A new phenotype of patients with post-COVID-19 condition is characterised by a pattern of complex ventilatory dysfunction, neuromuscular disturbance and fatigue symptoms

Fridolin Steinbeis[1], Claudia Kedor[2], Hans-Jakob Meyer[1], Charlotte Thibeault[1,3], Mirja Mittermaier[1,3], Philipp Knape[1], Katharina Ahrens[1], Gabriele Rotter[4], Bettina Temmesfeld-Wollbrück[1], Leif Erik Sander[1,5], Florian Kurth[1,6,7], Martin Witzenrath[1,5], Carmen Scheibenbogen[2] and Thomas Zoller[1]

[1]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Infectious Diseases, Respiratory Medicine and Critical Care, Berlin, Germany. [2]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Institute of Medical Immunology, Berlin, Germany. [3]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany. [4]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Social Medicine, Epidemiology and Health Economics, Berlin, Germany. [5]German Center for Lung Research (DZL), Berlin, Germany. [6]Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany. [7]Department of Medicine I, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany.

Corresponding author: Thomas Zoller (thomas.zoller@charite.de)

Shareable abstract (@ERSpublications)
Patients with post-COVID-19 condition, fatigue and exertional malaise frequently suffer from dyspnoea. Dyspnoea in this patient group might be caused by a novel pattern of complex ventilatory dysfunction and neuromuscular disturbance. https://bit.ly/3WKhDrN

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Abstract

Background Patients with post-COVID-19 condition frequently suffer from chronic dyspnoea. The causes and mechanism for dyspnoea in these patients without evidence of structural lung disease are unclear.

Methods Patients treated for COVID-19 at Charité University Hospital in Berlin received pulmonary function testing including respiratory muscle strength tests and completed health-related quality-of-life questionnaires during follow-up. Patients with post-COVID-19 condition during outpatient follow-up with fatigue and exertional intolerance (PCF) were compared to patients with post-COVID-19 condition with evidence of chronic pulmonary sequelae (post-COVID-19 restriction (PCR)) as well as to patients without post-COVID-19 condition (NCF).

Results A total of 170 patients presented for follow-up. 36 participants met criteria for PCF, 28 for PCR and 24 for NCF. PCF patients reported dyspnoea in 63.8%. % predicted value of respiratory muscle strength (median (IQR)) was reduced in PCF (55.8 (41.5–75.9)) compared to NCF and PCR (70.6 (66.3–88.9) and 76.8 (63.6–102.2), respectively; p=0.011). A pattern of reduced forced vital capacity (FVC), but normal total lung capacity (TLC), termed complex ventilatory dysfunction defined as TLC − FVC >10% predicted was observed and occurred more frequently in PCF (88.9%) compared to NCF and PCR (29.1% and 25.0%, respectively; p<0.001).

Conclusion Dyspnoea in PCF is characterised by reduced respiratory muscle strength and complex ventilatory dysfunction indicating neuromuscular disturbance as a distinct phenotype among patients with post-COVID-19 condition. These observations could be a starting point for developing personalised rehabilitation concepts.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and resulting coronavirus disease 2019 (COVID-19) has caused serious morbidity and mortality worldwide [1]. Acute, subacute and long-term effects of COVID-19 can involve multiple organ systems including vascular endothelial cells, lung, heart,

brain, kidney, intestine, liver, pharynx and other tissues, potentially through direct organ damage [2, 3]. New and persisting symptoms for >3 months after SARS-CoV-2 infection which cannot be explained by an alternative diagnosis are commonly referred to as long-COVID, and different terms have been introduced by multiple institutions such as post-COVID-19 condition [4] or post-COVID-19 syndrome [5]. An estimated 6% of COVID-19 survivors reported ongoing respiratory problems, cognitive sequelae or fatigue after 3 months of infection [6]. However, all current definitions of post-COVID-19 condition are based on broadly defined symptoms and symptom complexes, and their underlying pathophysiology is still not fully understood [7].

Current evidence suggests that cellular damage, a robust innate immune response with inflammatory cytokine production and a procoagulant state induced by SARS-CoV-2 infection are factors potentially contributing to post-COVID-19 sequelae such as dyspnoea, fatigue, and cognitive and mental disturbances, which are the three most frequently described clusters of post-COVID condition [8–12]. Dyspnoea has been well characterised as a major clinical symptom of post-COVID condition after severe and critical COVID-19 and is correlated with impaired lung function in terms of pulmonary restriction, and with reduced diffusion capacity [13, 14] as a possible consequence of pulmonary remodelling. However, dyspnoea also frequently occurs in those patients after mild SARS-CoV-2 infection, sharing clinical characteristics with those commonly described in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) with the lead symptoms being fatigue and exertional intolerance [15] but without evidence of chronic pulmonary injury. Understanding of the exact mechanism of respiratory sequelae in this distinct patient group is as yet unclear, however, and needs further investigation.

We hypothesise that patients suffering from post-COVID-19 condition who have fatigue and exertional intolerance also have a reduction in respiratory muscle strength, causing a dysfunctional breathing pattern which is distinct from typical pulmonary sequelae after COVID-19 such as obstruction, restriction or impaired diffusion capacity. Based on clinical observations, we describe a new breathing abnormality termed complex ventilatory dysfunction (CVD), defined as total lung capacity (TLC) – forced vital capacity (FVC) >10% predicted value and absence of restriction (TLC $\geqslant$ lower limit of normal (LLN)).

This study aims to explore different phenotypes in the group of patients with post-COVID-19 condition. We analysed pulmonary function, blood gas analysis and patient-reported outcomes in patients suffering from post-COVID-19 condition with fatigue and exertion intolerance and compared these parameters to those of COVID-19 convalescents without COVID-19 fatigue symptoms and with patients suffering from post-COVID-19 condition with pulmonary sequelae characterised by dyspnoea and pulmonary restriction.

