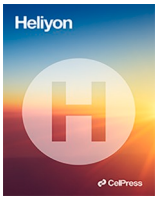
Heliyon 10 (2024) e27964

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Pulmonary function 3–6 months after acute COVID-19: A systematic review and multicentre cohort study

Merel E.B. Cornelissen [a,b,c,*], Asabi Leliveld [a,b,c], Nadia Baalbaki [a,b,c], Debbie Gach [d,e], Ivo van der Lee [f], Esther J. Nossent [a], Lizan D. Bloemsma [a,b,c], Anke H. Maitland-van der Zee [a,b,c], on behalf of the P4O2 Consortium

[a] *Department of Pulmonary Medicine, Amsterdam UMC, University of Amsterdam, 1105, AZ Amsterdam, the Netherlands*
[b] *Amsterdam Institute for Infection and Immunity, Amsterdam, the Netherlands*
[c] *Amsterdam Public Health, Amsterdam, the Netherlands*
[d] *Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, the Netherlands*
[e] *School of Nutrition and Translational Research in Metabolism, Faculty of Health, Medicine and Life Sciences, Maastricht University, the Netherlands*
[f] *Department of Pulmonology, Spaarne Hospital, the Netherlands*

ARTICLE INFO

Keywords:
Post COVID-19
Pulmonary function
Transfer factor for carbon monoxide
Long COVID

ABSTRACT

Aims: To describe pulmonary function 3–6 months following acute COVID-19, to evaluate potential predictors of decreased pulmonary function and to review literature for the effect of COVID-19 on pulmonary function.

Materials and methods: A systematic review and cohort study were conducted. Within the P4O2 COVID-19 cohort, 95 patients aged 40–65 years were recruited from outpatient post-COVID-19 clinics in five Dutch hospitals between May 2021–September 2022. At 3–6 months post COVID-19, medical records data and biological samples were collected and questionnaires were administered. In addition, pulmonary function tests (PFTs), including spirometry and transfer factor, were performed. To identify factors associated with PFTs, linear regression analyses were conducted, adjusted for covariates.

Results: In PFTs (n = 90), mean ± SD % of predicted was 89.7 ± 18.2 for forced vital capacity (FVC) and 79.8 ± 20.0 for transfer factor for carbon monoxide (DLCO). FVC was <LLN in 24.4%, and DLCO was <LLN in 40.2% of patients. Univariable analyses showed that higher age, severe acute infection, pulmonary embolism during acute infection, and male sex were associated with lower DLCO. Multivariable analysis showed that age (adjusted difference [95%CI] = -0.07 [-0.13,-0.02] per one year increase) and severe acute infection (−0.80 [-1.54,-0.05]) were independently associated with a decreased DLCO. In literature we found days on oxygen supplementation, female sex, longer length of hospital stay, obesity and higher age to be associated with lower DLCO after COVID-19.

Conclusion: A low DLCO 3–6 months following acute COVID-19 was observed more often than a low FVC, both in the P4O2 COVID-19 study and the literature review.

* Corresponding author. Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands.
E-mail address: m.e.b.cornelissen@amsterdamumc.nl (M.E.B. Cornelissen).

https://doi.org/10.1016/j.heliyon.2024.e27964
Received 29 August 2023; Received in revised form 22 February 2024; Accepted 8 March 2024
Available online 13 March 2024

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a pandemic of coronavirus disease 2019 (COVID-19), causing major impact on global health and economies. The clinical characteristics and pathogenesis of the acute phase of COVID-19 have been well-described [1]. Nonetheless, the number of COVID-19 cases globally exceeds 600 million [2] and a growing public concern exists regarding the long-term health consequences, which still remain unclear [3,4].

Observational studies indicate that over 30 percent of survivors experience long-lasting morbidity and decreased physical functioning following initial illness, substantially increasing the health and economic burden of the pandemic [5,6]. 'Long COVID' or 'post COVID-19 condition' has been defined as symptoms that occur three months from the onset of acute illness and last for at least two months [7–10]. Most common symptoms are fatigue, dyspnoea, muscle weakness, headache, loss of taste and smell, and cognitive decline [7,11]. These symptoms can impair functional ability even in previously healthy patients and those with mild initial disease [7,12].

It seems likely that the lungs are one of the organs most affected by COVID-19 because of the nature of the acute infection, which is dominantly characterized by a spectrum of mild respiratory tract symptoms to severe pneumonia causing respiratory insufficiency [13,14]. Long term pulmonary damage caused by COVID-19 is a great concern [14]. Pulmonary function tests (PFTs) are a valuable tool to assess respiratory diseases. Spirometry can identify airflow obstruction or restrictive impairment, while transfer factor for carbon monoxide (DLCO) is a test to assess the lungs' ability to transfer gas from inspired air to the bloodstream. The transfer factor is mainly used for the diagnosis of disease of the parenchyma of the lung [15].

Several studies reported pulmonary function between 1 and 6 months following acute COVID-19 [4,16–18]. In most studies, it is unknown whether these patients still have symptoms and suffer from post COVID-19 condition. A meta-analysis by Long et al. [19] showed that abnormalities in pulmonary function (including low transfer factor, reduced lung volume, or airflow obstruction) occur in 20% of patients after COVID-19 and can persist for several months. Of these abnormalities, decreased DLCO was the most common, but reduced lung volume measurements were also observed in some studies. Airflow obstruction after COVID-19, defined as forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) $<$ 70%, was relatively uncommon [19].

It remains unclear whether patient characteristics or features of the acute illness can predict the occurrence of long-term consequences of COVID-19. A few studies have found that age, sex, and severity of COVID-19 appeared to be predictors of impaired DLCO [4,16,17,20]. However, other studies did not find these associations [17,21]. Other potential predictors, such as pulmonary comorbidities, pulmonary complications during infection, and smoking need to be further evaluated. Obtaining a better understanding of predictors of long-term morbidity after COVID-19 may aid identifying patients at risk and developing better treatment strategies.

