JIM Original Article

doi: 10.1111/joim.13614

Risk factors for impaired respiratory function post COVID-19: A prospective cohort study of nonhospitalized and hospitalized patients

Tove Björsell[1,2,3], Josefin Sundh[4], Anna Lange[5], Clas Ahlm[6], Mattias N.E. Forsell[6], Staffan Tevell[1,2,7], Anders Blomberg[3], Alicia Edin[8], Johan Normark[6,9] & Sara Cajander[5]

From the [1]Department of Infectious Diseases, Karlstad Hospital, Karlstad, Sweden; [2]Centre for Clinical Research and Education, Region Värmland, Karlstad, Sweden; [3]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [4]Department of Respiratory Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [5]Department of Infectious Diseases, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [6]Department of Clinical Microbiology, Umeå University, Umeå, Sweden (E-mail: Johan.normark@umu.se); [7]Faculty of Medicine and Health, School of Medical Sciences, Örebro University, Örebro, Sweden; [8]Anesthesiology and Intensive Care Medicine, Department of Surgical and Perioperative Sciences, Umeå University, Umeå, Sweden; and [9]Wallenberg Centre for Molecular Medicine, Umeå University, Umeå, Sweden , (E-mail: Johan.normark@umu.se)

Abstract. Björsell T, Sundh J, Lange A, Ahlm C, Forsell MNE, Tevell S, et al. Risk factors for impaired respiratory function post COVID-19: A prospective cohort study of nonhospitalized and hospitalized patients. *J Intern Med.* 2023;**293**:600–614.

Background. Severe COVID-19 increases the risk for long-term respiratory impairment, but data after mild COVID-19 are scarce. Our aims were to determine risk factors for reduced respiratory function 3–6 months after COVID-19 infection and to investigate if reduced respiratory function would relate to impairment of exercise performance and breathlessness.

Methods. Patients with COVID-19 were enrolled at the University Hospitals of Umeå and Örebro, and Karlstad Central Hospital, Sweden. Disease severity was defined as mild (nonhospitalized), moderate (hospitalized with or without oxygen treatment), and severe (intensive care). Spirometry, including diffusion capacity (DL_{CO}), was performed 3–6 months after hospital discharge or study enrollment (for nonhospitalized patients). Breathlessness (defined as $\geq$1 according to the modified Medical Research Council scale) and functional exercise capacity (1-min sit-to-stand test; 1-MSTST) were assessed.

Results. Between April 2020 and May 2021, 337 patients were enrolled in the study. Forced vital capacity and DL_{CO} were significantly lower in patients with severe COVID-19. Among hospitalized patients, 20% had reduced DL_{CO}, versus 4% in nonhospitalized. Breathlessness was found in 40.6% of the participants and was associated with impaired DL_{CO}. A pathological desaturation or heart rate response was observed in 17% of participants during the 1-MSTST. However, this response was not associated with reduced DL_{CO}.

Conclusion. Reduced DL_{CO} was the major respiratory impairment 3–6 months following COVID-19, with hospitalization as the most important risk factor. The lack of association between impaired DL_{CO} and pathological physiological responses to exertion suggests that these physiological responses are not primarily related to decreased lung function.

Keywords: breathlessness, COVID-19, diffusion capacity, post-acute COVID-19 syndrome, spirometry

Introduction

As of December 2022, over 600 million cases of COVID-19 have been reported worldwide with more than 6 million deaths [1]. In acute COVID-19, the clinical presentation varies from asymptomatic or mild flu-like disease to severe pneumonitis and respiratory failure. In severe disease manifestation, a hyperinflammatory state with disturbed coagulation may lead to disseminated pulmonary microthrombi and diffuse alveolar damage, causing a diffusion barrier and a mismatch between pulmonary ventilation and perfusion [2]. In cases with extended trajectories,

Johan Normark and Sara Cajander shared senior authors.

alveolar septal fibrous proliferation and pulmonary consolidation may explain the clinical feature of reduced pulmonary compliance [3]. Because of the large number of SARS-CoV-2-cases worldwide, the residual lung function in survivors from severe COVID-19 has become a major research interest.

There is mounting evidence that lung function is impaired after a severe COVID-19 infection, with reduced diffusion capacity (DL_{CO}) being the main feature [4–7]. A systematic review of 11 studies investigating lung function in patients following COVID-19-related hospitalization reports that up to one third of patients demonstrated impaired DL_{CO} 1 year after hospital discharge [8]. However, recent data show that the risk of developing chronic hypoxemia is very low, and that the impaired gas exchange can improve over time [9]. In parallel, persisting symptoms, lasting months to years after disease onset, have proved to be common in both hospitalized and nonhospitalized patients. Today this is referred to as post-acute COVID-19 syndrome (PACS), probably comprising multiple clinical phenotypes [10–13]. Breathlessness has been reported as one of the most common symptoms in PACS, with a prevalence of up to 60% [14]. Still, data are scarce when it comes to the residual lung function in relation to the clinical presentation after nonhospitalized COVID-19.

The aims of this study were to determine risk factors for reduced respiratory function 3–6 months after COVID-19 infection and to investigate whether reduced respiratory function related to impairment of exercise performance and breathlessness.

Methods

Study population

Data were provided from the ongoing multicenter CoVUm (host-pathogen interactions, immune response, and clinical outcome of COVID-19) study executed at three sites: Umeå and Örebro University Hospitals and Karlstad Central Hospital, Sweden. The Swedish Ethical Review Authority provided ethical clearance (number, 2020-01557). The CoVUm study was conducted in compliance with the Helsinki declaration.

Nonhospitalized patients aged ≥15 years and hospitalized patients aged ≥18 years with a positive PCR-test for SARS-CoV-2 were eligible for inclusion in the study. Exclusion criteria were inability to provide informed consent and inability to read and communicate in Swedish. The present study included subjects from the CoVUm cohort ($n = 542$) with complete spirometry data within 3–6 months after hospital discharge or, for nonhospitalized patients, study enrollment ($n = 337$) (Fig. 1). Participants were recruited between April 2020 and May 2021. None of the participants were vaccinated against SARS-CoV-2 at the time of inclusion.

At inclusion, age, sex, body mass index (BMI), smoking habits, and comorbidities were documented. Information on the highest level of care and oxygen treatment/respiratory support was obtained from electronic case report files. Disease severity was scored as mild (not hospitalized), moderate (hospitalized with or without oxygen treatment), and severe (admitted to the Intensive Care Unit). Obesity was defined as BMI ≥30. All data were collected and managed using REDCap electronic data capture tools hosted at Umeå University [15, 16].

Lung function tests

Lung function tests were carried out 3–6 months after inclusion (mild disease) or hospital discharge (moderate and severe disease). Dynamic spirometry, including forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), was performed, and the FEV_1/FVC-ratio was calculated. Diffusion capacity of the lungs for carbon monoxide (DL_{CO}) was measured using the single-breath test. At Umeå and Örebro University Hospitals, lung function tests were carried out using a Jaeger Master Screen PFT (Vyaire, Mettawa, IL, US) at the Departments of Clinical Physiology, according to clinical routine. At Karlstad Central Hospital, research nurses performed the lung function tests using a Medikro Pro spirometer (Medikro, Kuopio, Finland). The latter study individuals did not contribute to DL_{CO} comparative analyses. Lung function tests were executed according to the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines [17, 18]. Reference values for FEV_1, FVC, and DL_{CO} were calculated using The Global Lung Function Initiative (GLI) Network guidelines [19]. Impaired FEV_1, FVC, and DL_{CO} were defined as values less than the lower limit of normal (LLN).