Methods

Pa-COVID-19 is a prospective observational cohort study investigating the pathophysiology of acute COVID-19 and its chronic morbidity in patients with confirmed SARS-CoV-2 infection treated at Charité – Universitätsmedizin Berlin. The study collects data on epidemiology, demography, medical history, symptoms, clinical course and treatment as well as longitudinal data and biosamples during acute COVID-19 as well as during follow-up visits [16]. Patients were enrolled either at hospital admission or in case of initial outpatient treatment in our outpatient clinic. All patients enrolled tested positive for SARS-CoV-2 by polymerase chain reaction testing, were aged >18 years and gave informed consent (inclusion criteria). Patients were excluded if they or a legal guardian were not able to give informed consent or had a condition prohibiting blood sampling. Initial COVID-19 severity was stratified by need of respiratory support: outpatient without need for oxygen (NOO), hospitalised without need for oxygen (NOH), low-flow oxygen supply *via* nasal prongs (LFO), high-flow oxygen supply (HFO), invasive mechanical ventilation (IMV) and extracorporeal membrane oxygenation (ECMO). This study was approved by Charité ethical committee (EA2/066/20).

In this analysis, we report data from patients who presented for the first time to our outpatient department for follow-up in the post-acute phase after COVID-19 (minimum time from infection to presentation 3 months as per definition of post-COVID-19 syndrome and a maximum time of 8 months).

Patient classification

Following our clinical hypothesis, patients with post-COVID-19 condition (defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection with no other explanation) were stratified according to one of two predominant clinical phenotypes: patients with i) fatigue and exertional intolerance (post-covid fatigue, (PCF) group) and patients with ii) pulmonary sequelae *i.e.* pulmonary restriction and dyspnoea (post-covid restriction (PCR) group). Those two patient groups were compared to iii) patients without post-COVID-19 condition and without fatigue (non-chronic fatigue (NCF)).

Criteria for classification of patients were as follows: PCF patients had i) self-reported subjective fatigue, ii) exertional intolerance and iii) a minimum score of 12 points in the fatigue screening questionnaire (supplementary table S2). PCR was defined as i) pulmonary restriction in pulmonary function testing (see Pulmonary function testing below) and ii) a self-reported symptom of dyspnoea according to modified Medical Research Council Dyspnoea Scale ⩾1 [17]. NCF was defined as a negative control for PCF with i) absence of self-reported fatigue as well as exertional intolerance and ii) a total fatigue score <12. After applying these criteria, no participant met criteria for more than one classification.

Pulmonary function testing

Pulmonary function testing was performed as described previously [14] in accordance with international standards. Reference equations were based on the Global Lung Function Initiative reference equations and according to European Respiratory Society (ERS) statement on respiratory muscle testing [18–22]. Pulmonary function results were interpreted in accordance with American Thoracic Society (ATS) and ERS guidelines [23]. Pulmonary restriction was defined as TLC<LLN. We introduced a new pattern of impaired pulmonary function predominantly detected in patients with PCF and termed it complex ventilatory dysfunction (CVD). CVD was defined as TLC % pred – FVC % pred >10% and TLC⩾LLN. This pattern was derived from the prior definition of complex restriction first described by Clay *et al.* [24]. with the difference that in CVD TLC is not reduced and no restriction is present. Airway occlusion pressure ($P_{0.1}$% pred), inspiratory muscle strength (P_{Imax} % pred) and respiratory capacity ($P_{0.1}$ (kPa)/P_{Imax} (kPa)) were measured in addition to standard pulmonary functions tests to assess respiratory capacity, potentially influenced by neuromuscular function deficits, in accordance with ATS/ERS Statement on Respiratory Muscle Testing [25]. We abstained from exercise testing in patients with PCF to avoid the risk of post-exertional malaise in individuals with PCF.

Fatigue screening

All patients completed a fatigue screening questionnaire consisting of 12 items described elsewhere (see table 2) [15]. Scoring was applied according to symptom severity by patient self-reporting; 0 points were given for no symptoms, one point for mild, two points for moderate and three points for severe symptom load. PCF was defined as fatigue ⩾1 and exertional intolerance ⩾1 and a total score of all symptoms ⩾12. Development of the screening questionnaire was derived from the Canadian Consensus Criteria (CCC) [26], a set of diagnostic criteria used to diagnose ME/CFS. NCF was defined as no fatigue and exertional intolerance and a total score <12.

Symptom burden and mental health quality of life

A list of 43 frequently reported post-COVID-19 symptoms was assessed by a physician upon presentation at follow-up visits (supplementary figure S1). Patient Health Questionnaire (PHQ) and the Post-traumatic Stress Disorder Checklist (PCL-5) [27, 28] were performed to assess a patient's mental health status and mental health quality of life. St. George's Respiratory Questionnaire (SGRQ) was performed to assess respiratory health quality of life [29]. SGRQ outcome was previously shown to be associated with alterations in lung function in patients after SARS-CoV-2 infection [14].

Statistics

The Pa-COVID Study is an explorative study developed at the very beginning of the COVID-19 pandemic. Descriptive statistics were applied to calculate median, interquartile range (IQR) and mean±SD. t-test was applied to assess differences between two normally distributed variables, and the Mann–Whitney U-test was used for non-normally distributed data. Differences in continuous variables between three or more groups were analysed by one-way ANOVA or Kruskal–Wallis test. Chi-square test was used for analysis of categorical variables. To analyse risk factors for PCF and PCR, uni- and multivariate logistic regression was used. Multivariate analysis was adjusted for age and sex. Following the design of the study, calculations performed are explorative in nature and p-values are interpreted descriptively. Asterisks are used to improve legibility and are employed as follows: *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.

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Results

643 hospitalised patients with acute SARS-CoV-2 infection were enrolled into the Pa-COVID Study. In addition, a total of 41 patients, initially not hospitalised due to SARS-CoV-2 infection, were enrolled upon presentation at our outpatient clinic during follow-up. A total of 170 patients presented between month 3 and month 8 post symptom onset (figure 1) for follow-up examinations. Of these, 88 patients (51.8%) met criteria for one of the clinical phenotypes: n=36 met criteria for PCF, n=24 met criteria for NCF and n=28 met criteria for PCR.

