Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Respiratory Medicine 202 (2022) 106968

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Functional limitations 12 months after SARS-CoV-2 infection correlate with initial disease severity: An observational study of cardiopulmonary exercise capacity testing in COVID-19 convalescents

Fridolin Steinbeis [a], Philipp Knape [a], Mirja Mittermaier [a,b], Elisa Theresa Helbig [a], Pinkus Tober-Lau [a], Charlotte Thibeault [a], Lena Johanna Lippert [a], Weiwei Xiang [a], Moritz Müller-Plathe [a], Sarah Steinbrecher [a], Hans-Jakob Meyer [a], Raphaela Maria Ring [a], Christoph Ruwwe-Glösenkamp [a], Florian Alius [a], Yaosi Li [a], Holger Müller-Redetzky [a], Alexander Uhrig [a], Tilman Lingscheid [a], Daniel Grund [a], Bettina Temmesfeld-Wollbrück [a], Norbert Suttorp [a,c], Leif Erik Sander [a,b,c], Florian Kurth [a,d], Martin Witzenrath [a,c], Thomas Zoller [a,e,*]

[a] *Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Infectious Diseases and Respiratory Medicine, Charitéplatz 1, 10117, Berlin, Germany*
[b] *Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117, Berlin, Germany*
[c] *German Center for Lung Research (DZL), Berlin, Germany*
[d] *Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine, And Department of Medicine I, University Medical Centre Hamburg-Eppendorf, 20359, Hamburg, Germany*
[e] *Swiss Tropical and Public Health Institute, Basel, Switzerland*

A B S T R A C T

Background: Cardiopulmonary Exercise Testing (CPET) provides a comprehensive assessment of pulmonary, cardiovascular and musculosceletal function. Reduced CPET performance could be an indicator for chronic morbidity after COVID-19.
Methods: Patients ≥18 years with confirmed PCR positive SARS-CoV-2 infection were offered to participate in a prospective observational study of clinical course and outcomes of COVID-19. 54 patients completed CPET, questionnaires on respiratory quality of life and performed pulmonary function tests 12 months after SARS-CoV-2 infection.
Results: At 12 months after SARS-CoV-2 infection, 46.3% of participants had a peak performance and 33.3% a peak oxygen uptake of <80% of the predicted values, respectively. Further impairments were observed in diffusion capacity and ventilatory efficiency. Functional limitations were particularly pronounced in patients after invasive mechanical ventilation and extracorporeal membrane oxygenation treatment. Ventilatory capacity was reduced <80% of predicted values in 55.6% of participants, independent from initial clinical severity. Patient reported dyspnea and respiratory quality of life after COVID-19 correlated with CPET performance and parameters of gas exchange. Risk factors for reduced CPET performance 12 months after COVID-19 were prior intensive care treatment (OR 5.58, p = 0.004), SGRQ outcome >25 points (OR 3.48, p = 0.03) and reduced D_{LCO} (OR 3.01, p = 0.054).
Conclusions: Functional limitations causing chronic morbidity in COVID-19 survivors persist over 12 months after SARS-CoV-2 infection. These limitations were particularly seen in parameters of overall performance and gas exchange resulting from muscular deconditioning and lung parenchymal changes. Patient reported reduced respiratory quality of life was a risk factor for adverse CPET performance.

1. Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). Although SARS-CoV-2 infection affects multiple organs [1], sequelae of COVID-19 most frequently causes respiratory symptoms and functional limitations, followed by neurological and cardiac symptoms [2]. Twelve months after symptom onset, resting pulmonary function including reduced Diffusion Capacity of the Lungs for Carbon Monoxide (D_{LCO}) remains reduced and persisting pulmonary restriction can be observed in many patients

* Corresponding author. Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Infectious Diseases and Respiratory Medicine, Charitéplatz 1, 10117, Berlin, Germany.
E-mail address: thomas.zoller@charite.de (T. Zoller).

https://doi.org/10.1016/j.rmed.2022.106968
Received 3 June 2022; Received in revised form 18 August 2022; Accepted 22 August 2022
Available online 28 August 2022

[2–4]. Chest computed tomography (CT) abnormalities were reported in 39% of patients one year after onset of symptoms showing lung parenchymal damage including pulmonary fibrosis [2]. Particularly those patients with the most severe pulmonary involvement following COVID-19 acute respiratory distress syndrome (ARDS) showed the worst long term pulmonary outcome after 12 months [5], and even one year after COVID-19, health-related quality of life is reduced and patient-reported symptom load remains high in many patients [4,5].

Cardiopulmonary exercise testing (CPET) and invasive CPET has lately been used in evaluating COVID-19 convalescents [6–18] based on the observation that resting pulmonary function tests cannot reliably predict exercise performance and that overall health status correlates better with exercise tolerance than with resting measurements [19]. CPET provides a holistic assessment of pulmonary, cardiovascular and skeletal muscle function and is considered an independent prognostic factor for chronic morbidity [19].

Thus far, reduced exercise capacity has been documented in COVID-19 convalescents up to six months post symptom onset with a reduced peak oxygen uptake (pVO_2) and impaired ventilatory efficiency being the two most common abnormalities [7,9,10,12,14–17]. Respiratory and cardiac sequelae as well as muscular deconditioning have all been proposed by different studies as potential mechanisms underlying the reduced functional capacity [9–11,20], a phenomenon also reported in SARS convalescents up to 2 years after infection [21]. Reduced peak VO_2 has been associated with dyspnea [9,12,17], hospitalization and ICU treatment [9,11]. However, previous studies have focused on short- and medium-term outcomes after COVID-19 only, and one-year follow-up studies on CPET characteristics and associated factors are missing.

