0.0003
VO ₂ peak/HRpeak, % predicted*	207	75.8±18.4	45	61.4±18.9	<0.0001
VEpeak, % predicted*	208	65.9±17.4	45	58.0±16.7	0.011
VE/MVV, %	206	80.5±19.3	45	78.7±19.3	0.42
BFpeak, breaths/min	208	31±6	45	32±7	0.62
VE/VCO ₂ slope	201	34±9	43	37±10	0.031
petCO ₂ @AT, mm Hg	176	35.1±6.2	35	32.2±5.8	0.016
VE/VCO ₂ nadir	184	35.1±6.8	37	39.9±9.1	0.0016

BFpeak, peak breathing frequency; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; DLCO, diffusion capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; KCO, Krogh factor (diffusion capacity of the lung for carbon monoxide per alveolar volume); PetCO₂@AT, end-tidal pressure of carbon dioxide at anaerobic threshold; RV, residual volume; SD, standard deviation; TLC, total lung capacity; VC, vital capacity; VE/MVV, ratio of ventilation to maximum voluntary ventilation; VEpeak, peak ventilation; VE/VCO₂ nadir, ratio of ventilation to carbon dioxide output; VE/VCO₂ slope, slope of the relation between ventilation and carbon dioxide output; VO₂@AT, oxygen uptake at anaerobic threshold; VO₂peak, peak oxygen uptake; VO₂peak/HRpeak, ratio of peak oxygen uptake to peak heart rate. *Reference values were calculated as described [29] (see online suppl. Table 1 for details).

Table 4. Characteristics, pulmonary function, and CPET parameters of patients stratified by survival status at 5 years

	Alive (n = 159)		Deceased (n = 65)		p value
	n	mean ± SD	n	mean ± SD	
Age at time of CPET, years	159	64±10	65	69±8	0.0013
BMI, kg/m ²	159	27.6±4.7	65	25.8±5.2	0.011
Time since COPD diagnosis, years	104	9±7	39	11±7	0.27
Pulmonary function					
FEV ₁ /FVC, %	156	57.0±13.0	65	52.2±13.6	0.019
FEV ₁ , % predicted	159	47.2±15.4	65	41.5±14.2	0.013
VC, % predicted	156	68.6±17.5	65	65.5±17.2	0.25
RV, % predicted	124	209.4±57.5	58	201.6±75.1	0.52
RV/TLC, %	123	165.8±26.7	58	160.1±33.0	0.53
TLC, % predicted	124	119.2±20.9	58	113.6±26.2	0.28
DLCO, % predicted	64	42.4±15.6	32	31.9±13.3	0.0010
KCO, % predicted	66	56.7±20.2	32	44.8±17.7	0.0063
CPET					
Maximum power, % predicted*	158	57.3±16.4	65	47.1±17.6	<0.0001
VO ₂ peak, % predicted*	159	63.6±15.8	65	50.8±16.6	<0.0001
VO ₂ @AT, % predicted*	139	76.9±16.6	54	64.3±17.4	<0.0001
VO ₂ peak/HRpeak, % predicted*	157	76.7±17.6	64	62.7±20.6	<0.0001
VEpeak, % predicted*	158	66.8±16.8	64	58.9±16.9	0.0044
VE/MVV, %	157	81.0±19.5	64	80.0±18.8	0.96
BFpeak, breaths/min	158	31±6	64	32±6	0.18
VE/VCO ₂ slope	154	34±10	59	37±9	0.0021
petCO ₂ @AT, mm Hg	137	35.5±6.0	49	32.3±5.8	0.0007
VE/VCO ₂ nadir	144	34.6±6.8	52	39.6±8.3	<0.0001

BFpeak, peak breathing frequency; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; DLCO, diffusion capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; KCO, Krogh factor (diffusion capacity of the lung for carbon monoxide per alveolar volume); PetCO₂@AT, end-tidal pressure of carbon dioxide at anaerobic threshold; RV, residual volume; SD, standard deviation; TLC, total lung capacity; VC, vital capacity; VE/MVV, ratio of ventilation to maximum voluntary ventilation; VEpeak, peak ventilation; VE/VCO₂ nadir, ratio of ventilation to carbon dioxide output; VE/VCO₂ slope, slope of the relation between ventilation and carbon dioxide output; VO₂@AT, oxygen uptake at anaerobic threshold; VO₂peak, peak oxygen uptake; VO₂peak/HRpeak, ratio of peak oxygen uptake to peak heart rate. *Reference values were calculated as described [29] (see online suppl. Table 1 for details).