Patient characteristics

Table 1 summarises demographic and clinical characteristics of the study population. Patients with PCF were younger in age compared to those with PCR, and the proportion of females was higher in PCF (75.0%) than in NCF and PCR groups (29.2 and 17.9%, respectively; p<0.001). Initial COVID-19 disease severity was skewed towards mild and moderate (NOO, NOH, LFO) in PCF and NCF patients compared to severe and critical (HFO, IMV, ECMO) in PCR (table 1).

Post-COVID-19 symptom burden

Post-COVID-19 symptom burden of the 15 most frequently occurring symptoms was similar in patients categorised with PCF and PCR but showed a different distribution (see figure 2a–f). The two most common symptoms reported in PCF and PCR patients were fatigue and dyspnoea. As part of the definition, fatigue occurred in all PCF patients, but a relevant proportion of PCR patients also reported fatigue in the post-COVID-19 phase (100% and 39.2% respectively; figure 2b). Likewise, dyspnoea occurred in all patients with PCR, but also in a relevant proportion of PCF patients (63.8%, figure 2c). Cognitive impairment was seen more often in PCF patients, compared to NCF and PCR (figure 2d). Cough and joint pain were equally distributed in PCF and PCR (figure 2e, f).

Pulmonary function

Pulmonary function revealed differences between PCF, NCF and PCR patients. Per definition, patients in the PCR group showed pulmonary restriction and showed reduced TLC and FVC compared to PCF and NCF (figure 3a, b). Pulmonary restriction is associated with lung parenchymal changes after severe acute COVID-19 and has been described in detail previously [14]. Diffusing capacity of the lung for carbon

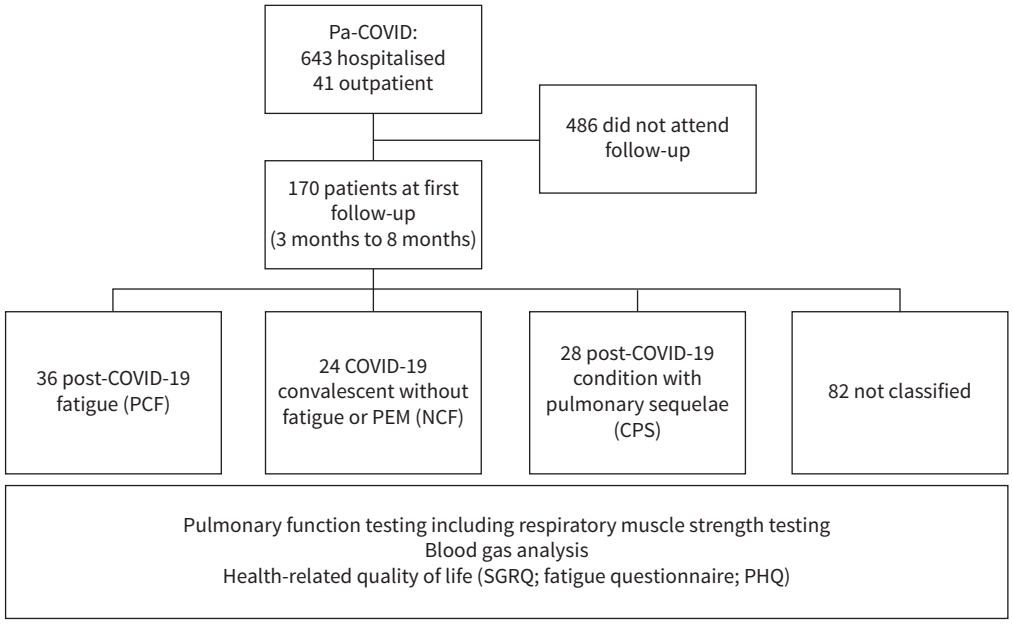

FIGURE 1 Study flow chart: 643 hospitalised and 41 outpatient participants were enrolled into the Pa-COVID-19 study. 170 patients presented for the first time between month 3 and 8 post symptom onset for follow-up in the outpatient department. These patients were stratified into patients with post-COVID-19 condition with fatigue (PCF) and post-exertional malaise (PEM), patients without chronic COVID-19 fatigue (NCF) and patients with post-COVID-19 condition and chronic pulmonary sequelae (PCR). SGRQ: St. George's Respiratory Questionnaire; PHQ: Patient Health Questionnaire.