Breathlessness and functional exercise test

Breathlessness was assessed 3 and 6 months after discharge of hospitalized patients or after

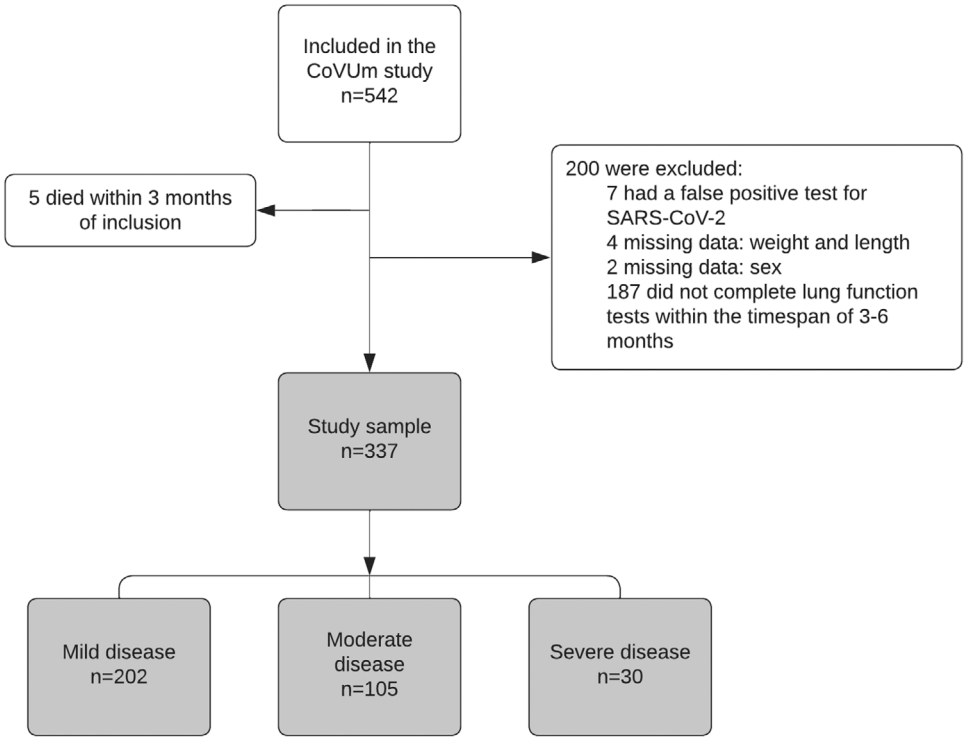

Fig. 1 *Inclusion flowchart. Source: Extraction of the study sample from the CoVUm study.*

enrollment of nonhospitalized patients, according to the modified Medical Research Council (mMRC) dyspnoea scale—range 0–4, and the higher the value, the more breathlessness the patient experiences [20]. The cutoff for breathlessness was set at mMRC ≥ 1, corresponding to "breathlessness when hurrying on the level or walking up a slight hill" or less demanding physical activities. The use of the mMRC scale in the study was implemented in November 2020 to measure perceived dyspnea in daily life. As a result, participants who were included early in the study were not assessed with the mMRC scale at 3–6 months.

A 1-min sit-to-stand test (1-MSTST) [21] was performed at a scheduled study visit 3 months after hospital discharge or study enrollment (non-hospitalized patients). The 1-MSTST involves the performance of as many sit-to-stand actions as possible in 1 min without using the upper limbs. A pulse oximeter was used to record oxygen saturation and heart rate before and after the test. Strassman's reference values (number of executed repetitions) for participants aged 20–79 years were used to calculate the 2.5th and 25th percentile [22]. A decrease in oxygen saturation of more than 4% units during the test [23] or an increase in heart rate of $\leq 5\%$ or $\geq 132\%$ of the baseline value was considered pathological. As no reference values for heart rate during the 1-MSTST were available, the higher cutoff for heart rate was defined as more than two standard deviations from the mean in this cohort. During aerobic exercise, the normal physiological response is a rise in heart rate [24]. However, as no scientific conformity could be found stating the lower cutoff, this was set at an increase in heart rate of $\leq 5\%$.

Statistics

Statistical analysis and graphical processing were carried out using IBM SPSS Statistics (version 28), Jamovi (version 2.3.18.0), and GraphPad prism (version 9.0.0). Data are reported as numbers observed (N), and the percentage of the total number of observations (%), mean with standard deviation (SD) (normally distributed values), or median with interquartile range (IQR) (non-normally distributed values). Missing data were handled by complete case analysis. One-way

ANOVA or *t*-test was used for group comparison of parametric data, Kruskal–Wallis was used for group comparison of nonparametric data, and chi-square test was used to compare categorical variables.

We performed multiple linear regression with percent of predicted FVC (FVC%pred), percent of predicted FEV_1 (FEV_1%pred), percent of predicted diffusion capacity (DL_{CO}%pred), and the number of repetitions executed during the 1-MSTST, respectively, as outcomes in order to analyze which factors were associated with lung function and physical performance. Independent variables were sex, chronic lung disease, cardiovascular disease, hypertension, diabetes, smoking (current or previous), obesity (BMI ≥30), severity of COVID-19 (mild, moderate, and severe), and age (<40, 40–59, and >59 years).

Multiple logistic regression with adjustment for respective lung values and potential confounding factors (same as above) was used to analyze factors associated with mMRC ≥1, pathological heart rate, and oxygen desaturation during the 1-MSTST, respectively.

No correction for multiple testing was performed due to the explorative nature of the analysis of this study. Statistical significance was set at $p < 0.05$.

Results

Characteristics of the study population

Out of 542 participants in the CoVUm cohort, 337 completed dynamic spirometry, and 313 completed the diffusion capacity test at 3–6 months. The median age of participants with completed spirometry was 51 years (IQR 39–60), and 50.7% were men. Median time from disease onset to lung function tests was 101 days (IQR 96–106) for nonhospitalized patients and 124 days (IQR 111–145) for hospitalized patients. At the 3-month visit, 275 study participants with completed spirometry performed the 1-MSTST. Further baseline characteristics of the cohort are presented in Table 1.

Severe COVID-19 is the strongest risk factor for long-term impairment of lung function

At 3–6 months, 6.5% of participants exhibited FVC <LLN, 6.8% showed FEV_1 <LLN, and 11.2% presented with DL_{CO} <LLN. Both FVC%pred and DL_{CO}%pred were inversely associated with increased disease severity. The FEV_1/FVC-ratio was significantly higher in the severe group, when compared with the mild group (Table 2). Among nonhospitalized participants, 4% showed DL_{CO} <LLN 3–6 months after onset of disease, as compared with 20% of those who were hospitalized.

Multiple linear regression showed that disease severity (moderate and severe disease) was independently associated with lower FVC%pred. Current/previous smoking and severe disease was also independently associated with lower FEV_1%pred. Cardiovascular disease, current/previous smoking, disease severity (moderate and severe), and age ≥60 were associated with lower DL_{CO}%pred (Table 3). Figure 2a illustrates diffusion capacity in relation to age, sex, and severity (nonhospitalized/hospitalized).

Breathlessness is associated with impaired diffusion capacity and female sex

Breathlessness at 3–6 months was assessed in 254 participants. A total of 103 (40.6%) participants reported mMRC ≥1. Among men, 49 (37.4%) reported mMRC ≥1 compared to 54 (43.9%) of women, $p = 0.292$. DL_{CO} <LLN, female sex, smoking (current or previous), disease severity (moderate and severe), and age 40–59 years were all independently associated with mMRC ≥1 (Table 4). Figure 2b illustrates diffusion capacity in relation to age, sex, and breathlessness. Taken together, the individuals with DL_{CO} below LLN are predominantly hospitalized male patients experiencing breathlessness.

Pathological oxygen desaturation and heart rate responses are not associated with impaired diffusion capacity

The median sit-to-stand repetitions performed in 1 min during the 1-MSTST was 35 (IQR 28–48). A total of 117 (42.9%) participants performed ≤25th percentile of the number of repetitions in 1 min and 15 (5.5%) ≤2.5th percentile.