This study aims to investigate the impact of COVID-19 on exercise capacity 12 months after symptom onset in a cohort of COVID-19 convalescents of different disease severity during the acute phase and compares the results to a German reference population [22]. Moreover, we explored whether CPET results correlated with impairments of health-related quality of life, patient reported symptoms, and impaired resting pulmonary function 12 months after acute COVID-19 to test whether CPET can be used as a diagnostic tool for objective evaluation of subjective symptoms and limitations in this patient group.

2. Methods

All patients aged 18 and older with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection presenting as in- or outpatients were offered participation in a prospective observational study on clinical course and outcomes of COVID-19 (the Pa-COVID-19 study) during the acute- or post-acute phase of infection, conducted at Charité-Universitätsmedizin Berlin, a tertiary care university medical centre in Germany [23]. All participants or their legal representatives gave written informed consent before study inclusion and the study was conducted according to Good Clinical Practice (International Council for Harmonization, ICH 1996) guidelines. The study was approved by Charité ethics committee (EA2/066/20) and was registered at the German clinical trials register and WHO international clinical trials registry platform (DRKS00021688). At the time of hospital discharge, all COVID-19 convalescents who consented to participate in the Pa-COVID-19 study were, according WHO recommendations [24], invited to attend follow-up visits 3, 6 and 12 months after symptom onset. These patients underwent clinical evaluation, pulmonary function testing, CPET, and completed health-related quality of life questionnaires. The present analysis includes patients who attended follow-up visits as outpatients between March 2021 and November 2021 and agreed to undergo CPET.

2.1. COVID-19 severity groups

Two sets of criteria were used to classify participants according to disease severity: the level of respiratory care (intensive care unit (ICU) admission vs. non-ICU treatment) and the severity of lung impairment during the acute phase of COVID-19. For the latter classification, patients were stratified into six groups as previously described [5]: (i) no need for supplemental oxygen and not hospitalized (NOO); (ii) hospitalized without supplemental oxygen (NOH); (iii) hospitalized with low-flow supplemental oxygen via nasal cannula (LFO); (iv) high-flow oxygen (HFO); (v) invasive mechanical ventilation (IMV) and (vi) extracorporeal membrane oxygenation (ECMO). Patients were stratified according to the highest level of care or disease severity during acute COVID-19.

2.2. Cardiopulmonary exercise testing (CPET)

CPET was performed using a cycle ergometer (Ergosana, Bitz, Germany) with a progressive incremental ramp until physical exhaustion of the patient. Borg CR10 scale was used for quantification of dyspnea [25]. Continuous measurement for CPET were recorded according to international standards, respiratory parameters were measured in a breath-by-breath mode (Cardiovit CS-200, Ganshorn, Schiller Group, Niederlauer, Germany) [19]. Absolute and relative contraindications for CPET were applied according to the ATS/ACCP Statement on Cardiopulmonary Exercise Testing [18]. The following parameters were obtained during CPET and used in this analysis: maximum performance (Watt; W); peak oxygen uptake (pVO_2; ml/min/kg); heart rate (HR;/min); O_2-pulse at maximum performance (ml/beat); ventilation (VE; l/min); breathing reserve (BR; %), ventilatory equivalents ($EqO_2 \approx VE/CO_2$; $EqCO_2 \approx VE/VCO_2$); slope of VE/VCO_2 ($VE/VCO_{2\ slope}$); alveolar-arterial oxygen pressure difference ($AaDO_2$) and arterial-alveolar difference in CO_2 ($aADCO_2$); end-tidal partial pressure CO_2 ($PETCO_2$); percent difference between first and minimum ventilatory equivalents (ΔEqO_2 and $\Delta EqCO_2$). The suffix max (e.g. VE_{max}) indicates the highest measured value at maximum performance, min indicated the lowest measured value. Reported VO_2 in this study is controlled for body weight and is expressed as ml/min/kg. Capillary blood gas analysis was performed at rest and at maximum work rate (ABL825FLEX, Radiometer, Krefeld, Germany). Reference values for CPET were calculated based on the German reference Population (Study of Health in Pomerania (SHIP)) and results are expressed as percent predicted value (ppv) [22]. Due to the ongoing pandemic, clinical examination as well as point-of-care antigen testing were performed prior to CPET [26].

2.3. Pulmonary function tests

Pulmonary function was examined using Ganshorn PowerCube Body+ and Diffusion+ (Schiller Group, Niederlauer, Germany) and performed according to the German, European, and American recommendations for pulmonary function testing [27–29]. Reference values were calculated based on the Global Lung Function Initiative (GLI) reference equations (GLI-2012) and results were expressed as percent predicted value (ppv) [30]. Interpretation of diffusing capacity values were adapted from the ERS/ATS official technical standards and the subsequent correspondence [31,32]. Pulmonary restriction or obstruction was defined according to the "ATS/ERS Task Force: Standardisation of Lung Function Testing" as total lung capacity (TLC) <5th percentile of the lower limit of normal (LLN) and forced expiratory volume/forced vital capacity (FEV1/FVC) < LLN [33].

2.4. Symptom assessment and health-related quality of life

Forty-three COVID-19 associated symptoms were evaluated at each study visit at baseline and during follow-up in a patient interview, including dyspnea and the unidimensional rating of activity limitation according to mMRC (Modified Medical Research Council) Dyspnea Scale [34] (Table S2). mMRC stratifies severity of dyspnea and ranges from 0 (dyspnea only with strenuous exercise) to 4 (dyspnea when dressing);

grade 0 was considered as "no dyspnea", grade 1–4 as exertional dyspnea. To capture overall impact on health, daily life and wellbeing in patients after COVID-19, the St. George's Respiratory Questionnaire (SGRQ) was used [35]. SGRQ ranges from 0 to 100, with higher scores indicating reduced quality of respiratory well-being. A total score of 25 or higher, as suggested by the GOLD (Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease), was used as threshold for limitations in health and wellbeing.