TABLE 1 Patient characteristics, pulmonary function and symptom burden

	All	PCF	PCR	NCF	p-value
Patients n	170	36	28	24	
Basic demographic characteristics					
Age years, median (IQR)	59 (46–67)	58 (44–65)	62 (48–69)	54 (36–62)	0.143
Sex female, n (%)	66 (38.8)	27 (75.0)	5 (17.9)	7 (29.2)	<0.001
Disease severity, n (%)					
NOO	38 (22.4)	10 (27.8)	1 (3.6)	5 (20.8)	0.042
NOH	25 (14.7)	9 (25.0)	1 (3.6)	4 (16.7)	0.067
LFO	45 (26.5)	10 (27.8)	1 (3.6)	11 (45.8)	0.002
HFO	22 (12.9)	5 (13.9)	9 (32.1)	1 (4.2)	0.023
IMV	24 (14.1)	1 (2.8)	9 (32.1)	3 (12.5)	0.004
ECMO	16 (9.4)	1 (2.8)	7 (25.0)	0 (0.0)	0.002
Dexamethasone treatment, n (%)	49 (28.8)	6 (16.6)	6 (21.4)	9 (27.5)	0.167
Pulmonary function tests					
TLC % predicted, median (IQR)	96.8 (84.9–108.5)	108.4 (98.5–118.29)	73.0 (70.0–78.9)	99.5 (91.2–107.3)	<0.001
FVC % predicted, median (IQR)	88.9 (73.1–98.4)	88.2 (74.4–96.9)	69.8 (60.4–76.4)	97.3 (88.6–104.3)	<0.001
TLC – FVC % predicted, median (IQR)	9.0 (2.5–19.1)	21.3 (15.1–24.9)	4.3 (0.0–10.0)	4.3 (3.9–11.4)	<0.001
FEV_1 % predicted, median (IQR)	91.9 (78.5–100.2)	89.4 (80.1–99.7)	74.2 (58.4–81.9)	100.6 (89.8–112.6)	<0.001
FEV_1 % predicted/FVC % predicted, median (IQR)	102.0 (98.0–107.9)	100.4 (97.3–105.5)	102.4 (98.9–108.8)	107.7 (97.8–111.3)	0.112
D_{LCO} % predicted, median (IQR)	78.0 (65.1–86.4)	77.8 (66.8–86.4)	64.5 (51.1–69.6)	82.8 (74.5–91.1)	<0.001
K_{CO} % predicted, median (IQR)	89.6 (81.3–98.6)	87.9 (78.0–93.5)	98.5 (81.1–102.3)	89.3 (84.0–97.7)	0.440
P_{Imax} % predicted, median (IQR)	68.8 (53.0–89.9)	55.8 (41.5–75.9)	76.8 (63.6–102.2)	70.6 (66.3–88.9)	0.011
Restriction, n (%)	38 (22.4)	0 (0.0)	28 (100.0)	1 (4.2)	<0.001
CVD, n (%)	73 (42.9)	32 (88.9)	7 (25.0)	7 (29.1)	<0.001
Symptom burden					
Fatigue, n (%)	95 (55.9)	36 (100.0)	17 (60.7)	0	<0.001
Exertional intolerance, n (%)	87 (51.2)	36 (100.0)	13 (46.4)	0	<0.001
Fatigue score, median (IQR)	6.0 (2.0–12.0)	14.0 (12.0–18.0)	2.0 (1.0–8.0)	0 (0.0–1.0)	<0.001
Dyspnoea, n (%)	80 (47.1)	23 (63.8)	28 (100.0)	5 (20.8)	<0.001
SGRQ, median (IQR)	21.3 (4.9–43.1)	43.33 (29.9–66.1)	41.6 (26.4–56–8)	1.46 (0.0–9.2)	<0.001
PHQ – Major depression, n (%)	19 (11.2)	11 (30.5)	1 (3.6)	2 (8.3)	<0.001
PHQ – Anxiety disorder, n (%)	12 (7.1)	5 (13.9)	2 (7.1)	2 (8.39)	0.155

PCF: post-COVID-19 condition with fatigue and post-exertional malaise; PCR: post-COVID-19 condition with chronic respiratory sequelae; NCF: COVID-19 convalescents with no fatigue; NOO: no oxygen, outpatient; NOH: no oxygen, hospitalised; LFO: low-flow oxygen therapy; HFO: high-flow oxygen therapy; IMV: invasive mechanical ventilation; ECMO: extracorporeal membrane oxygenation; TLC: total lung capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: CO diffusion capacity; K_{CO}: transfer coefficient; P_{Imax}: respiratory muscle strength; CVD: complex ventilator dysfunction; SGRQ: St. George's Respiratory Questionnaire; PHQ: Patient Health Questionnaire.

monoxide (D_{LCO}) was reduced in PCR patients because of the lower ventilated alveolar volume in patients with pulmonary restriction, with normal transfer coefficient of the lung for carbon monoxide (K_{CO}) (figure 3g, h). Interestingly, inspiratory muscle strength (P_{Imax}) was clearly reduced in patients with PCF compared to those classified as NCF and PCR (55.8 *versus* 70.6 and 76.8 % predicted (p<0.001), respectively; figure 3e). Reduced ventilatory capacity resulting in slightly lower FVC was seen in patients with PCF compared to NCF (figure 3a). TLC was not reduced in these patients, leading to an increased difference between TLC and FVC (TLC – FVC, figure 3c). CVD, defined as difference between TLC and FVC (% predicted) >10% without evidence of restriction (TLC⩾LLN), occurred more frequently in PCF than in NCF and PCR (88.9 *versus* 29.1 and 25.0%, respectively; p<0001) (table 1). No difference was seen in $P_{0.1}$ between subgroups, but both PCF and PCR showed increased $P_{0.1}/P_{Imax}$ as a sign of increased load on the ventilatory system. None of these lung functional changes had an impact on blood gas analysis (pH, carbon dioxide tension and oxygen tension; see figure 3i, j, k).

Patient-reported health-related quality of life

Interestingly, respiratory quality of life as measured by SGRQ was similarly impaired in PCF and PCR patients (median (IQR) score: 43.3 (29.9–66.1) *versus* 41.6 (26.4–56.8), respectively) (figure 4a). Fatigue symptom load, as assessed by the fatigue screening questionnaire, was highest in patients with PCF, and markedly lower in those of the NCF and PCR groups (median (IQR): 14.0 (12.0–18.0) *versus* 0 (0.0–1.0) *versus* 2.0 (1.0–8.0), respectively) (figure 4b). Mental health, as measured by PHQ questionnaire, was impaired in PCF compared to NCF and PCR, with higher scores for depression disorder (figure 3c), and higher proportions of patients classified as major depression and anxiety disorder (30.5% *versus* 8.3%

TABLE 2 Risk factors associated with post-COVID-19 condition and fatigue (PCF) and post-COVID-19 condition respiratory sequelae (PCR)