Twenty-five (9.1%) participants showed a pathological reduction in oxygen saturation (≥4% units) and 9.5% exhibited a pathological heart rate response, as defined in methods, during the test (Fig. 3). Among these, a majority suffered from mild COVID-19 disease (82.7%) and 48.1% were men. Only two patients in the group who showed an increase in heart rate with ≤5% were treated with beta-blocking agents.

Table 1. *Characteristics of the study population of 337 COVID-19 patients divided by disease severity and pathological heart rate and/or oxygen saturation reaction during the 1-MSTST*

Characteristics	Total ($n = 337$)	Mild ($n = 202$)	Moderate ($n = 105$)	Severe ($n = 30$)	Pathological 1-MSTST ($n = 47$)
Age, median (IQR)	51 (39–60)	46 (33–57)	57 (45–65)	57 (50–64)	45 (29–56)
Sex, *n* (%)					
Male	171 (50.7)	84 (41.6)	65 (61.9)	22 (73.3)	23 (48.9)
Female	166 (49.3)	118 (58.4)	40 (38.1)	8 (26.7)	24 (51.1)
BMI, median (IQR)	26.3 (23.5–30.2)	24.9 (22.7–27.3)	29.7 (25.8–32.5)	31.3 (28.6–34)	24.3 (22–29.3)
Smoker, *n* (%)[a]					
Smoker	6 (1.9)	4 (3.1)	1 (1)	1 (3.6)	2 (4.3)
Ex-smoker	84 (26)	38 (19.6)	38 (37.6)	8 (28.6)	10 (21.3)
Level of education, *n* (%)[b]					
Lower	26 (8.1)	11 (5.5)	13 (14.3)	2 (6.9)	1 (2.1)
Medium	112 (34.9)	64 (31.8)	33 (36.3)	15 (51.7)	18 (38.3)
Higher	183 (57)	126 (62.7)	45 (49.5)	12 (41.4)	28 (59.6)
Comorbidity, *n* (%)					
Hypertension	73 (21.7)	22 (10.9)	40 (38.1)	11 (36.7)	5 (10.6)
Chronic lung disorder	60 (17.8)	32 (15.8)	22 (21)	6 (20)	4 (8.5)
-Asthma	57 (16.9)	31 (15.3)	21 (20)	5 (16.7)	4 (8.5)
Cardiovascular disease	26 (7.7)	9 (4.5)	14 (13.3)	3 (10)	5 (10.6)
Autoimmune disease	22 (6.5)	10 (5)	10 (9.5)	2 (6.7)	2 (4.3)
Diabetes mellitus	19 (5.6)	5 (2.5)	13 (12.4)	1 (3.3)	0 (0)
Tumor/cancer	5 (1.5)	2 (1)	3 (2.9)	0 (0)	0 (0)
Kidney disease	3 (0.9)	0 (0)	3 (2.9)	0 (0)	0 (0)
CCI, mean (SD)	0.34 (0.73)	0.22 (0.58)	0.58 (0.95)	0.37 (0.67)	0.15 (0.42)
Drugs before inclusion, *n* (%)					
Inhaled bronchodilators	38 (11.3)	19 (9.4)	15 (14.3)	4 (13.3)	4 (8.5)
Inhaled corticosteroids	36 (10.7)	13 (6.4)	19 (18.1)	4 (13.3)	3 (6.4)
Immunomodulatory treatment	9 (2.7)	3 (1.5)	6 (5.7)	0 (0)	1 (2.1)
Disease severity of COVID-19					
Mild	202 (59.9)	–	–	–	39 (83)
Moderate	105 (31.2)	–	–	–	4 (8.5)
Severe	30 (8.9)	–	–	–	4 (8.5)
Days admitted to hospital, median (IQR)	6 (4–10)	0 (0)	5 (3–8)	17 (9–24)	7 (3–20)
Days admitted to ICU, median (IQR)	7 (2–11)	0 (0)	0 (0)	7 (2–11)	7 (4–16)
Treatment during admission, *n* (%)					
Corticosteroids	95 (28.2)	0 (0)	68 (64.8)	27 (90)	7 (14.9)
Corticosteroids + IL-6-inhibitors	10 (3)	0 (0)	1 (1)	9 (30)	2 (4.3)
Remdesivir	23 (6.8)	0 (0)	13 (12.4)	10 (33.3)	2 (4.3)
Maximal level of oxygen treatment/respiratory support during admission, *n* (%)					
No oxygen treatment/respiratory support	224 (66.5)	202 (100)	22 (21)	0 (0)	39 (83)

(*Continued*)

Table 1. *(Continued)*

Characteristics	Total ($n = 337$)	Mild ($n = 202$)	Moderate ($n = 105$)	Severe ($n = 30$)	Pathological 1-MSTST ($n = 47$)
Oxygen therapy through mask or nasal cannula	40 (11.9)	0 (0)	39 (37.1)	1 (3.3)	2 (4.3)
High flow nasal cannula	61 (18.1)	0 (0)	44 (41.9)	17 (56.7)	5 (10.6)
NIV/CPAP	2 (0.6)	0 (0)	0 (0)	2 (6.7)	1 (2.1)
Mechanical ventilation	10 (3)	0 (0)	0 (0)	10 (33.3)	0 (0)

Note: 1-MSTST, 1-min sit-to-stand test; BMI, body mass index; lower education level, Swedish compulsory school of 9 years; medium education level, 2–3 years beyond compulsory school; higher education level, college or university studies; CCI, Charlson Comorbidity Index; ICU, intensive care unit; NIV, noninvasive ventilation; CPAP, continuous positive airway pressure.
[a]Available data in 323 participants.
[b]Available data in 321 participants.

Table 2. *Lung function outcomes at 3–6 months after COVID-19 divided by disease severity*

Characteristics	Mild ($n = 202$)	Moderate ($n = 105$)	Severe ($n = 30$)	p-Value
Spirometry at 3–6 months[a]				
FVC, L	4.34 (3.71–5.13)	4 (3.2–4.9)	3.85 (3.19–4.43)	**<0.001**
FVC, % of predicted	105 (96.2–112)	94.3 (85.9–106)	89.8 (79.9–93.9)	**<0.001**
FVC <LLN, *n* (%)	5 (2.5)	11 (10.5)	6 (20)	**<0.001**
FEV_1, L	3.36 (2.9–3.92)	3.17 (2.58-3.79)	3.08 (2.73–3.65)	**0.059**
FEV_1, % of predicted	101 (91.9–108)	95.1 (86.6–105)	94.6 (81.9–103)	**0.008**
FEV_1 <LLN, *n* (%)	8 (4)	9 (8.6)	6 (20)	**<0.001**
FEV_1/FVC	0.78 (0.74–0.82)	0.80 (0.75–0.83)	0.83 (0.81–0.85)	**<0.001**
Diffusion capacity at 3–6 months[a,b]				
DL_{CO}, mmol/min/kPa/L	8.03 (6.84–10.1)	7.34 (6.4–8.88)	6.87 (5.3–9.1)	**<0.001**
DL_{CO}, % of predicted	98.4 (90.1–107)	89.3 (80.1–97.6)	75.4 (64.2–95.1)	**<0.001**
DL_{CO} <LLN, n (%)	8 (4)	13 (14.8)	14 (50)	**<0.001**
mMRC at 3–6 months[a], *n* (%)[c]				
mMRC 0	118 (72.4)	28 (40)	5 (23.8)	**<0.001**
mMRC ≥1	45 (27.6)	42 (60)	16 (76.2)	**<0.001**

Note: Reported as median (IQR) unless specified otherwise. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusion capacity; LLN, lower limit of normal; mMRC, modified Medical Research Council Dyspnoea Scale. Significance set at $p < 0.05$. Statistical test: Kruskal–Wallis test for continuous variables and chi-square test for analysis of all category variables among the three groups.
[a]3–6 months after hospital discharge or study enrollment (nonhospitalized patients).
[b]Available data in 313 participants.
[c]Available data in 254 participants.