Table 5. Characteristics, pulmonary function, and CPET parameters of patients stratified by survival status at 10 years

	Alive (n = 40)		Deceased (n = 95)		p value
	n	mean ± SD	n	mean ± SD	
Age at time of CPET, years	40	63±10	95	68±8	0.0058
BMI, kg/m ²	40	28.6±4.4	95	26.4±5.0	0.022
Time since COPD diagnosis, years	4	12±6	59	10±7	0.58
Pulmonary function					
FEV ₁ /FVC, %	38	65.3±7.6	95	52.4±13.0	<0.0001
FEV ₁ , % predicted	40	59.4±20.3	95	41.3±13.0	<0.0001
VC, % predicted	38	71.7±20.0	95	64.4±16.6	0.034
RV, % predicted	10	189.7±98.1	86	204.3±71.1	0.43
RV/TLC, %	10	168.0±50.1	86	162.0±31.6	0.90
TLC, % predicted	10	108.5±31.6	86	114.7±25.2	0.38
DLCO, % predicted	7	52.7±24.3	44	33.3±12.9	0.022
KCO, % predicted	7	64.6±26.3	45	48.0±18.1	0.086
CPET					
Maximum power, % predicted*	39	63.5±17.3	95	48.4±17.1	<0.0001
VO ₂ peak, % predicted*	40	72.6±15.7	95	51.6±15.7	<0.0001
VO ₂ @AT, % predicted*	36	81.9±17.9	79	65.4±16.6	<0.0001
VO ₂ peak/HRpeak, % predicted*	39	85.6±16.6	94	63.5±19.5	<0.0001
VĖpeak, % predicted*	39	71.6±20.9	94	59.4±16.2	0.0012
VĖ/MVV, %	39	68.4±15.3	93	79.7±18.3	0.0005
BFpeak, breaths/min	39	30±6	94	32±6	0.18
VĖ/VCO ₂ slope	40	33±9	89	37±9	0.0004
petCO ₂ @AT, mm Hg	36	35.8±5.8	73	32.8±5.8	0.0042
VĖ/VCO ₂ nadir	36	32.5±7.4	79	38.8±7.9	<0.0001

BFpeak, peak breathing frequency; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; DLCO, diffusion capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; KCO, Krogh factor (diffusion capacity of the lung for carbon monoxide per alveolar volume); PetCO₂@AT, end-tidal pressure of carbon dioxide at anaerobic threshold; RV, residual volume; SD, standard deviation; TLC, total lung capacity; VC, vital capacity; VĖ/MVV, ratio of ventilation to maximum voluntary ventilation; VĖpeak, peak ventilation; VĖ/VCO₂ nadir, ratio of ventilation to carbon dioxide output; VĖ/VCO₂ slope, slope of the relation between ventilation and carbon dioxide output; VO₂@AT, oxygen uptake at anaerobic threshold; VO₂peak, peak oxygen uptake; VO₂peak/HRpeak, ratio of peak oxygen uptake to peak heart rate. * Reference values were calculated as described [29] (see online suppl. Table 1 for details).