	PCF				PCR			
	OR (95% CI)	p-value	aOR (95% CI)	p-value	OR (95% CI)	p-value	aOR (95% CI)	p-value
Age	0.99 (0.97–1.02)	0.78	-		1.02 (0.99–1.05)	0.10	-	
Sex (female)	7.31 (3.15–16.95)	<0.001	-		0.29 (0.10–0.80)	0.01	-	
ICU treatment	0.35 (0.14–0.85)	0.02	0.41 (0.16–1.07)	0.07	23.65 (6.74–82.94)	<0.001	21.07 (5.92–75.00)	<0.001
Hospitalisation	0.69 (0.30–1.59)	0.38	1.12 (0.42–2.97)	0.83	9.51 (1.25–72.5)	0.03	6.70 (0.85–52.60)	0.07
Outpatient treatment	1.46 (0.63–3.37)	0.38	0.90 (0.34–2.39)	0.83	0.11 (0.01–0.80)	0.03	0.15 (0.02–1.17)	0.07
Pulmonary restriction	0.00	1.00	0.00	1.00	-	-	-	-
Reduced D_{LCO}	0.98 (0.47–2.05)	0.95	1.44 (0.63–3.31)	0.39	8.95 (2.95–27.16)	<0.001	7.70 (2.50–23.71)	<0.001
Complex ventilatory dysfunction	18.15 (6.03–54.65)	<0.001	17.36 (5.38–56.06)	<0.001	0.38 (0.15–0.96)	0.04	0.48 (0.19–1.24)	0.48
P_{Imax} <60% predicted	3.96 (1.84–8.52)	<0.001	2.12 (0.90–5.02)	0.08	0.29 (0.10–0.88)	0.03	0.31 (0.094–1.06)	0.06
SGRQ total score >25	4.28 (1.97–9.25)	<0.001	5.25 (2.18–12.62)	<0.001	5.58 (2.33–13.37)	<0.001	6.18 (2.47–15.46)	<0.001
Dyspnoea	2.12 (0.99–4.53)	0.05	2.43 (1.04–5.67)	0.04	-	-	-	-
Fatigue	-	-	-	-	1.07 (0.47–2.45)	0.88	1.31 (0.55–3.11)	0.54
Exertional intolerance	-	-	-	-	0.80 (0.35–1.80)	0.58	0.89 (0.39–2.09)	0.80
Depression	6.93 (2.53–18.97)	<0.001	6.40 (2.12–19.37)	0.001	0.26 (0.03–1.99)	0.19	0.27 (0.03–2.19)	0.22

Associated risk factors including demographic characteristics, lung functional alterations and symptom burden for PCF and PCR, adjusted for age and sex. PCF: post-COVID-19 condition with fatigue and post-exertional malaise (PEM); PCR: post-COVID-19 condition with chronic respiratory sequelae; ICU: intensive care unit; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{Imax}: respiratory muscle strength; SGRQ: St. George's Respiratory Questionnaire.

versus 3.6%) (table 1). No distinct differences were seen between PCF and PCR patients for post-traumatic stress disorder, though scores were higher compared to NCF (figure 3d).

Risk factors for post-COVID-19 condition with fatigue or respiratory sequelae

Univariate and multivariate logistic regression were performed to analyse associated risk factors for PCF and PCR (table 2). Female sex was associated with PCF (OR 7.31, 95% CI 3.15–16.95; p<0.001), and male sex with PCR. The odds for PCR were higher after intensive care unit treatment (OR 23.65, 95% CI 6.74–82.94; p<0.001). Impaired respiratory quality of life, as measured by SGRQ score >25, was associated with both PCF and PCR (OR 4.28 (95% CI 1.97–9.25) and 5.58 (95% CI 2.33–13.37); p<0.001). The lung functional pattern of CVD was associated with PCF (OR 18.15, 95% CI 6.03–54.65; p<0.001) as well as with reduced inspiratory muscle strength (OR 3.96, 95% CI 1.84–8.52, p<0.001), but not with PCR. Both observations remained valid in multivariate analysis.

Discussion

This study analysed respiratory quality of life and patient-reported outcomes in patients during follow-up after acute COVID-19 from a prospective observational study at Charité University Medical Centre in Berlin. Study outcomes of participants were analysed depending on presence or absence of fatigue and exertional intolerance (PCF, NCF), and compared those to patients with respiratory symptoms and evidence of lung injury after COVID-19 (PCR).

Based on clinical observation and prior data, we hypothesised that pulmonary function is altered in two different ways in patients with post-COVID-19 condition, reflecting two distinct patient groups and clinical phenotypes.

First, a relevant number of patients with primary symptoms being fatigue and exertional intolerance experience a clinically mild SARS-CoV-2 infection and show no measurable limitation in pulmonary function in terms of obstruction, restriction or diffusion capacity, but still experience dyspnoea. We hypothesised that neuromuscular disturbances and resulting functional deficits could contribute to persisting dyspnoea seen in this patient group despite normal body plethysmography. A second group of patients with respiratory symptoms show evidence of lung injury and improving symptoms over the first 12 months of follow-up [14].

These patients usually have initially severe pulmonary involvement due to pro-inflammatory and pro-fibrotic lung parenchymal changes [30, 31] causing VQ mismatch, ultimately resulting in reduced D_{LCO} and pulmonary restriction [14]. Based on these considerations, we defined two patient groups and a control group: one group defined by the presence of chronic fatigue and exertional intolerance (PCF), and