Multiple linear regression showed that current/previous smoking, obesity, and moderate disease severity were associated with a lower number of repetitions performed during the 1-MSTST (Table 4). Multiple logistic regression showed no association with impaired diffusion capacity and a pathological oxygen desaturation reaction or heart rate response during the 1-MSTST. Age ≥60 years was associated with a lower risk of pathological heart rate response compared to those aged 16–39. Two separate populations could be discerned when DL_{CO} was plotted against heart rate and oxygen saturation responses, respectively (Figs. 4 and 5). As depicted, individuals with pathological

Table 3. *Multivariable linear regression of lung function outcomes at 3–6 months after COVID-19 (n = 337)*

		FVC % of predicted		FEV_1 % of predicted		DL_{CO} % of predicted	
Variables	*N* (%)	*β*-coefficient (95% CI)	*p*	*β*-coefficient (95% CI)	*p*	*β*-coefficient (95% CI)	*p*
Sex							
Male	171 (50.7)	Ref		Ref		Ref	
Female	166 (49.3)	2.03 (−1.02 to 5.08)	0.192	1.56 (−1.73 to 4.86)	0.351	1.98 (−1.33 to 5.28)	0.240
Chronic lung disease	60 (17.8)	0.6 (−3.33 to 4.52)	0.764	−2.92 (−7.16 to 1.31)	0.176	−2.68 (−6.96 to 1.59)	0.217
Cardiovascular disease	26 (7.7)	−0.25 (−6.09 to 5.58)	0.932	0.87 (−5.43 to 7.17)	0.786	−7.69 (−14.12 to −1.27)	**0.019**
Hypertension	73 (21.7)	−3.87 (−8.26 to 0.52)	0.084	−3.71 (−8.45 to 1.03)	0.124	−2.45 (−7.28 to 2.37)	0.317
Diabetes	19 (5.6)	−3.22 (−10 to 3.56)	0.350	−0.95 (−8.26 to 6.37)	0.799	6.79 (−0.72 to 14.29)	0.076
Smoker or previous smoker	90 (27.9)	−3.28 (−6.71 to 0.15)	0.061	−4.89 (−8.59 to −1.18)	0.010	−3.98 (−7.71 to −0.26)	0.036
Obesity	89 (26.6)	−2.63 (−6.64 to 1.38)	0.198	−1.13 (−5.46 to 3.19)	0.606	2.45 (−1.97 to 6.86)	0.227
Severity of COVID−19							
Mild disease	202 (59.9)	Ref		Ref		Ref	
Moderate disease	105 (31.2)	−5.08 (−8.84 to −1.33)	0.008	−1.34 (−5.4 to 2.71)	0.515	−6.66 (−10.83 to −2.48)	0.002
Severe disease	30 (8.9)	−14.8 (−20.71 to −8.89)	<0.001	−7.26 (−13.63 to −0.89)	0.026	−20.59 (−27.2 to −14.01)	<0.001
Age groups (years)							
16–39	86 (25.5)	Ref		Ref		Ref	
40–59	156 (46.3)	1.51 (−2.27 to 5.3)	0.432	2.46 (−1.63 to 6.54)	0.237	0.24 (−3.81 to 4.28)	0.908
60+	95 (28.2)	2.15 (−2.61 to 6.91)	0.374	4.34 (−0.79 to 9.48)	0.097	−7.75 (−12.89 to −2.62)	0.003

Note: Multivariable linear regression calculated for the dependent variables FVC % of predicted, FEV_1 % of predicted and DL_{CO} % of predicted. Reported with *β*-coefficient and 95% confidence interval (CI). FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusion capacity; ref, reference group. Significance set at $p < 0.05$.

responses to physical activity are predominantly nonhospitalized individuals without impaired diffusion capacity.

Discussion

This study demonstrates that there is an association between disease severity and reduced lung function 3–6 months after a COVID-19 infection, with as many as 50% of patients with severe COVID-19 displaying impaired diffusion capacity at follow-up. Although a majority of women in this study presented with mild COVID-19 disease in the acute phase, they experienced a higher risk of increased breathlessness at 3–6 months. Finally, patients with reduced lung function or diffusion capacity were distinct from those with a pathological heart rate response or oxygen desaturation during the 1-MSTST, suggesting that these physiological signs represent different phenotypic disease entities.

In coherence with previous studies investigating this topic, this study concludes that the lung

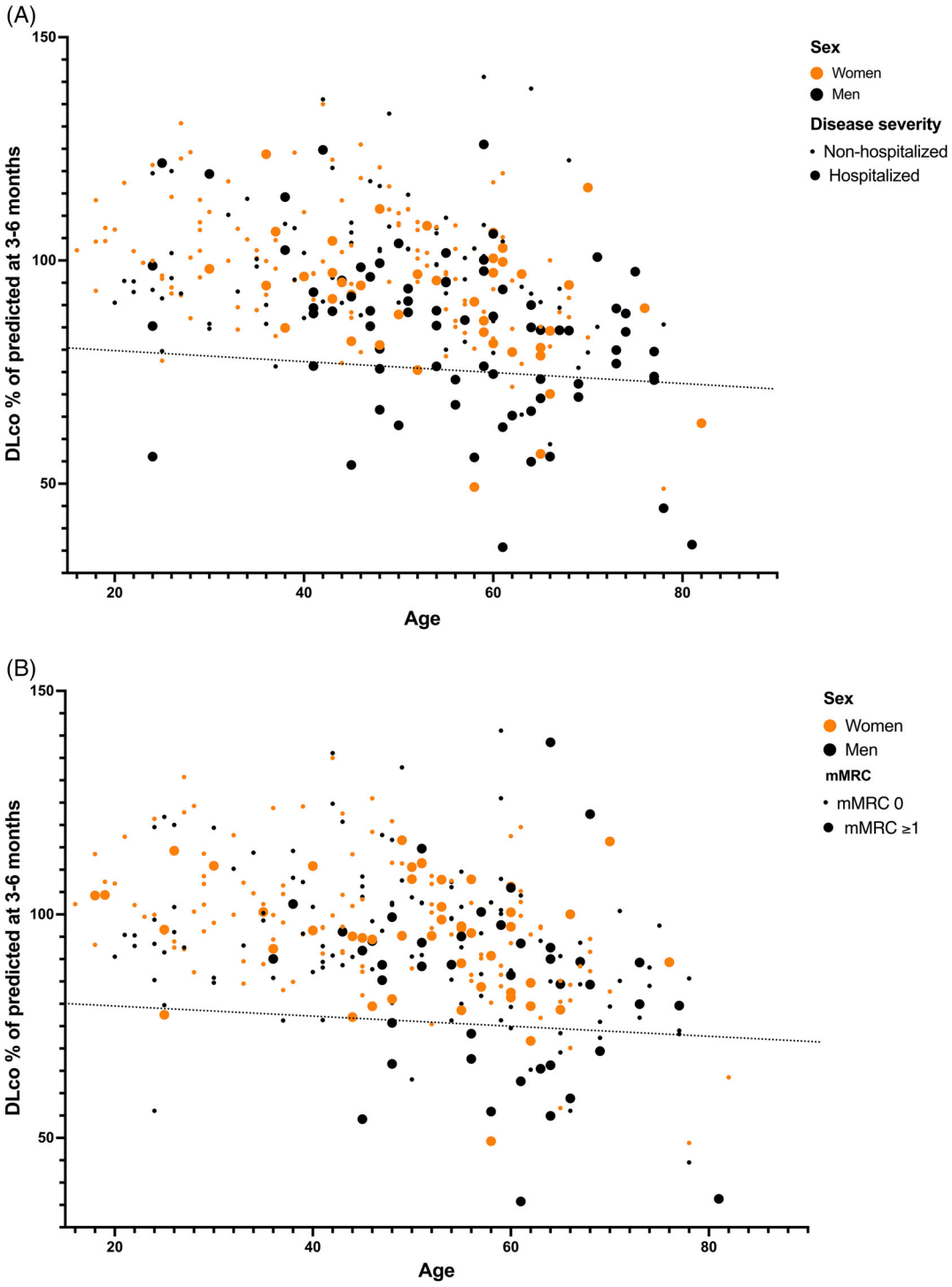

Fig. 2 *(a and b) Diffusion capacity divided by age, sex, disease severity, and mMRC. The dotted line is set at the lower limit of normal (LLN). (a) The percentage of predicted values of diffusion capacity (DL_{CO}) related to age, sex, and disease severity. (b) The percentage of predicted values of DL_{CO} related to age, sex, and the modified Medical Research Council (mMRC) dyspnoea scale.*