2.5. Data analysis

Descriptive statistics were used to calculate median, inter-quartile range (IQR), mean and standard deviations (SD). Differences between two variables were analysed by *t*-test for normally distributed or Mann-Whitney-U Test for non-normally distributed data. Difference in continuous variables between three or more groups were analysed by one-way ANOVA or for non-normal distribution by Kruskal-Wallis test. Fischer's exact test (for sample size <5 per group) or Chi-square test were used for analysis of categorical variables. Logistic regression was computed for reduced CPET performance and reduced peak VO_2 as a binary dependent variables. Confounders for this model were determined by clinical relevance (age, sex, BMI). P-values are interpreted descriptively. Asterisks represent * for $p < 0.05$; **$p < 0.01$; ***$p < 0.001$ and ****$p < 0.0001$. IBM SPSS (IBM SPSS Statistics 27.0), JMP (version 14.2.0), and GraphPad PRISM (Version 9.0.0) were used for statistical analysis and graphical processing.

3. Results

3.1. Patient characteristics

Between May 2021 and December 2021, 198 patients had follow-up visits in the outpatient department and 135 attended a follow-up examination at month 12. All patients were offered CPET testing at month 12. Of these, 66 agreed to perform CPET. In 12 participants CPET was contraindicated due to acute cardiac events (pulmonary artery embolism, angina pectoris) or acute ventilatory or respiratory failure (exacerbated chronic obstructive lung disease) or were not able to perform CPET due to orthopaedic limitations (joint pain). No other exclusion criteria were applied. 54 patients completed CPET at month 12 (Fig. 1). A subset of 10 patients had an additional CPET at month 6.

Median age of all 54 participants who completed CPET at month 12 was 56 years (IQR 45–63), with 22/54 (40.74%) female participants and 32/54 (59.26%) male participants (Table 1). Of all participants, 29/54 (53.70%) were treated as outpatients or at a non-ICU ward and 25/54 (46.30%) on ICU (Table s1). Initial disease severity of acute COVID-19 was distributed as follows: 12/54 (22.22%) were never hospitalized and received no supplemental oxygen (NOO), 9/54 (16.67%) were hospitalized without need for oxygen (NOH), 8/54 (14.82%) were treated with low-flow oxygen (LFO), 7/54 (12.96%) with high-flow oxygen (HFO), 12/54 (22.22%) were treated with mechanical ventilation (IMV), and 6/54 (11.11%) were treated with ECMO. Median age was lower in non-ICU compared to ICU and NOO group compared to hospitalized patients (NOH, LFO, HFO, IMV, ECMO) (Table s1). Also BMI was lower in non-ICU treated individuals than in ICU patients (24.08 [IQR 22.41–26.95] vs. 29.41 [25.41–33.94] kg/m2; $p < 0.001$, Table s1). No patients required long-term oxygen therapy.

3.2. CPET and COVID-19 severity

Reduced cardiopulmonary function defined as peak performance <80% (ppv) and peak VO_2 <80% (ppv) was seen in 25/54 (46.3%) and 18/54 (33.3%) patients, respectively (Table 1). Patients in the highest severity groups (IMV and ECMO) showed the most severe limitations (Table s1). Twelve months after SARS-CoV-2 infection, peak cardiopulmonary performance (Watt; ppv) was reduced in patients with a higher degree of respiratory failure during acute COVID-19 (Fig. 2a). Also, peak VO_2 (ml/min/kg; ppv) was reduced in patients who received HFO or IMV as maximum respiratory support and lowest for patients who received ECMO treatment (Fig. 2b). No difference was seen between patients following HFO and IMV regarding cardiopulmonary performance (Watt) and pVO_2 at month 12.

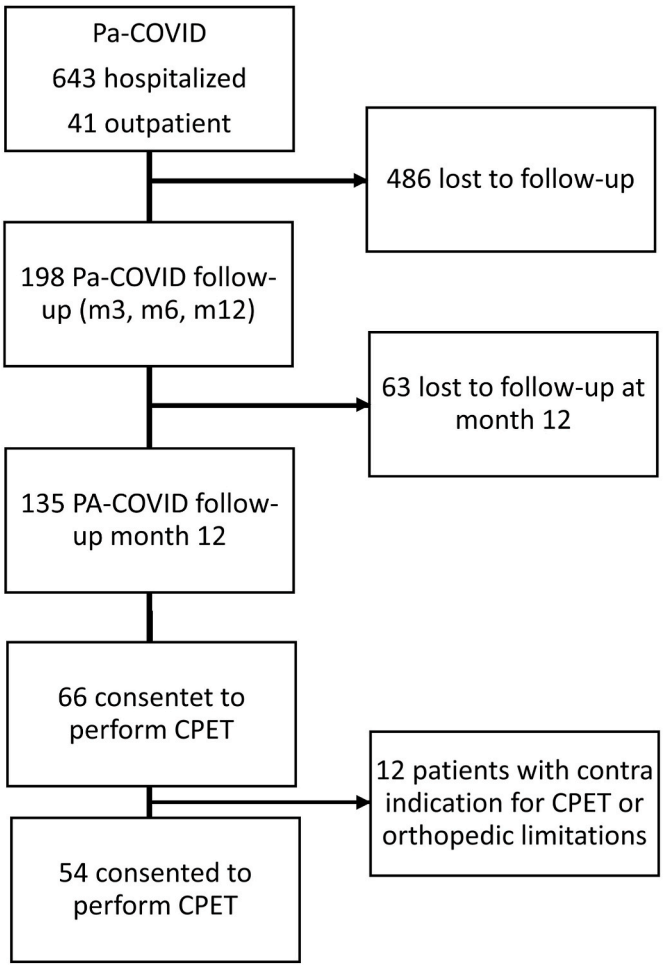

Fig. 1. Pa-COVID-19 study: 643 patients were enrolled into the Pa-COVID-19 study during their hospital treatment, additional 41 patients were enrolled at their first follow-up visit at the outpatient department. In total, 198 patients were examined during follow-up. Of these patients, 66 agreed to perform CPET, though 12 were excluded from CPET due to contra indications or orthopaedic limitations. Thus, a total of 54 patients with varying COVID-19 severity participated in this study.