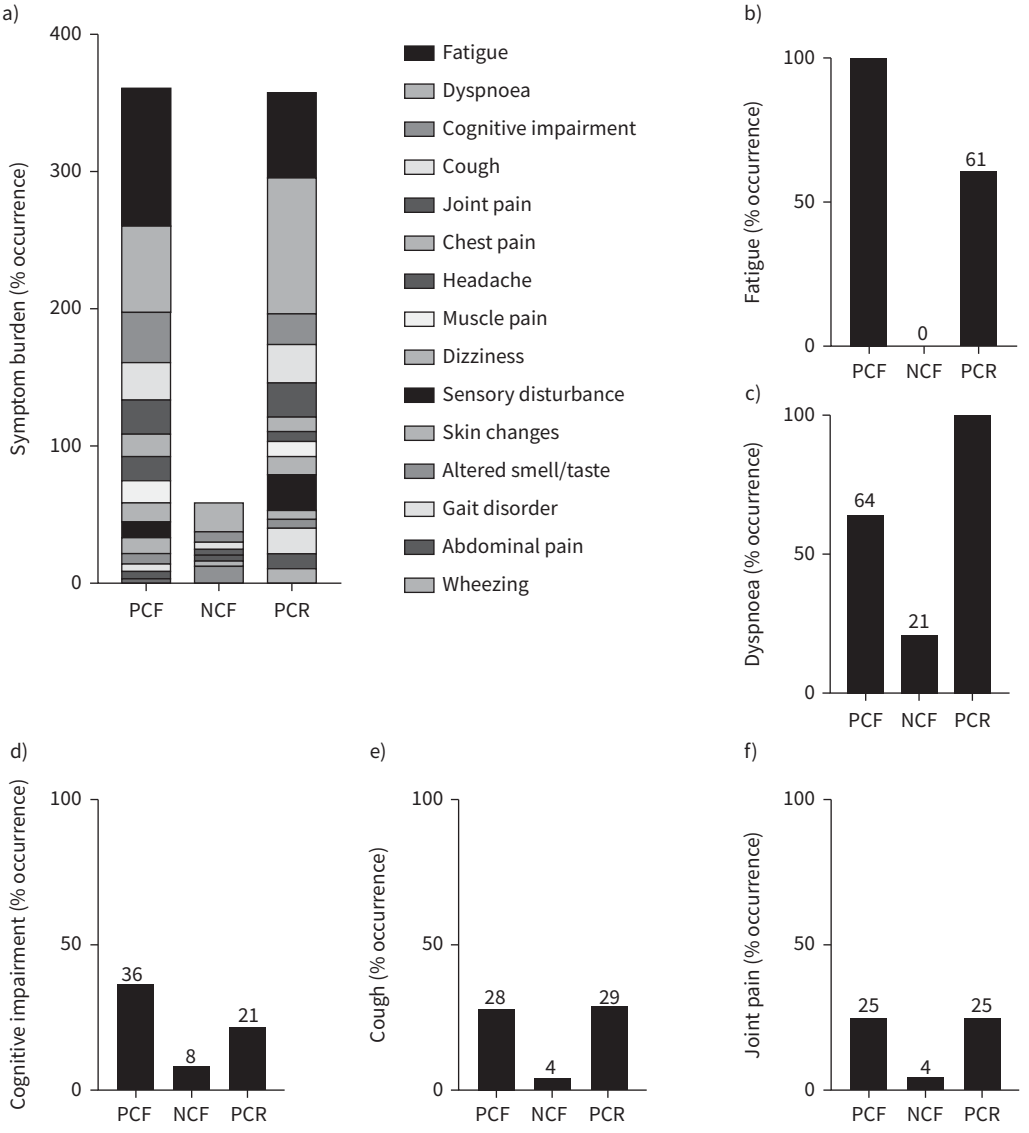

FIGURE 2 Symptom burden of patients with post-COVID-19 condition. a) Cumulative abundance of the 15 most frequently occurring symptoms in PCF, NCF and PCR shows similar overall symptom burden in patients with PCF and PCR with divergent distribution. b–f) The five most common symptoms stratified by PCF, NCF and PCR. As per definition, dyspnoea was present in all PCR patients; however, it was also observed in a high proportion of PCF patients. PCF: post-COVID-19 condition with fatigue and PEM; PEM: post-exertional malaise; NCF: COVID-19 convalescents with no fatigue; PCR: post-COVID-19 condition with chronic respiratory sequelae.

another group with post-COVID-19 condition with the lead symptoms of dyspnoea and pulmonary restriction (PCR). A third group showing neither signs of fatigue or exertional intolerance was defined for comparison (NCF).

Findings from this study support our initial hypothesis confirming the existence of a subgroup of patients whose persisting respiratory symptom load correlates well with reduced ventilatory capacity as expressed by reduced inspiratory muscle strength [32].

Correspondingly, Regmi *et al.* [33] report that a diaphragm muscle weakness might be causative for the exertional dyspnoea observed up to 15 months after hospitalisation for COVID-19 in the respective patients. Consequently, FVC is reduced due to neuromuscular causes (reduced P_{Imax}) with preserved TLC, resulting in an unusual ventilatory pattern, which we termed complex ventilatory dysfunction (CVD). We suggest that CVD explains the high proportion of patients with PCF suffering from dyspnoea, leading to