Table 6. Two different models for the calculation of predictive variables for survival in multivariate Cox analysis

	HR (95% CI)	χ ²	p value
Model 1*			
Age, years	1.031 (1.003; 1.059)	4.71	0.030
Dyspnoea	1.640 (1.173; 2.291)	8.39	0.0038
VO ₂ peak, mL/kg/min	0.886 (0.830; 0.946)	12.96	0.0003
Model 2†			
Dyspnoea	1.519 (1.103; 2.093)	6.35	0.012
VO ₂ peak, % predicted	0.965 (0.949; 0.981)	18.34	<0.0001

CI, confidence interval; GOLD, global initiative for chronic obstructive lung disease; HR, hazard ratio; VO₂peak, peak oxygen uptake; FEV₁, forced expiratory volume in 1 s. * Model 1 included age, gender, GOLD, grade, degree of dyspnoea, VO₂peak (mL/kg/min), minute ventilation/carbon dioxide output at the anaerobic threshold, and systolic maximum pressure (mm Hg). † Model 2 included GOLD, grade, degree of dyspnoea, VO₂peak (% predicted), maximum power (% predicted), and FEV₁ (% predicted).

patients with grade IV COPD. Survival according to GOLD category is shown in online supplementary Figure 1 (see www.karger.com/doi/10.1159/000519750 for all online suppl. material). Survival at 3, 5, and 10 years was 93%, 93%, and 62%, respectively, in category A, 83%, 76%, and 73%, respectively, in category B, 88%, 88%, and 77%, respectively, in category C, and 84%, 75%, and 48%, respectively, in category D.

Figure 3 shows survival in relation to the mBODE index. Survival at 3, 5, and 10 years was 90%, 85%, and 78%, respectively, in patients with an mBODE score of 0–2,

92%, 86%, and 70%, respectively, in those with an mBODE score of 3–4, 82%, 79%, and 51%, respectively, in those with an mBODE score of 5–6, and 77%, 55%, and 25%, respectively, in those with an mBODE score of 7–10. In an analysis of individual components of the mBODE index (Fig. 4), the degree of patient dyspnoea was found to be an excellent differentiator of survival from the third year onwards. Categories of VO₂peak (% predicted) also differentiated survival well from the third year onwards (except for the categories 60% to <70% predicted vs. >40% to <60% predicted).

Fig. 2. All-cause mortality according to GOLD grades. GOLD, global initiative for chronic obstructive lung disease.

Fig. 3. Survival according to the mBODE index ($n = 275$). mBODE, modified BMI, airflow obstruction, dyspnoea, and exercise capacity.

Fig. 4. Survival according to individual components of the mBODE index ($n = 275$). BMI, body mass index; FEV₁, forced expiratory volume in 1 s; mBODE, modified BMI, airflow obstruction, dyspnoea, and exercise capacity; mMRC, modified medical research council dyspnoea scale; VO₂peak, peak oxygen uptake.

Parameters Relevant to Prognosis

Multivariable stepwise Cox analysis was performed including significant values in univariate analysis, for example, age, gender, VO₂peak (mL/kg/min), COPD grade, degree of dyspnoea, V_E/VCO₂ nadir, and systolic maxi-

um pressure (mm Hg). In this analysis, age, degree of dyspnoea, and VO₂peak were independently predictive of survival (Table 6). A second multivariable forward stepwise Cox analysis was performed including VO₂peak (% predicted), COPD grade, degree of dyspnoea, maximum

Fig. 5. VO₂peak for discrimination of survival at 5 years. In ROC analysis (upper panels), VO₂peak = 14.6 mL/kg/min and VO₂peak = 55% predicted were identified as the optimal thresholds for prediction of survival at 5 years. Kaplan-Meier plots (lower panels) show survival in patient subgroups defined based on these thresholds. AUC, area under the curve (reported with 95% confidence interval); VO₂peak, peak oxygen uptake; ROC, receiver operating characteristic.

power (% predicted), FEV₁ (% predicted), and DLCO (%pred.). In this analysis, degree of dyspnoea and VO₂peak (% predicted) were independently predictive of survival (Table 6). Backward and forward analysis yielded the same results.