Ventilation: VE_{max} was reduced <80% in 30/54 (55.6%) patients, no correlation was seen with respect to initial COVID-19 severity (Table 1, Fig. 2c). A reduced breathing reserve (<20%) was observed in 5/54 (9.3%) patients. Similarly, no trend was seen in the distribution with regard to initial disease severity for BR (ppv) (Table 1, Fig. 2d).

Cardio circulatory: Reduced O_2 pulse 12 months post symptom onset (as defined by < 80% ppv) was seen in 9/54 patients (16.7%) (Table 1) and was more common in individuals following severe or critical acute COVID-19 (Table s1). Marked differences in O_2 pulse at maximal load was seen between patients following ICU treatment compared to non-ICU treatment. Subgroup analysis of patients classified by acute COVID-19 severity revealed a reduction in O_2 pulse in those patients following HFO, IMV and ECMO 12 months after symptom onset (Fig. 2e).

Gas exchange: No patient showed VE/VCO_2slope >35 i.e. indicating hyperventilation (Table 1). However, VE/VCO_2slope was higher in patients following ICU treatment 12 months after acute COVID-19.

Table 1
Characteristics of all participants who underwent CPET (n=54). Distribution of demographic characteristics, comorbidities and categorical outcome of pulmonary function and CPET according to disease severity can be found in the supplement. Abbreviations: CCI – Charlson Comorbidity Index. *missing values: Smoking history n = 3; Immunosuppression: n = 1.

	All (n = 54)
Age (median (IQR))	56 (45–63)
Sex female (n (%))	22 (40.7)
Sex male (n (%))	32 (59.3)
BMI (median (IQR))	26.2 (23.4–31.2)
Smoking	
Smoking history* (n (%))	21 (38.9)
Comorbidities	
CCI 0 (n (%))	18 (33.3)
CCI >5 (n (%))	5 (9.1)
Chronic lung disease (n (%))	10 (18.5)
Chronic heart disease (n (%))	24 (44.4)
Chronic kidney disease (n (%))	6 (11.1)
Diabetes (n (%))	7 (13.0)
COVID-19 severity & complications	
NOO (n (%))	9 (16.7)
NOH (n (%))	5 (9.3)
LFO (n (%))	8 (14.8)
HFO (n (%))	5 (9.3)
IMV (n (%))	10 (18.5)
ECMO (n (%))	6 (11.1)
Tracheotomy (n (%))	11 (20.4)
Thromboembolism (n (%))	9 (16.7)
Pulmonary function	
Restriction (n (%))	11 (20.4)
FEV1 ppv (median (IQR))	90.0 (79.9–100.1)
FVC ppv (median (IQR))	87.4 (80.1–94.7)
TLC ppv (median (IQR))	96.9 (85.6–108.2)
DLCO ppv (median (IQR))	76.5 (65.3–87.7)
KCO ppv (median (IQR))	90.0 (81.3–98.7)
Obstruction (n (%))	1 (1.9)
D_{LCO} reduced (n (%))	29 (53.7)
Dyspnea (MMRC>0)	30 (55.6)
SGRQ >25 (n (%))	28 (51.9)
CPET	
Max. performance (Watt) < 80%	25 (46.3)
VO2 at VT1 (ml/min/kg) < 40%	2 (3.7)
Peak VO2 (ml/min/kg) < 80%	18 (33.3)
O2-pulse max <80 ppv	9 (16.7)
VE max <80%	30 (55.6)
BR <20%	5 (9.3)

According to the initial severity of respiratory failure, VE/VCO_2slope was highest in subgroups of highest initial disease severity (IMV and ECMO) (Fig. 2f). $AaDO_2$ and $aADCO_2$ at rest did not differ (data not shown), but were higher in patients following ICU treatment at maximal performance (Fig. 2g and h). Analysis of minimum EqO_2 and $EqCO_2$ for patients, reflecting physiological adaption to exertion, was higher in patients with increasing acute COVID-19 disease severity (Fig. 2 I and j). This trend was also confirmed when analyzing the percentage difference in EqO_2 and $EqCO_2$ (ΔEqO_2 and $\Delta EqCO_2$) between baseline and lowest Eq values to assess physical adaption to exercise. Patients who underwent ICU treatment showed a reduced adaption with a loss in ΔEqO_2 and $\Delta EqCO_2$ (Fig. 2k and l).

3.3. Correlation of patient reported outcomes with CPET results

A total of 30/54 (55.56%) patients reported to suffer from dyspnea at month 12 (MMRC>0; Table 1). Patients who reported exertional dyspnea 12 months after COVID-19, had a markedly reduced CPET performance and VO_2 peak (Fig. 3a and b), however, at the same time no difference in heart rate at maximal exertion was observed (3e). O_2 pulse was lower in patients reporting dyspnea (Fig. 3f). Gas exchange and ventilatory efficiency were reduced in patients reporting shortness of breath as compared to patients without respiratory symptoms, as demonstrated by higher VE/VCO_2slope, EqO_{2min} and $EqCO_{2min}$ (Fig. 3g, j and k). Impaired respiratory quality of life reported by patients with a SGRQ total score >25 points showed similar effects in CPET, and differences in performance and VO_2 was even more pronounced (Figure s1a and b). Parameters of gas exchange (VE/VCO_2slope and EqO_2, $EqCO_2$), however, did not differ markedly (Figure s1 g, j and k).