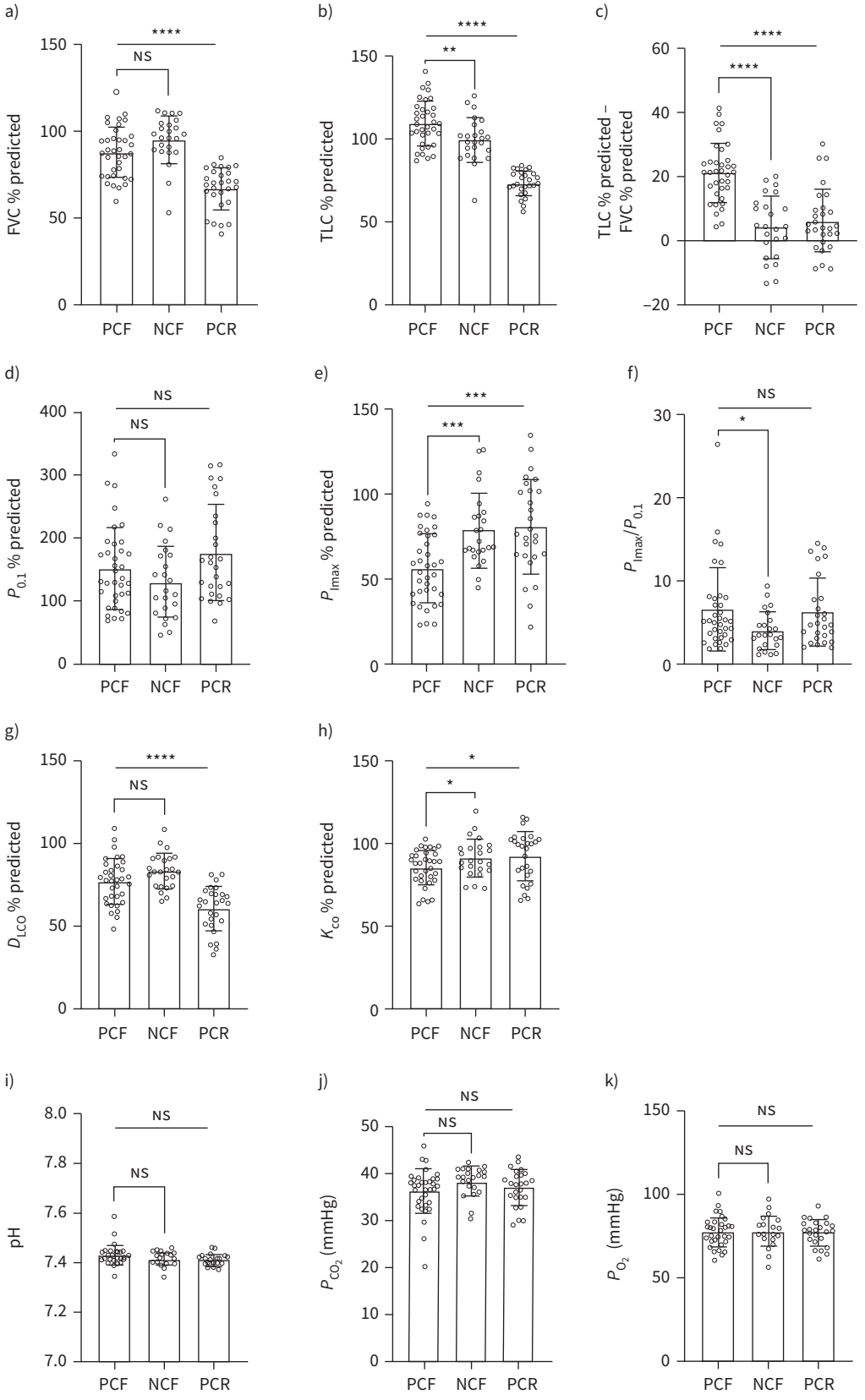

FIGURE 3 Pulmonary function and gas exchange. a,b,g,h) Pulmonary restriction and impaired D_{LCO} are hallmarks of PCR after severe and critical acute COVID-19; however, they are not seen in PCF. c,e) Reduced respiratory muscle strength and complex ventilatory dysfunction (P_{Imax}; TLC – FVC) are however associated

with PCF. i–k) No alterations in gas exchange were seen between different phenotypes. PCF: post-COVID-19 condition with fatigue and post-exertional malaise (PEM); NCF: COVID-19 convalescents with no fatigue; PCR: post-COVID-19 condition with chronic respiratory sequelae; TLC: total lung capacity; FVC: forced vital capacity; $P_{0.1}$: airway occlusion pressure; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide; P_{Imax}: respiratory muscle strength; P_{CO_2}: carbon dioxide tension; P_{O_2}: oxygen tension.

an inability to execute a forced expiration, with consecutively increased residual volume. Findings in this study are in line with those of other groups reporting reduced muscle strength measured as handgrip strength as part of the wide array of symptoms occurring in PCF [34, 35]. Reduced respiratory muscle strength (P_{Imax}), such as observed in patients suffering from chronic COVID-19 fatigue, has not been reported previously in this context. Interestingly, HENNIGS *et al*. [36] pointed towards a respiratory muscle dysfunction as a novel aspect of COVID-19 sequelae in hospitalised patients. In this study, P_{Imax} was reduced in both hospitalised and non-hospitalised patients and was lower in women compared to men. However, no discrimination between the underlying post-COVID-19 conditions (*i.e.* PCF or PCR) has been made. Moreover, a recent clinical trial among patients with post-COVID-19 condition and dyspnoea showed that respiratory muscle training over 8 weeks had positive effects on dyspnoea symptoms, inspiratory muscle strength and overall physical fitness [37]. We hypothesise that PCF patients might exhibit morphological alterations, as described in skeletal muscles with immune-mediated microvascular activation, altered capillary basement membrane and activated macrophages, that explain muscular fatigue and reduced P_{Imax} [38]. Although persistent respiratory symptoms after SARS-CoV-2 infection are common, there is a lack of established treatments [39, 40]. To date, there is a lack of evidence-based rehabilitation and non-pharmacological treatment concepts to address persisting symptoms after acute SARS-CoV-2 infection. These initial observations, to be supported by further evidence, may constitute a starting point for developing different rehabilitation concepts for patients according to their clinical phenotype. Whereas patients with respiratory symptoms exhibiting the PCR phenotype may benefit from classical rehabilitation with systematic physical training [41], different concepts and the inclusion of neuro-rehabilitative concepts may be needed for patients with respiratory symptoms and the PCF phenotype. Indeed, it is of great importance that patients with fatigue and post-exertional malaise with reduced respiratory muscle strength and dyspnoea are not exposed to physical stress and exercise testing, to avoid post-exertional deterioration of post-COVID-19 symptoms.

This study has limitations. This *post hoc* analysis from a nonrandomised single centre study population was suited to support our initial hypotheses, but the results needs to be confirmed in data from larger cohorts. Owing to the design of this study, physical and mental health status, as well as lung functional analyses before study inclusion were missing. Hence, it cannot be ruled out that previous health conditions related to metabolic, cardiovascular, pulmonary or neuromuscular and mental disorders might have confounded lung functional assessment and symptom burden in the post-COVID-19 condition as well. Patient enrolment only took place during the pre-Omicron era. Further, the length of time for inclusion ranging from 3 to 8 months is variable, but was chosen to also include patients after severe and critical COVID-19 who, due to prolonged hospital treatment, presented at a later point of time after hospital discharge. Nevertheless our data shed light on a potentially highly relevant pathophysiological mechanism in the post-COVID-19 condition.