ROC curves for VO₂peak were therefore created to identify the optimal threshold for prediction of 5-year

survival (Fig. 5). A VO₂peak of 14.6 mL/kg/min (or 55% predicted) was an excellent discriminator of survival from the second year onwards. The optimal threshold for prediction of 1- and 3-year survival was 14.3 mL/kg/min (or 44% predicted at 1 year and 56% predicted at 3 years) (online suppl. Fig. 2–5). Comparison of ROC curves for VO₂peak (% predicted) and 3 multidimensional prognos-

Fig. 6. ROC analysis of VO₂peak and multidimensional prognostic indices for discrimination of survival at 3 (left) and 5 (right) years. ADO, age, dyspnoea, and airflow obstruction; AUC, area under the curve (reported with 95% confidence interval); DOSE, dyspnoea, airflow obstruction, current smoking status, and exacerbations; mBODE, modified BMI, airflow obstruction, dyspnoea, and exercise capacity; VO₂peak, peak oxygen uptake; ROC, receiver operating characteristic.

tic indices (mBODE, age, dyspnoea, and airflow obstruction, and dyspnoea, airflow obstruction, current smoking status, and exacerbations) demonstrated that VO₂peak had a higher area under the curve (indicating greater discriminative ability) than the multidimensional indices for the prediction of survival at 3 and 5 years (Fig. 6).

Consequently, we analysed whether addition of VO₂peak to the GOLD categories A–D (grouped as A/B and C/D because of the low numbers of patients in categories A and C) would improve differentiation of prognosis. The 5-year survival in patients with VO₂peak <14.6 mL/kg/min versus ≥14.6 mL/kg/min was 60% versus 86% in Group A/B and 64% versus 90% in Group C/D. In a comparable analysis of patients with VO₂peak <55% predicted versus ≥55% predicted, 5-year survival was 0% versus 85% in Group A/B and 61% versus 90% in Group C/D (Fig. 7).

Discussion

Our study of 312 patients with COPD and a mean follow-up of >5 years demonstrates clearly that VO₂peak, a surrogate marker for cardiopulmonary exercise capacity,

has a highly significant influence on survival. Our results suggest that the assessment of prognosis in patients with COPD could be further improved by the addition of VO₂peak to established prognostic indicators.

Survival probability in our study population (75% and 57% after 5 and 10 years, respectively) reflects the impaired prognosis of patients with COPD and was somewhat lower than reported previously in smaller studies by Hiraga et al. [19] (86% and 68% after 5 and 10 years, respectively; *n* = 120), Tojo et al. [22] (93% and 76% after 5 and 10 years, respectively; *n* = 69), and Oga et al. [20] (80% at 5 years; *n* = 150). The mean age, gender distribution, FEV₁, and VO₂peak in our study population were within the range reported in the 3 previous studies [19, 20, 22]; a possible explanation for the difference in survival could be geographical variation (the previous studies were conducted in Japan). Survival at 3 and 5 years stratified by mBODE score was broadly comparable with data from a previous study of 444 patients with COPD in the USA and Spain (which reported 3- and 5-year survival of 93% and 89%, respectively, in those with an mBODE score of 0–2 points, 89% and 81%, respectively, in those with an mBODE score of 3–4

Fig. 7. Kaplan-Meier analysis of survival in patients stratified by GOLD category and VO₂peak. GOLD, global initiative for chronic obstructive lung disease; VO₂peak, peak oxygen uptake.

points, 85% and 66%, respectively, in those with an mBODE score of 5–6 points, and 70% and 54%, respectively, in those with an mBODE score of 7–10 points) [18].

Recommendations for the management of COPD suggest that multidimensional indices such as BODE allow a better assessment of prognosis than individual parameters [2, 25]. However, VO₂peak demonstrated superiority

Fig. 8. Suggested inclusion of VO_2peak in the GOLD ABCD refined assessment tool. COPD, chronic obstructive pulmonary disease assessment test; GOLD, global initiative for chronic obstructive lung disease; mMRC, modified medical research council dyspnoea scale; VO_2peak , peak oxygen uptake.

to specific multidimensional indices for the prediction of mortality in a previous analysis of 150 male patients with COPD [32], and in our study of 312 patients (74% male) with COPD. According to the GOLD 2020 recommendations, assessment of the severity of COPD is based on spirometric classification (GOLD grades I–IV) combined with categorization based on symptoms and history of moderate or severe exacerbations (GOLD categories A–D) [2]. We would like to suggest including VO_2peak in the categorization tool to improve estimation of prognosis if prospective studies are available (Fig. 8).