3.4. Correlation of CPET limitations with pulmonary function

Median (IQR) FEV-1 was 90.0 (79.9–100.1), FVC 87.4 (80.1–94.7) and TLC 96.9 (85.6–108.2) in all patients, D_{LCO} 76.5 (65.3–87.7) and K_{CO} 90.0 (81.3–98.7) (Table 1). Pulmonary restriction was present in 11/54 (20.37%) and reduced D_{LCO} in 29/54 (53.70%) patients 12 months after acute COVID-19 and was more common amongst patients with higher disease severity during acute COVID-19 (Table s1). Patients with restriction and reduced CO diffusing capacity in pulmonary function also showed limitations in CPET, particularly a reduced overall exercise capacity, a reduced maximum oxygen uptake and impairments in gas exchange (Figures s2 and s3).

3.5. CPET over time

In a subset of 10 patients, CPET at 6 months after COVID-19 symptom onset was available. Comparison of 6 versus 12 months CPET revealed an improvement in overall performance. pVO_2, BR, O_2 pulse, but VE/VCO_2slope did not show relevant differences (Figure s4).

3.6. Risk- and associated factors for adverse CPET performance

Risk factors for reduced performance and peak VO_2 as defined by < 80 *ppv* were examined using univariate and multivariate logistic regression. Univariate analysis showed that ICU treatment was associated with reduced CPET performance and peak VO_2 at month 12. The odds for impaired CPET performance were higher in patients with SGRQ outcome >25 points (OR 3.48 (95% CI 1.13–10.73) p = 0.030/aOR 3.60 (1.07–12.11); p = 0.039) and in patients with reduced D_{LCO} (OR 3.01 (0.98–9.22); p = 0.054/aOR 3.38 (1.03–11.09); p = 0.045) (Table 2). Similar results were shown for reduced peak VO_2, with an OR 5.50 (1.50–20.13), p = 0.010 (aOR 9.94 (2.14–46.13), p = 0.003) for SGRQ score >25 and OR 3.25 (0.96–11.04), p = 0.059 (aOR 3.88 (1.06–14.29), p = 0.041) for impaired D_{LCO}. Adjusting for apparent clinically relevant demographic confounders (age, sex, BMI) did not have relevant effects on associated risk factors.

4. Discussion

This study analysed cardiopulmonary limitations using CPET 12 months after acute COVID-19 and included correlation of results with patient reported outcomes and results of pulmonary function testing. The analysis shows that relevant impairments in CPET persist in individuals 12 months after acute COVID-19 in terms of overall performance, ventilatory, circulatory and gas exchange parameters. Reduced CPET performance was associated with initial COVID-19 severity, SGRQ score >25 and impaired D_{LCO}. Most relevant impairments in CPET 12 months after acute COVID-19 were observed in overall exercise capacity, maximum oxygen uptake, diffusion capacity and breathing efficiency, and the degree of impairment was particularly pronounced in patients after severe ARDS after ECMO treatment.

Previous investigations of functional impairment after COVID-19 were limited to shorter observation periods. In a Norwegian multicenter study including 156 patients, 20% of patients were initially treated on ICU and 13% received invasive mechanical ventilation for a median time of 9 days (no patients treated with ECMO) [12]. pVO_2 was reduced <80%ppv in 31% of patients three months after acute COVID-19, similar as compared to 33% after 12 months in our dataset. Significant differences in pVO_2 were also seen between ICU and non-ICU patients (90% vs. 82%, respectively) – a difference still relevant and