Journal of Internal Medicine, 2023; 293: 600–614

Table 4. *Multivariable logistic and linear regression of breathlessness, pathological cardiopulmonary reactions to the 1-MSTST, and the number of repetitions during the 1-MSTST at 3–6 months after COVID-19 (n = 337)*

		mMRC ≥1		Pathological oxygen saturation reaction during the 1-MSTST		Pathological heart rate reaction during the 1-MSTST		Number of repetitions during the 1-MSTST	
Variables	*N* (%)	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	*β*-coefficient (95% CI)	*p*
DL_{CO} <LLN at 3–6 months[a]	35 (11.2)	7.26 (1.87 to 28.11)	**0.004**	0.65 (0.09 to 4.85)	0.679	2.54 (0.5 to 12.94)	0.262	−6.08 (−12.45 to 0.30)	0.062
Sex									
Male	171 (50.7)	Ref		Ref		Ref		Ref	
Female	166 (49.3)	3.35 (1.62 to 6.91)	**0.001**	1.05 (0.4 to 2.74)	0.923	0.73 (0.3 to 1.75)	0.479	−2.23 (−5.59 to 1.13)	0.193
Chronic lung disease	60 (17.8)	2.23 (0.97 to 5.15)	0.060	0.87 (0.23 to 3.38)	0.844	0.66 (0.18 to 2.43)	0.528	3.57 (−0.88 to 8.02)	0.115
Cardiovascular disease	26 (7.7)	1.62 (0.48 to 5.53)	0.439	3.99 (0.8 to 19.98)	0.092	1.59 (0.27 to 9.49)	0.612	0.23 (−6.32 to 6.78)	0.945
Hypertension	73 (21.7)	1.11 (0.42 to 2.95)	0.831	0.4 (0.07 to 2.28)	0.305	0.79 (0.14 to 4.5)	0.794	−3.38 (−8.36 to 1.60)	0.183
Diabetes	19 (5.6)	2.59 (0.5 to 13.28)	0.255	<0.001 (0 to inf)	0.989	<0.001 (0 to inf)	0.989	−6.15 (−14.08 to 1.77)	0.127
Smoker or previous smoker	90 (27.9)	2.18 (1.07 to 4.47)	**0.033**	0.46 (0.13 to 1.59)	0.220	2.13 (0.78 to 5.86)	0.141	−4.02 (−7.84 to −0.20)	**0.039**
Obesity	89 (26.6)	1.32 (0.52 to 3.33)	0.560	2.21 (0.62 to 7.97)	0.224	1.2 (0.32 to 4.48)	0.783	−4.63 (−9.23 to −0.03)	**0.048**
Severity of COVID-19									
Mild disease	202 (59.9)	Ref		Ref		Ref		Ref	
Moderate disease	105 (31.2)	3.12 (1.33 to 7.33)	**0.009**	0.13 (0.02 to 1.18)	0.070	0.25 (0.05 to 1.29)	0.097	−6.3 (−10.76 to −1.83)	**0.006**
Severe disease	30 (8.9)	6.79 (1.51 to 30.49)	**0.012**	1.45 (0.25 to 8.44)	0.679	0.24 (0.02 to 2.83)	0.257	−5.06 (−12.52 to 2.4)	0.182
Age groups									
16–39	86 (25.5)	Ref		Ref		Ref		Ref	
40–59	156 (46.3)	2.82 (1.15 to 6.94)	**0.024**	1.27 (0.42 to 3.83)	0.669	0.43 (0.17 to 1.11)	0.080	1.55 (−2.45 to 5.55)	0.445
60+	95 (28.2)	2.61 (0.89 to 7.59)	0.079	2.08 (0.5 to 8.63)	0.313	0.18 (0.04 to 0.87)	**0.033**	−3.34 (−8.43 to 1.75)	0.197

Note: Multivariable logistic regression calculated for the dependent variable mMRC ≥1 at 3–6 months, pathological heart rate and oxygen saturation responses during the 1-min sit-to-stand test (1-MSTST) at 3 months. Reported with odds ratio and 95% confidence interval (CI). Multivariable linear regression calculated for the number of repetitions during the 1-MSTST. Reported with *β*-coefficient and 95% confidence interval (CI). DL_{co}, diffusion capacity; LLN, lower limit of normal; mMRC, modified Medical Research Council Dyspnoea Scale; ref, reference group.

[a]3–6 months after hospital discharge or study enrollment (nonhospitalized patients). Significance should be in bold $p < 0.05$.

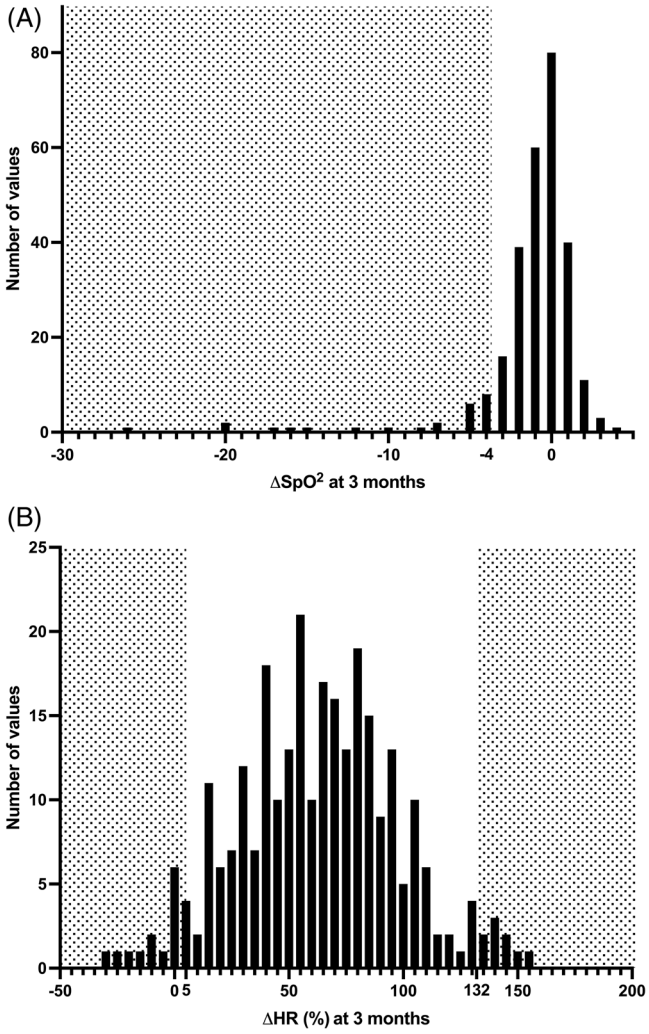

Fig. 3 *(a and b) Cutoff values for the 1-min sit-to-stand test. The dotted areas in the graphs represent pathological values. (a) The difference in oxygen saturation (SpO_2) before and after the 1-min sit-to-stand test (1-MSTST). The cutoff value for ΔSpO_2 is set at −4% units; (b), the percentage difference in heart rate (HR) before and after the 1-MSTST. The cutoff values for ΔHR (%) are set at 5% and 132%.*

function response after 3–6 months was associated with the degree of disease severity during the acute phase [4–8]. Furthermore, smoking was associated with decreased diffusion capacity. Smoking is known to cause COPD, which in turn may reduce diffusion capacity due to the development of emphysema [25, 26].