In our prognosis models, dyspnoea and age were also significantly associated with survival. It has long been known that the degree of dyspnoea has significantly more prognostic relevance than grading according to lung function values in patients with COPD [33–36]. Dyspnoea is a substantial correlate of hyperinflation in patients with COPD, which often results in dynamic hyperinflation and disturbance of ventilatory efficiency [2]. A significant association of age with mortality in patients with COPD has also been observed in previous studies [19, 20, 22]. Several studies have shown that ventilatory insufficiency is characteristic of COPD patients [37], and in some of these its prognostic value could be demonstrated [24]. The present study could demonstrate the significant influence of VE/VCO_2 nadir on prognosis by univariate calculation albeit not by multivariable analysis.

Even though the method seems time-consuming (approximately 45 min per patient), it may deliver many relevant information on cardiopulmonary performance and may lead to further examinations (echocardiography,

left/right heart catheter). Further, it is the only examination method that may indicate the existence of dynamic hyperinflation.

Limitations include the retrospective nature of the study and a relevant bias in the selection of patients, as only patients who had undergone CPET were included for evaluation. The set of history, clinical, and functional parameters could not completely be documented in all patients. Echocardiographic and 6-min walking distance data were not available for the present analyses. Therefore, the coincident existence of pulmonary hypertension cannot completely be ruled out. However, patients with obvious clinical aspects of right heart overload were excluded from analysis.

All patients followed a single CPET protocol; however, VO_2peak was not significantly altered by the use of different CPET protocols in previous studies of patients with COPD [38, 39]. Established parameters of ventilatory mechanics (e.g., dynamic hyperinflation, inspiratory capacity) were not available for analysis. These and other parameters (e.g., ventilatory inefficiency) taken together allow even better to depict the complex pathophysiology of COPD [34, 40, 41]. Especially the parameter of VE/VCO_2 slope is influenced by the degree of COPD and is therefore being underestimated in advanced stages of the disease [37]. The probably, in this respect, even better parameter of VE/VCO_2 intercept was not available for analysis in our study. In 265/312 of patients, we were able to determine the anaerobic threshold [42]. It is a well-known fact that some COPD patients do not reach the anaerobic threshold because of mechanical (pulmonary) limitations during exercise.

In conclusion, we confirm in a large study population with a substantial duration of follow-up that $\text{VO}_{2\text{peak}}$ is a highly significant predictor of survival in patients with COPD. Our data support the incorporation of this surrogate marker of impaired cardiopulmonary capacity into the clinical assessment of patients with COPD alongside established markers (FEV_1 , exacerbation frequency, and symptoms). Prospective studies are needed to confirm our findings with regard to the prognostic relevance of exercise data.

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Statement of Ethics

The study was approved by the ethical committee of the University of Greifswald (Reg.-Nr. BB 051/2018, April 01, 2018). All patients were informed of the study either by phone or during follow-up visits, and those participating provided written informed consent for the collection of data.

Conflict of Interest Statement

R.E. received honoraria for scientific lectures from Actelion, GSK, United Therapeutics, AstraZeneca, Novartis, Berlin-Chemie, Boehringer Ingelheim, and OMT, and research funding from Boehringer Ingelheim and Actelion, Germany. M.H. received per-

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Author Contributions

R.E., S.G., and B.S. were involved in the study conception. R.E., S.G., and A.O. were involved in the study design. A.Mü, M.H., J.W., B.T., G.H., A.Ho, M.W, A.He, and A.Ma included patients in this study. A.O. was the study statistician. R.E., S.G., G.H., B.S., A.Mü, and A.O were involved in the analysis. B.S., R.E., G.H., and A.O. were involved in interpreting the data. R.E. and B.S. wrote the first draft. All authors read and revised the draft of the work. All authors read and approved the final manuscript. Claire Mulligan PhD (Beacon Medical Communications Ltd, Brighton, UK) edited the final draft of the manuscript prepared by the authors.

Data Availability Statement

With publication, we declare to make data (deidentified participant data, data dictionary, and statistical analysis plan) if requested available. This should be done through our statisticians Dr. Anne Obst (anne.obst@med.uni-greifswald.de) and based upon a data access agreement.

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