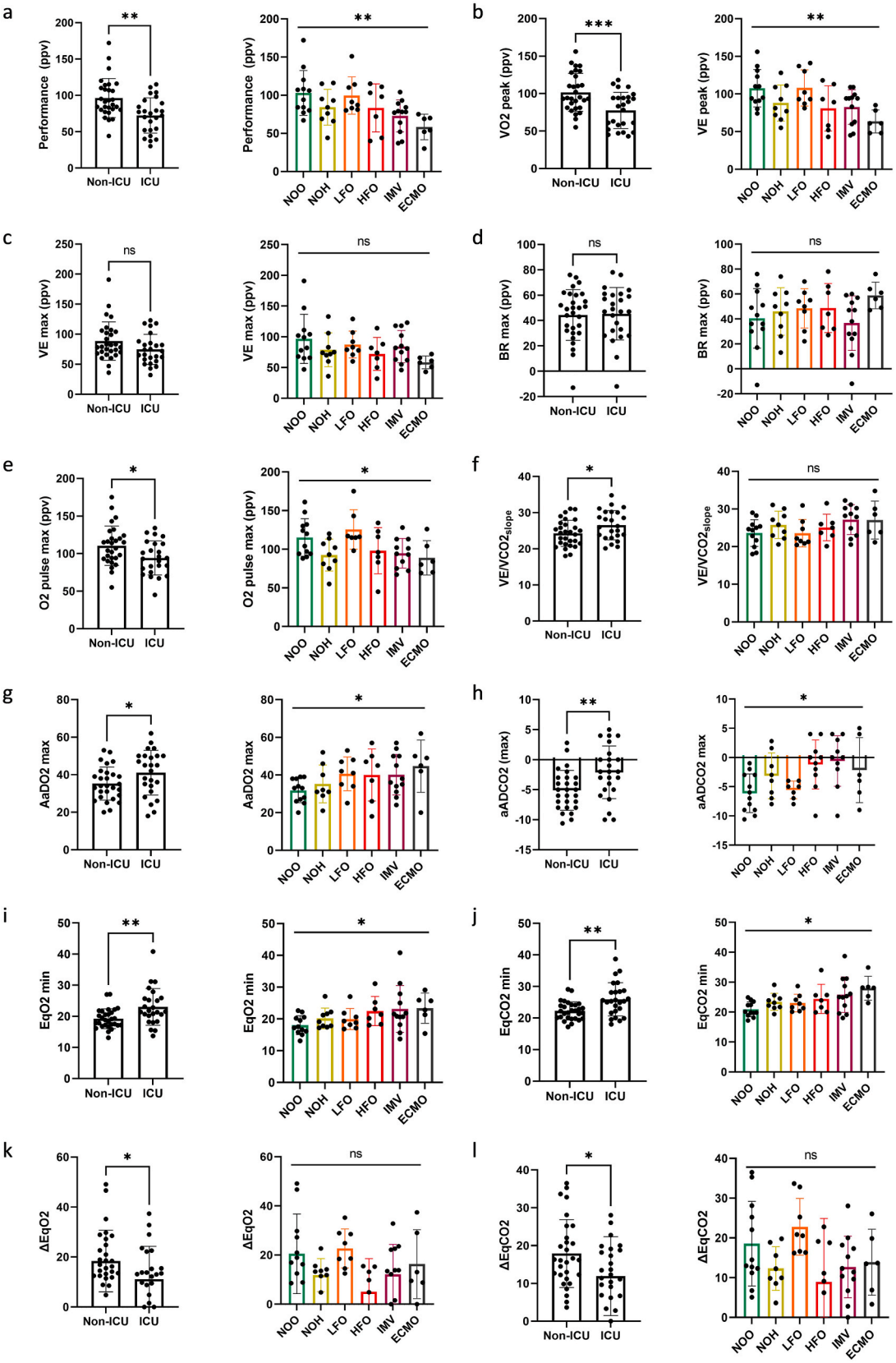

Fig. 2. CPET outcome 12 months after acute COVID-19 stratified by disease severity: Percent predicted values of CPET performance and peak VO_2 are reduced 12 months after disease onset in patients following ICU treatment and correlate with the level of respiratory support during COVID-19. Gas exchange as shown by VE/VCO_{2slope}, $AaDO_{2max}$ and $aADCO_{2max}$ (measured at maximum exertion) as well as minimum EqO_2 and $EqCO_2$ correlate with initial COVID-19 severity 12 months after SARS-CoV-2 infection. ΔEqO_2 and $\Delta EqCO_2$ represent the percentage change between baseline and lowest level of the respective equivalent. Physiological adaption to exercise was less pronounced in patients post ICU treatment.

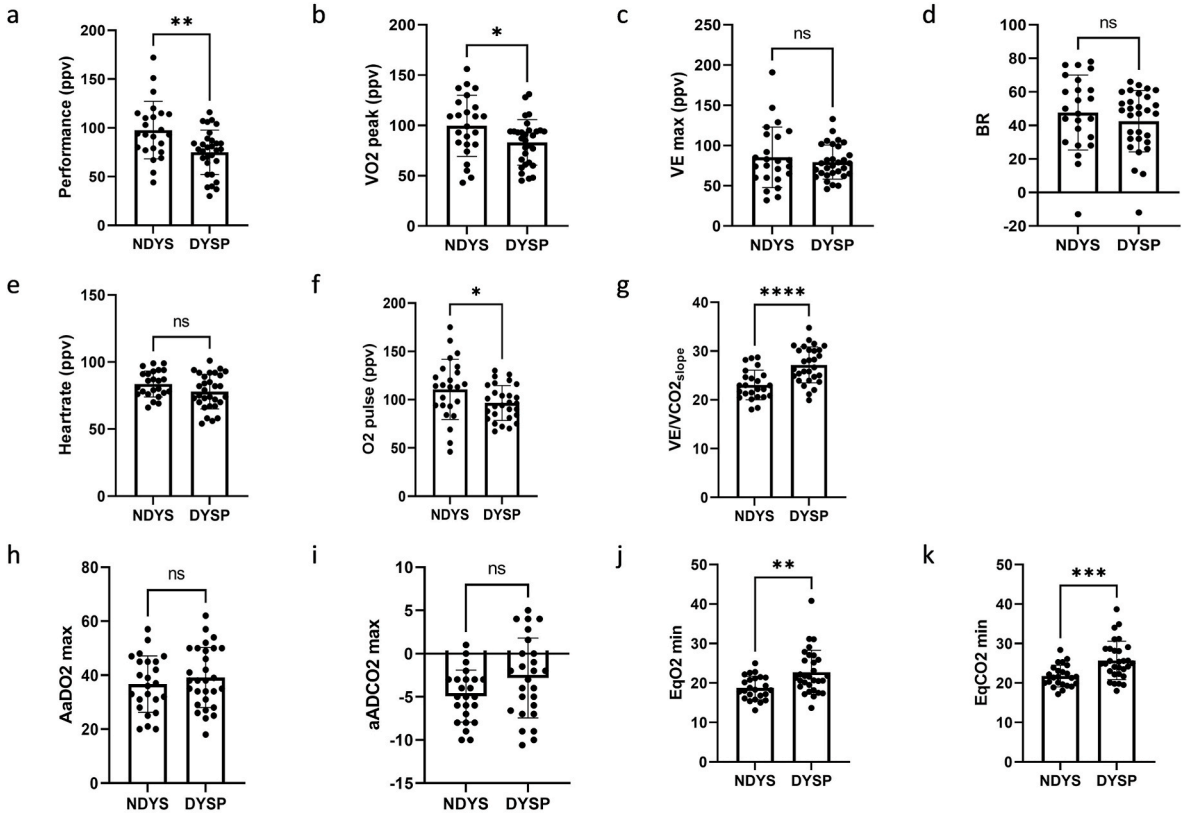

Fig. 3. CPET outcome 12 months after acute COVID-19 in patients with (MMRC >0) and without dyspnea (MMRC = 0): In patients reporting dyspnea, percent predicted values of CPET performance, VO_2 (peak), VE and BR, HR, O_2 pulse are reduced 12 months after disease onset. Gas exchange as shown by VE/VCO_{2slope}, peak $AaDO_2$ and $aADCO_2$ as well minimum $EqCO_2$ show a correlation with dyspnea 12 months after acute COVID-19. Abbreviation: NDYS – no dyspnea (MMRC = 0); DYSP – dyspnea (MMRC >0).