Several other studies have shown that diffusion capacity is reduced in women after COVID-19 disease [27–30]. In this study, which also includes nonhospitalized patients, we could not identify this phenomenon when applying reference values according to GLI. Therefore, this study suggests that sex does not impact lung function 3–6 months after COVID-19. Different sex hormones between men and women have been described to play a role for short- and long-term symptoms of COVID-19 disease. For example, male sex is known to be an important risk factor for severe acute disease and mortality. In contrast, it has been reported that premenopausal women present with milder COVID-19 disease in the acute phase, suggesting a protection by female hormones [31–33]. In support of this view, a recently published report by Sund et al. showed that estrogen supplementation in postmenopausal women was associated with a decreased risk of dying from COVID-19 [34]. As disease severity is the major risk factor for decreased lung function post COVID-19, this protection would also result in a reduced risk of impaired lung function in women. However, female sex hormones may not only be protective during COVID-19 disease, as these have been suggested

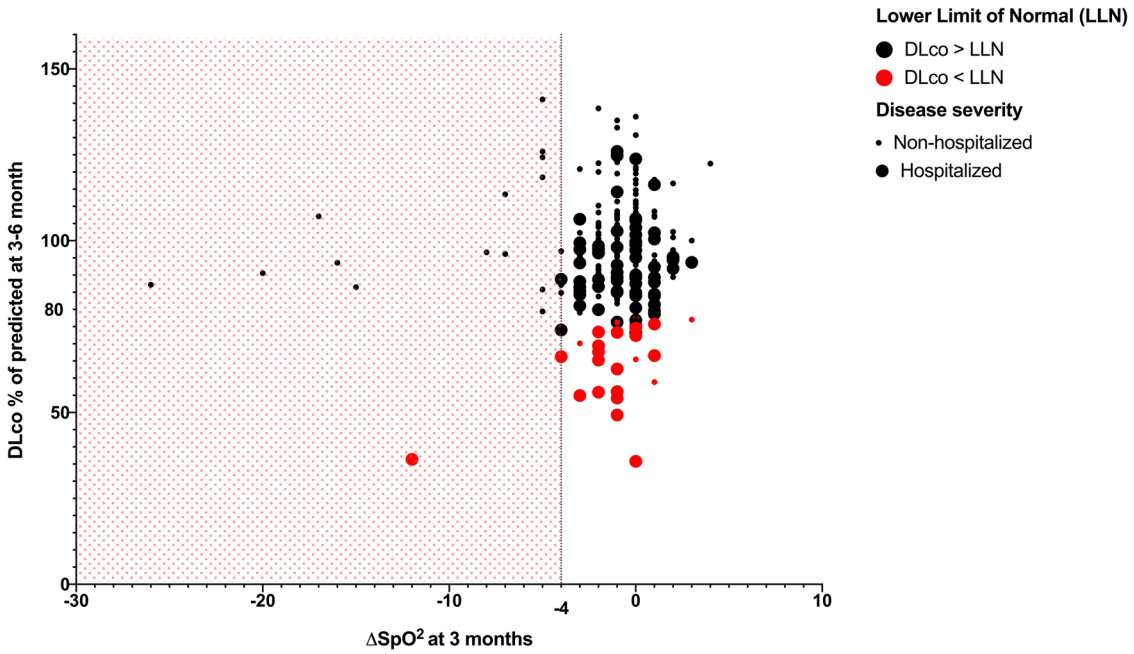

Fig. 4 *Diffusion capacity related to oxygen saturation during exercise. The percentage of predicted values of diffusion capacity (DL_{CO}) related to delta oxygen saturation (SpO_2) after the 1-MSTST, impaired diffusion capacity, and disease severity. Impaired diffusion capacity is defined as DL_{CO} under the lower limit of normal (LLN). The red dotted area represents the group with abnormal desaturation at the 1-min sit-to-stand test (1-MSTST).*

to partly be involved in the persistent symptoms seen in PACS [35, 36].

The next important finding of this study was that female sex was associated with breathlessness. Nearly half (42%) of the female study population reported breathlessness at 3–6 months after COVID-19 disease. The pathophysiology behind PACS after COVID-19-infection is still unknown, but female sex has been reported as a risk factor [37–39]. Recently, the hyperventilation syndrome was proposed as an explanation to the persistent breathlessness seen in PACS [40, 41]. Taverne et al. examined 10 patients with previous COVID-19 infection, who reported persistent breathlessness without signs of abnormal lung function. Six of these patients were diagnosed with hyperventilation syndrome and, interestingly, the majority were women [41]. Although the pathophysiology behind the hyperventilation syndrome is still unknown, it has been suggested that it is caused by an abnormal ventilatory control [42]. Another aspect to take into consideration is that the mMRC scale is subjective and that there could be a sex difference in how breathlessness is experienced. In view of this, Ekström et al. showed that breathlessness in the general population was twice as common in women as in men and that this could be explained by the smaller absolute lung volumes in women [43].

In addition to impaired lung function and persistent subjective breathlessness, we found that a significant proportion of the participants (17%) exhibited an abnormal heart rate response and/or oxygen desaturation during exercise (1-MSTST). In three participants, oxygen saturation rate was reduced by more than 20% units during exercise. Interestingly, as shown in Figs. 4 and 5, this oxygen desaturation rate phenomenon was not associated with impaired diffusion capacity. These data suggest another etiology than persistent lung injury to be the basis of this condition. We propose that the pathological heart rate and oxygen saturation responses could be signs of autonomic dysfunction, which has been reported as one of the clinical features of PACS [44–46]. In-line with our results, Baranauskas et al. showed that patients with a history of COVID-19 disease displayed a reduced heart rate response to exercise compared to controls [47]. Correspondingly, Kurtoğlu et al. investigated heart rate variability in patients with a history of COVID-19 and found signs of