Conclusion

In conclusion, our data suggest that in post-COVID-19 syndrome with fatigue and exertional intolerance, respiratory muscle strength may be reduced as an indicator of a neuromuscular functional deficit. This observation may explain persisting dyspnoea in this patient group in contrast to patients with initially severe disease who either improve in lung function over time or are able to compensate persistent organic pulmonary sequelae by training effects during recovery. Reduced P_{Imax} in patients with PCF is also associated with an increased residual volume (TLC – FVC (% predicted)) that we termed complex ventilatory dysfunction. The results need to be interpreted in the context of the study's limitations, *i.e.* as a non-randomised, single centre study with only limited information on the patients' health condition prior to SARS-CoV-2 infection with potential influence on lung function pattern or patient-reported quality of life. Further systematic studies of sequelae following recovery from acute COVID-19 will be necessary to develop an evidence-based approach for improving treatment options for patients affected. This includes the development of integrated multidisciplinary diagnostic and rehabilitation strategies taking into consideration the different patient phenotypes and their potentially different underlying pathophysiological mechanisms in PCF *versus* PCR patients.

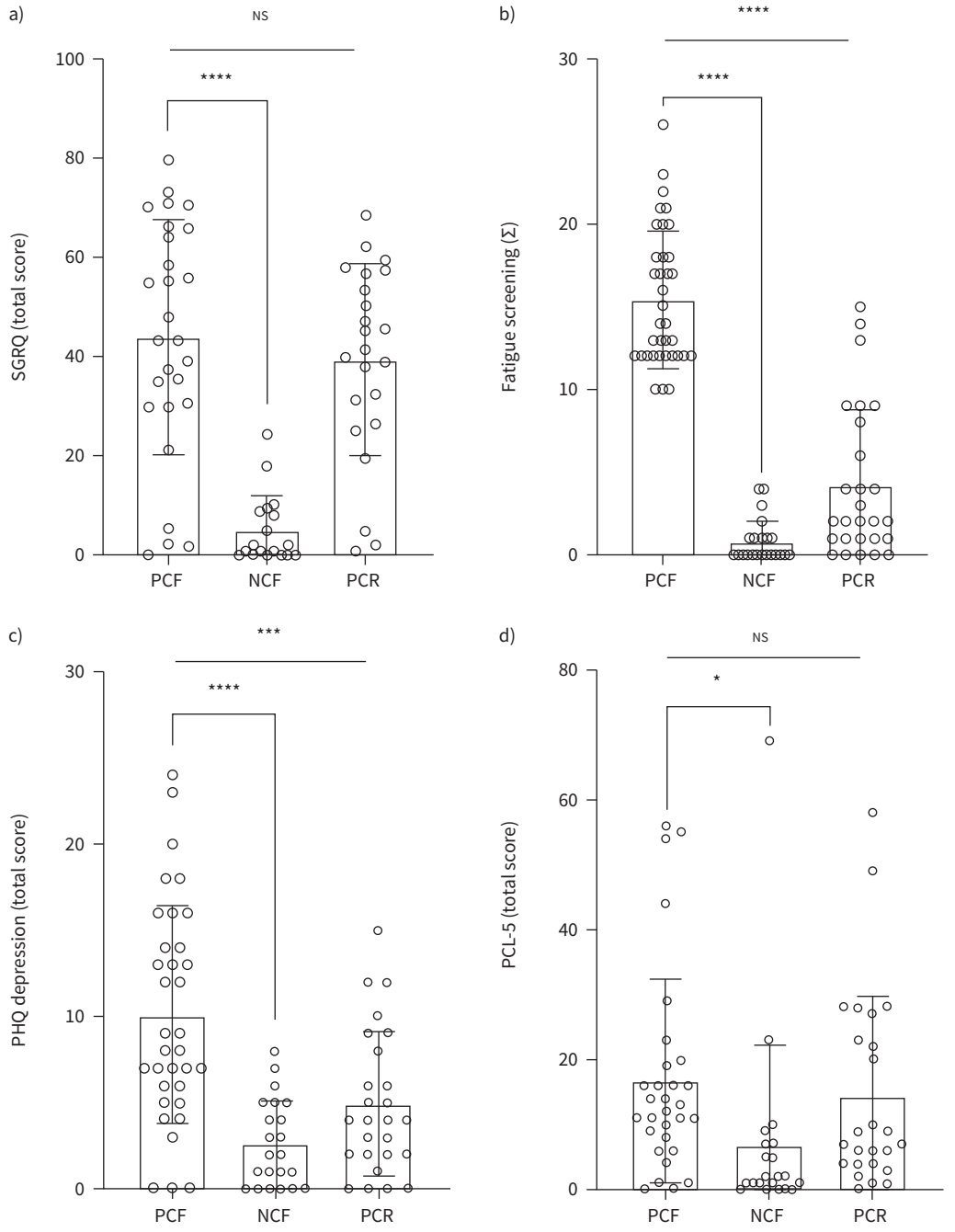

FIGURE 4 Patient-reported outcome: a) Respiratory quality of life was equally impaired in PCF and PCR as expressed by SGRQ score. b) Cumulative score of the fatigue questionnaire assessing post-COVID-19 chronic fatigue syndrome-specific symptoms based on the Canadian consensus criteria was highest in patients with PCF, and markedly lower in PCR and NCF controls. c,d) Total score of PHQ depression was increased in PCF compared to patients with NCF and PCR, with no marked differences regarding post-traumatic stress disorder (PCL-5). PCF: post-COVID-19 condition with fatigue and post-exertional malaise (PEM); NCF: COVID-19 convalescents with no fatigue; PCR: post-COVID-19 condition with chronic respiratory sequelae; SGRQ: St. George's Respiratory Questionnaire; PHQ: Patient Health Questionnaire.

Provenance: Submitted article, peer reviewed.

Data availability: Deidentified participant data available on request from the authors.

This study is registered at https://drks.de/ with identifier number DRKS00021688.

Ethics statement: The study was approved by Charité ethics committee (EA2/066/20).

Author contributions: F. Steinbeis, C. Kedor, M. Mittermaier, P. Knape, M. Witzenrath, C. Scheibenbogen and T. Zoller developed the study design. F. Steinbeis, H-J. Meyer, M. Mittermaier, P. Knape and T. Zoller collected data and performed data analysis. All authors contributed substantially interpreting the data and writing the manuscript. F. Steinbeis, P. Knape, M. Mittermaier and T. Zoller had full access to the data.

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