Table 2
Association of demographic characteristics and clinical indicators with reduced performance and peak VO2 in CPET (<80% ppv) 12 months after acute COVID-19: Univariate analysis revealed ICU treatment, length of hospital stay, SGRQ score >25, and reduced DLCO during follow-up to be associated with reduced performance in CPET. Adjusting for clinically relevant demographic confounders (age, sex, BMI) confirmed these effects for ICU treatment, days hospitalized, patient reported outcome and reduced DLCO. Patient characteristics and comorbidities were collected at study inclusion. SGRQ outcome at 12 M FU was used for univariate and multivariate analysis.

	Reduced CPET performance (<80% ppv)				Reduced peak VO2 (<80% ppv)			
	OR (95% CI)	p	aOR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p
Age	1.04 (1.00–1.08)	0.084			1.02 (0.99–1.08)	0.201		
BMI	1.06 (0.97–1.17)	0.188			1.06 (0.97–1.16)	0.212		
Sex (male)	0.92 (0.31–2.75)	0.876			3.13 (0.86–11.37)	0.083		
ICU Treatment	5.58 (1.73–17.98)	0.004	4.77 (1.35–16.90)	0.015	3.54 (1.07–11.66)	0.038	2.83 (0.79–10.20)	0.111
Days hospitalized	1.04 (1.01–1.07)	0.005	1.04 (1.01–1.07)	0.009	1.03 (1.01–1.05)	0.007	1.03 (1.00–1.05)	0.019
MMRC >0	2.62 (0.86–7.97)	0.091	2.13 (0.65–7.01)	0.212	2.91 (0.86–9.86)	0.087	3.35 (0.87–12.92)	0.079
SGRQ>25	3.48 (1.13–10.73)	0.030	3.60 (1.07–12.11)	0.039	5.50 (1.50–20.13)	0.010	9.94 (2.14–46.13)	0.003
Restriction	2.94 (0.76–11.34)	0.117	3.29 (0.71–15.36)	0.129	3.95 (1.04–15.04)	0.044	2.89 (0.67–12.37)	0.154
DLCO reduced	3.01 (0.98–9.22)	0.054	3.38 (1.03–11.09)	0.045	3.25 (0.96–11.04)	0.059	3.88 (1.06–14.29)	0.041

visible in this study at month 12.

VE/VCO_2slope is an established prognostic indicator for chronic lung disease and was higher in patients following ICU treatment. Breathing equivalents, as measured by VE/VO_2 (EqO_2) and VE/VCO_2 ($EqCO_2$) and the adaption under exercise conditions (ΔEqO_2 and $\Delta EqCO_2$) are another indicator of breathing efficiency and correlated well with COVID-19 severity. This might represent long-term pulmonary damage following SARS-CoV-2 infection with reduced breathing efficiency in the latter conditions and explain early exhaustion under exercise conditions. Also increased $AaDO_2$ and $aADCO_2$ in patients with higher COVID-19 severity might be a result of a ventilation/perfusion mismatch because of lung parenchymal changes.

In a subset of 10 patients where CPET was available longitudinally at month 6 and month 12, small improvements were seen in overall exercise capacity in all patients. This can mainly be attributed to the increased ventilatory capacity VE which was the only parameter improving markedly, whereas all other parameters including oxidative capacity pVO_2 remained almost at a constant level. A corresponding observation was made during follow-up of patients with pulmonary function testing where many patients with pulmonary restriction and ventilation/perfusion mismatch showed improvement over time within the first year after acute COVID-19 [5]. In line with radiologic improvements seen over time in clinical practice, these findings from CPET and pulmonary function testing can mainly be attributed to improved ventilation mechanics. It may be concluded from this observation that possible muscular deconditioning caused by acute COVID-19 and

associated immobility in the early phase of infection improves over time, contributing to improved exercise capacity.

Chronic dyspnea is one of the key symptoms of long-COVID syndrome, and the pathophysiology remains to be elucidated. In this study, mMRC scores and SGRQ >25 were used as established tools to measure dyspnea and respiratory health-related quality of life [36]. Interestingly, dyspnea correlated negatively with overall exercise capacity and oxygen uptake, and particularly with ventilatory efficiency and breathing equivalents. This was not the case for indicators of gas exchange (breathing equivalents), that were similar between patients with and without dyspnea. These observations indicate that impairment of ventilatory mechanics due to neural or muscular causes could play a more relevant role for dyspnea in COVID-19 convalescents than affection of the lung parenchyma. This finding is in line with earlier observations that dyspnea improves over 12 months of time mainly in patient groups with severe disease (where restriction is the predominant problem), but not in those with mild to moderate initial disease severity [5]. The role of neuromuscular causes of dyspnea therefore merits further investigation. Eventually, SGRQ was shown to be a useful tool to assess post-COVID-19 dyspnea correlating with CPET functional status also in a condition where pulmonary obstruction is not a predominant pathology.

Pulmonary restriction and reduced D_{LCO}, but not K_{CO}, are typical sequelae of severe courses of COVID-19 and most pronounced in patients who required ECMO treatment [5]. Analysis of CPET data in this study confirms the role of restriction across most relevant CPET outcomes. This is also reflected in a reduced breathing reserve as additional indicator for the relevance of impairment of ventilatory mechanics causing exercise limitation after severe COVID-19.