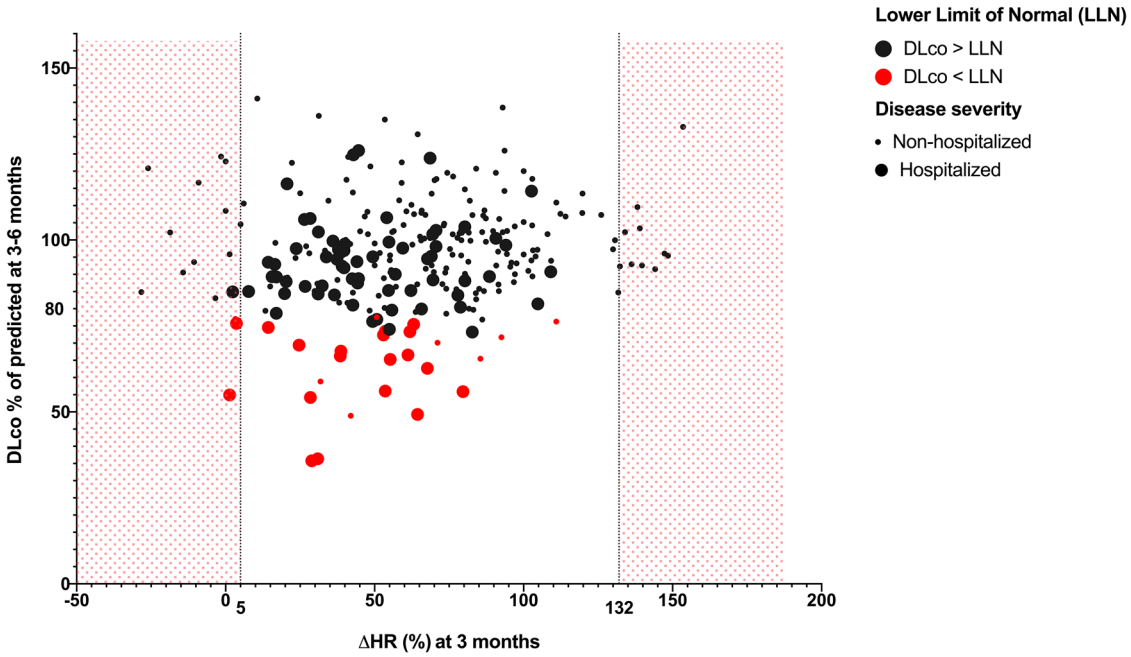

Fig. 5 *Diffusion capacity related to heart rate during exercise. The percentage of predicted values of diffusion capacity (DL_{CO}) related to delta HR after the 1-MSTST, impaired diffusion capacity, and disease severity. Impaired diffusion capacity is defined as DL_{CO} under the lower limit of normal (LLN). The red dotted areas represent the group with abnormal heart rate (HR) response during the 1-min sit-to-stand test (1-MSTST).*

autonomic cardiac dysfunction [48]. Ladlow et al. concluded that dysautonomia post COVID-19 is associated with objective functional limitations, but not with subjective symptoms or limitations [49]. This could explain why most patients with pathological oxygen desaturation and heart rate responses in the present study did not experience breathlessness. The impaired functional exercise capacity may also be impacted by cardiovascular sequelae post COVID-19, such as myocardial injury or inflammatory myocarditis [50]. The findings presented herein, especially the high occurrence of lung function impairment with a paucity of symptoms after COVID-19, warrants further investigation of the long-term respiratory effects of the disease.

Strengths

This prospective multicenter cohort study is unique in that it includes a large proportion of nonhospitalized patients. Its wide inclusion criteria contribute to a more nuanced and overall picture of the long-term consequences of COVID-19 compared to studies that only enroll patients with manifest post-COVID-19 symptoms. Employing objective lung function tests and physiological function tests strengthens the results of this study. In addition, the present study also applied the mMRC scale, which is an internationally validated scale to stratify severity of breathlessness.

Limitations

A limitation of this study was a restricted availability of spirometry for patients with mild disease during the first 3 months of the study period. Patients with symptoms may therefore have been prioritized and, thus, more common in this cohort than in a general population of COVID-19 patients. The wide time span for follow-up was chosen to include as many participants as possible but could also have affected the outcome. However, Chen et al. showed that the change rates of DL_{CO}%pred were significantly greater at 0–3 months than at 3–6 months after COVID-19 infection [30]. Another limitation is that the 1-MSTST, to our knowledge, has not previously been used to evaluate autonomic dysfunction in patients with PACS. Finally, baseline lung function data prior to COVID-19 were not available here. This was addressed by performing

multiple regression, to adjust for known confounders of impaired lung function.

Conclusion

The most important risk factor for developing long-term impairment of lung function and remaining symptoms of breathlessness is severe COVID-19 that requires hospitalization. Pathological oxygen desaturation and heart rate responses during exercise suggest that autonomic dysregulation may contribute to PACS in nonhospitalized patients, but this phenomenon was unrelated to breathlessness and reduced lung capacity. More research on lung function after COVID-19 disease is needed, especially with focus on longitudinal data.

Author contributions

Conceptualization and methodology: Anders Blomberg, Alicia Edin, Clas Ahlm, Johan Normark, Josefin Sundh, Sara Cajander. *Supervision*: Anders Blomberg, Johan Normark, Sara Cajander. *Resources*: Anders Blomberg, Alicia Edin, Clas Ahlm, Johan Normark, Mattias N.E. Forsell, Sara Cajander, Staffan Tevell. *Formal analysis*: Tove Björsell, Josefin Sundh. *Data curation*: Alicia Edin, Sara Cajander. *Writing—original draft*: Tove Björsell. *Writing—review and editing and visualization*: Anders Blomberg, Alicia Edin, Anna Lange, Clas Ahlm, Johan Normark, Josefin Sundh, Mattias N.E. Forsell, Sara Cajander, Staffan Tevell, Tove Björsell. *Funding acquisition*: Anders Blomberg, Clas Ahlm, Johan Normark, Mattias N.E. Forsell, Sara Cajander, Staffan Tevell. *Project administration*: Anna Lange, Johan Normark, Sara Cajander, Staffan Tevell.

Acknowledgments

We acknowledge our study nurses Ida-Lisa Persson and Anna Kauppi at the Department of Infectious Diseases in Umeå and Christine Degner, Anna Segerås and Lena Irvhage in Örebro, and the personnel at the Clinical Research Center at Umeå University Hospital and Örebro University Hospital for enrollment of study subjects and follow-up examinations. We also acknowledge our study nurses at the Department of Respiratory Medicine at Umeå University Hospital and Örebro University Hospital for the execution of lung function tests. Finally, we would like to acknowledge Ingela Marklund, and our study nurses Anna Joelsson, Veronica Dalevi, and Karin Törnqvist at Center for Clinical Research and Education, Region Värmland.

Conflicts of interest statement

The authors declare that they have no conflict of interests.

Funding information

Regional Research Council Mid Sweden (RFR-940474), Nyckelfonden Örebro (OLL-938628, OLL-961416), Swedish Research Council (2020-06235, 2016-06514), Swedish Heart-Lung Foundation (20200325, 20210078), Knut and Alice Wallenberg Foundation (VC-2020-0015), Umeå University and County Council of Västerbotten (#RV-938855), Region Värmland (LIVFOU-939646), ALF funding Region Örebro County, Wallenberg Center for Molecular Medicine (3455-22010).

Data availability statement

The data sets supporting the conclusions of this article and its supporting information are available from the corresponding author upon reasonable request.

References

1 World Health Organization. (2022, December 4). "WHO coronavirus disease (COVID-19) dashboard"Retrieved from: https://covid19.who.int
2 Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, et al. Organ-specific manifestations of COVID-19 infection. *Clin Exp Med.* 2020;**20**(4):493–506.
3 Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.* 2020;**8**(4):420–2.
4 Compagnone N, Palumbo D, Cremona G, Vitali G, Lorenzo RDe, Calvi MR, et al. Residual lung damage following ARDS in COVID-19 ICU survivors. *Acta Anaesthesiol Scand.* 2022;**66**(2):223–31.
5 Ye L, Yao G, Lin S, Fang Y, Chen Xi, Wang L, et al. The investigation of pulmonary function changes of COVID-19 patients in three months. *J Healthc Eng.* 2022;**2022**:9028835.
6 Steinbeis F, Thibeault C, Doellinger F, Ring RM, Mittermaier M, Ruwwe-Glösenkamp C, et al. Severity of respiratory failure and computed chest tomography in acute COVID-19 correlates with pulmonary function and respiratory symptoms after infection with SARS-CoV-2: an observational longitudinal study over 12 months. *Respir Med.* 2022;**191**:106709.
7 Noel-Savina E, Viatgé T, Faviez G, Lepage B, Mhanna LT, Pontier S, et al. Severe SARS-CoV-2 pneumonia: clinical, functional and imaging outcomes at 4 months. *Respir Med Res.* 2021;**80**:100822.
8 Guo T, Jiang F, Liu Y, Zhao Y, Li Y, Wang Y, et al. Respiratory outcomes in patients following COVID-19-related hospitalization: a meta-analysis. *Front Mol Biosci.* 2021;**8**:750558.
9 Sundh J, Ekström M, Palm A, Ljunggren M, Emilsson ÖI, Grote L, et al. COVID-19 and risk of oxygen-dependent