This study had limitations. The number of study subjects available was limited and recruited at a single study site. As participants were offered CPET as an additional test for COVID-19 related symptoms, the study population is neither representative of all patients included in the underlying Pa-COVID-19 study nor of the patient population treated at our center. A selection bias towards patients with higher symptom burden cannot be ruled out; however, this would only affect the categorical analyses performed. Also, chronic cardiac and pulmonary comorbidities present in 44.4% and 18.5% of patients, respectively, might have an effect on the results of this analysis, especially as those were skewed towards severe and critical COVID-19. The limited sample size in this study did not allow a detailed analysis of impact of comorbidities and will be further investigated in larger follow-up studies. A control group of patients with a disease comparable to COVID-19 was not available at this point of time, however, using a German reference population for CPET to calculate predicted values allowed for making reliable inferences about the magnitude of functional limitations [22]. Finally, CPET analysis focuses on maximal effort of the cardiopulmonary system and applicability of results to predict subjective exercise restrictions in everyday life may be limited.

5. Conclusion

This study adds evidence on clinically relevant functional limitations causing chronic morbidity in COVID-19 convalescents. Particularly patients with an initially severe clinical course (intensive care treatment, invasive mechanical ventilation, ECMO) suffer from relevant functional limitations with emphasis on a reduced mechanical ventilatory function potentially due to muscular deconditioning. With improving restriction and subsequent increase in ventilatory capacity, partial improvement over time within the first 12 months can be observed in some patients. Dyspnea and reduced quality of life correlate with major outcomes of CPET and mMRC as well as SGRQ scores are potential predictors for pathologic findings in CPET.

Funding

The Pa-COVID-19 study is supported by grants from the Berlin Institute of Health (BIH) and the German Federal Ministry of Education and Research (01KX2021 and 01KI20160A).

Author contributions

F.S., P.K. and T.Z. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. F.S., P.K., T.Z. and M.W. developed the study design, performed data analysis and interpretation and wrote the manuscript. M.M., E.T.H, P.T.L., C.T., L.J.L., W.X., M.M.P., S.S, H.J.M., R.M.R., C.R. G., F.A., Y.L., H.M.R., A.U., T.L., D.G., B.T.W., N.S., L.E.S. and F.K. contributed substantially to the study design data analysis and interpretation, and the writing of the manuscript.

Declaration of competing interest

M.W. received funding for research from Deutsche Forschungsgemeinschaft, Bundesministerium für Bildung und Forschung, Deutsche Gesellschaft für Pneumologie, European Respiratory Society, Marie Curie Foundation, Else Kröner Fresenius Stiftung, Capnetz Stiftung, International Max Planck Research School, Actelion, Bayer Health Care, Biotest, Boehringer Ingelheim, Noxxon, Pantherna, Quark Pharma, Silence Therapeutics, Takeda Pharma, Vaxxilon, and for lectures and advisory from Actelion, Alexion, Aptarion, Astra Zeneca, Bayer Health Care, Berlin Chemie, Biotest, Boehringer Ingelheim, Chiesi, Glaxo Smith Kline, Insmed, Novartis, Teva and Vaxxilon. T.Z. received funding for research from Bundesministerium für Bildung und Forschung, Else Kröner-Fresenius Stiftung and Gesellschaft für INTERNATIONALE ZUSAMMENARBEIT.

Acknowledgement

We thank the Pa-COVID-19 study group with Stefan Hippenstiel, Pinkus Tober-Lau, Sascha S. Haenel, David Hillus, Tilman Lingscheid, Holger Müller-Redetzky, Alexander Uhrig, Miriam S. Stegemann, Ralf H. Hübner, Kai-Uwe Eckardt, Martin Möckel, Felix Balzer, Claudia Spies, Steffen Weber-Karstens, Frank Tacke, Chantip Dang-Heine, Michael Hummel, Georg Schwanitz, Uwe D. Behrens, Maria Rönnefarth, Sein Schmidt, Alexander Krannich, Christof von Kalle, Victor M. Corman and Christian Drosten that contributed to set up and realization of the study platform; Linda Jürgens, Malte Kleinschmidt, Sophy Denker, Moritz Pfeiffer, Belén Millet-Pascual-Leone, Felix Machleidt, Sebastian Albus, Felix Bremer, Jan-Moritz Doehn, Tim Andermann, Carmen Garcia, Philipp M. Krause, Liron Lechtenberg, Yaosi Li, Panagiotis Pergantis, Till Jacobi, Teresa Ritter, Berna Yedikat, Lennart Pfannkuch, Christian Zobel, Ute Kellermann, Susanne Fieberg, Laure Bosquillon de Jarcy, Anne Wetzel, Christoph Tabeling, Markus Brack, Jan M. Kruse, Daniel Zickler, Andreas Edel, Britta Stier, Roland Körner, Nils B. Mueller and Philipp Enghard to obtaining informed consent and biosamples and Nadine Olk, Willi M. Koch, Saskia Zvorc, Lucie Kretzler, Lil A. Meyer-Arndt, Linna Li and Isabelle Wirsching, Paula Stubbemann, Jo Bagli, Olivia Zielonka and Vivien Schreiber to data collection.

M.M. is participant in the BIH-Charité Digital Clinician Scientist Program funded by the Charité –Universitätsmedizin Berlin, the Berlin Institute of Health, and the German Research Foundation (DFG). M.W. is supported by grants from the German Research Foundation, SFB-TR84 C6 and C9, SFB 1449 B2, by the German Ministry of Education and Research (BMBF) in the framework of CAPSyS (01ZX1304B), CAPSyS-COVID (01ZX1604B), SYMPATH (01ZX1906A), PROVID (01KI20160A), P4C (16GW0141), MAPVAP (16GW0247), NUM-NAPKON (01KX2021), and by the Berlin Institute of Health (CM-COVID).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.rmed.2022.106968.

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