chronic respiratory failure: a national cohort study. *Am J Respir Crit Care Med.* 2022;**206**:506–9.
10 Moreno-Pérez O, Merino E, Leon-Ramirez J-M, Andres M, Ramos JM, Arenas-Jiménez J, et al. Post-acute COVID-19 syndrome. incidence and risk factors: a mediterranean cohort study. *J Infect.* 2021;**82**(3):378–83.
11 Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. *BMJ.* 2021;**374**:n1648.
12 Peghin M, Palese A, Venturini M, Martino MDe, Gerussi V, Graziano E, et al. Post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients. *Clin Microbiol Infect.* 2021;**27**(10):1507–13.
13 Tenforde MW, Kim SS, Lindsell CJ, Rose EB, Shapiro NI, Files DC, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep.* 2020;**69**(30):993–8.
14 Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine.* 2021;**38**:101019.
15 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;**42**(2):377–81.
16 Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software partners. *J Biomed Inform.* 2019;**95**:103208.
17 Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J.* 2017;**49**(1):1600016.
18 Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med.* 2019;**200**(8):e70–88.
19 Quanjer PH, Stanojevic S, Cole TJ, Stocks J. GLI-2012 desktop software for large data sets. Global lung function initiative.
20 Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest.* 1988;**93**(3):580–6.
21 Bohannon RW, Crouch R. 1-Minute Sit-to-Stand Test: Systematic review of procedures, performance, and clinimetric properties. *J Cardiopulm Rehabil Prev.* 2019;**39**(1):2–8.
22 Strassmann A, Steurer-Stey C, Lana KD, Zoller M, Turk AJ, Suter P, et al. Population-based reference values for the 1-min sit-to-stand test. *Int J Public Health.* 2013;**58**(6):949–53.
23 Núñez-Cortés R, Rivera-Lillo G, Arias-Campoverde M, Soto-García D, García-Palomera R, Torres-Castro R. Use of sit-to-stand test to assess the physical capacity and exertional desaturation in patients post COVID-19. *Chron Respir Dis.* 2021;**18**:1479973121999205.
24 Fu Q, Levine BD. Exercise and the autonomic nervous system. *Handb Clin Neurol.* 2013;**117**:147–60.
25 D'Anna SE, Asnaghi R, Caramori G, Appendini L, Rizzo M, Cavallaro C, et al. High-resolution computed tomography quantitation of emphysema is correlated with selected lung function values in stable COPD. *Respiration.* 2012;**83**(5):383–90.
26 Laniado-Laborín R. Smoking and chronic obstructive pulmonary disease (COPD). Parallel epidemics of the 21 century. *Int J Environ Res Public Health.* 2009;**6**(1):209–24.
27 Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med.* 2021;**9**:747–54.
28 Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-Year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet.* 2021;**398**(10302):747–58.
29 Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* 2021;**397**(10270):220–32.
30 Chen M, Liu J, Peng P, Jian W, Gao Yi, Fang L, et al. Dynamic changes of pulmonary diffusion capacity in survivors of non-critical COVID-19 during the first six months. *EClinicalMedicine.* 2022;**43**:101255.
31 Ding T, Zhang J, Wang T, Cui P, Chen Z, Jiang J, et al. Potential influence of menstrual status and sex hormones on female severe acute respiratory syndrome coronavirus 2 infection: a cross-sectional multicenter study in Wuhan, China. *Clin Infect Dis.* 2021;**72**(9):e240–8.
32 Costeira R, Lee KA, Murray B, Christiansen C, Castillo-Fernandez J, Lochlainn MNi, et al. Estrogen and COVID-19 symptoms: associations in women from the COVID symptom study. *PLoS One.* 2021;**16**(9):e0257051.
33 Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect.* 2020;**81**(2):e16–25.
34 Sund M, Fonseca-Rodríguez O, Josefsson A, Welen K, Connolly A-MF. Association between pharmaceutical modulation of oestrogen in postmenopausal women in Sweden and death due to COVID-19: a cohort study. *BMJ Open.* 2022;**12**(2):e053032.
35 Stewart S, Newson L, Briggs TA, Grammatopoulos D, Young L, Gill P. Long COVID risk—a signal to address sex hormones and women's health. *Lancet Reg Health Eur.* 2021;**11**:100242.
36 Ortona E, Buonsenso D, Carfi A, Malorni W. The Long Covid Kids study group. Long COVID: an estrogen-associated autoimmune disease? *Cell Death Discov.* 2021;**7**(1):77.
37 Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis(Lond).* 2021;**53**(10):737–54.
38 Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 symptom burden: what is long-COVID and How should we manage it? *Lung.* 2021;**199**(2):113–9.
39 Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, et al. Characterising long COVID: a living systematic review. *BMJ Glob Health.* 2021;**6**(9):e005427.
40 Motiejunaite J, Balagny P, Arnoult F, Mangin L, Bancal C, Vidal-Petiot E, et al. Hyperventilation as one of the mechanisms of persistent dyspnoea in SARS-CoV-2 survivors. *Eur Respir J.* 2021;**58**(2):2101578.
41 Taverne J, Salvator H, Leboulch C, Barizien N, Ballester M, Imhaus E, et al. High incidence of hyperventilation syndrome after COVID-19. *J Thorac Dis.* 2021;**13**(6):3918–22.
42 Gardner WN. The pathophysiology of hyperventilation disorders. *Chest.* 1996;**109**(2):516–34.

43 Ekström M, Schiöler L, Grønseth R, Johannessen A, Svanes C, Leynaert B, et al. Absolute values of lung function explain the sex difference in breathlessness in the general population. *Eur Respir J.* 2017;**49**(5):1602047.
44 Stella AB, Furlanis G, Frezza NA, Valentinotti R, Ajcevic M, Manganotti P. Autonomic dysfunction in post-COVID patients with and witfhout neurological symptoms: a prospective multidomain observational study. *J Neurol.* 2022;**269**(2):587–96.
45 Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin Med (Lond).* 2021;**21**(1):e63–7.
46 Raj SR, Arnold AC, Barboi A, Claydon VE, Limberg JK, Lucci V-EM, et al. Long-COVID postural tachycardia syndrome: an American Autonomic Society statement. *Clin Auton Res.* 2021;**31**(3):365–8.
47 Baranauskas MN, Carter SJ. Evidence for impaired chronotropic responses to and recovery from 6-minute walk test in women with post-acute COVID-19 syndrome. *Exp Physiol.* 2021;**107**:722–32.
48 Kurtoğlu E, Afsin A, Aktaş İ, Aktürk E, Kutlusoy E, Çağaşar Ö. Altered cardiac autonomic function after recovery from COVID-19. *Ann Noninvasive Electrocardiol.* 2022;**27**(1):e12916.
49 Ladlow P, O'Sullivan O, Houston A, Barker-Davies R, May S, Mills D, et al. Dysautonomia following COVID-19 is not associated with subjective limitations or symptoms but is associated with objective functional limitations. *Heart Rhythm.* 2021;**19**:613–20.
50 Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *Eur Heart J.* 2022;**43**(11):1157–72.

Correspondence: Johan Normark, Department of Clinical Microbiology, Umeå University, Umeå, Sweden.
Email: Johan.normark@umu.se
Sara Cajander, Department of Infectious Diseases, Faculty of Medicine and Health, Örebro University, Örebro, Sweden.
Email: sara.cajander@oru.se

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supporting Information

Supporting Information

Supporting Information

Supporting Information ■