Therefore, the first aim of this study is to provide a literature overview of the current knowledge on the effect of COVID-19 on pulmonary function 3–6 months after infection. The second aim is to describe pulmonary function at 3–6 months following acute COVID-19 and to evaluate potential predictors for decreased pulmonary function in the Precision Medicine for more Oxygen (P4O2) COVID-19 cohort. The third aim is to study DLCO 12–18 months after acute COVID-19 in participants of the P4O2 COVID-19 cohort who have a DLCO $<$ lower limit of normal (LLN) at 3–6 months.

2. Materials and methods

2.1. Systematic review

The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [22] and was not registered in PROSPERO. PubMed was systematically searched from January 1, 2020 to April 21, 2023 to identify epidemiological studies examining pulmonary function 3–6 months after acute COVID-19. Search terms can be found in the Supplementary material 1. Papers in English of which full text was available and which were observational or cohort studies were included and (systematic) reviews were excluded. The use of the ATS/ERS recommendations was not used as an inclusion criterion. Furthermore, studies were excluded based on the following criteria: 1) not focused on (post) COVID-19, 2) no pulmonary function test or spirometry was performed, 3) not within the timeframe of 3–6 months after acute COVID-19, 4) performed in persons aged $<$18 years or 5) not performed in the general population. To make sure we included all available papers, we executed snowballing by searching through the references of the selected papers.

The following data were extracted from the included studies: first author, year, population characteristics (country, age, sample size), whether the study has been performed in post COVID-19 patients, follow-up time, and outcomes (lung function measurements, predictors for lung function, persistent symptoms). The Joanna Briggs Institute (JBI) checklist for Analytical Cross Sectional Studies [23] was performed to assess the risk of bias for all studies on predictors for lung function.

2.2. Cohort study

2.2.1. Study design and subjects

P4O2 COVID-19 is a multicentre, prospective, observational cohort study. The study was approved by the ethical board of the Amsterdam University Medical Centre (UMC). Details of the study have been described elsewhere [24]. In brief, patients were recruited between May 2021 and September 2022 from post-COVID-19 outpatient clinics in five hospitals in the Netherlands: the Amsterdam University Medical Centres (location AMC and VUMC), Leiden UMC, Spaarne Gasthuis in Haarlem, and VieCuri Medical Centre in Venlo. The post-COVID-19 outpatient clinic was part of standard follow-up care after hospitalization for COVID-19.

COVID-19 patients were invited at 3–6 months after hospital discharge if they suffered from any persisting symptoms. Additionally, patients who were not hospitalized but suffered from persisting symptoms were referred to the outpatient clinic by their general practitioner at 3–6 months after the date of positive polymerase chain reaction (PCR) or serology test for SARS-CoV-2.

The inclusion criteria for the P4O2 COVID-19 study were age 40–65 years, proven ex-COVID-19 (either a positive PCR test, a serology test, or a CORADS score $\geq$4), the ability to provide informed consent, having access to the internet and understanding the Dutch language. All participants gave their written informed consent. In total, 95 patients were included in the P4O2 COVID-19 study. In 90 of these patients, pulmonary function tests were performed. Therefore, the number of patients included in this study was 90.

2.2.2. Study visits

At the post-COVID-19 outpatient clinic, pulmonary function tests were performed. This assessment comprised spirometry (including FEV_1 and FVC), transfer factor (including DLCO and carbon monoxide transfer coefficient (KCO)) corrected for serum haemoglobin, and alveolar volume (V_A). A study visit was planned in parallel to the outpatient clinic visit. During this study visit, general characteristics such as demographics, educational level, smoking, medical history, medication use, self-reported symptoms, and health related quality of life were assessed using questionnaires. Clinical data about the acute phase of COVID-19 were collected from electronic medical records. 9–12 months later, a second study visit was executed where the same questionnaires were assessed. Patients with a FVC and/or FEV1 <90% predicted or DLCO <70% predicted at visit 1, also performed a PFT at visit 2.

2.2.3. Outcomes

The outcome of our analyses was pulmonary function 3–6 months after hospital discharge or, if not hospitalized, after positive PCR or serology test. Pulmonary function outcomes were expressed as a percentage of predicted values and as z-scores [25–27]. Z-scores are independent of age, height, sex and ethnicity (GLI 2012) [25,28]. Pulmonary function is impaired when FEV_1, FVC, FEV_1/FVC, DLCO, or KCO are below the LLN, which means having a z-score < -1.645 [8,25].

2.2.4. Predictors

Potential predictors of pulmonary function were selected based on literature and clinical expertise within our group. Potential predictors included in this study are pulmonary comorbidities (such as chronic obstructive pulmonary disease (COPD), and (fibrotic) interstitial lung disease (fILD)), and venous thromboembolism (VTE), pulmonary embolism during acute COVID-19, age, sex, smoking ((ex)-smoker vs. never smoker), body mass index (BMI) [29–31], COVID-19 severity (defined according to the World Health Organization (WHO) Clinical Progression Scale, based on oxygen supplementation during acute infection [32]), hospital duration (in days), and time since positive PCR (in days).

2.2.5. Statistical analysis

To identify demographic and clinical risk factors that were associated with decreased pulmonary function 3–6 months after COVID-19, regression analyses were conducted with z-scores of DLCO and FEV_1/FVC, and pulmonary restriction (defined as having an FVC < LLN and FEV_1/FVC > LLN) as outcomes. Covariates were selected via the construction of a directed acyclic graph (DAG) (Fig. S1) [33].

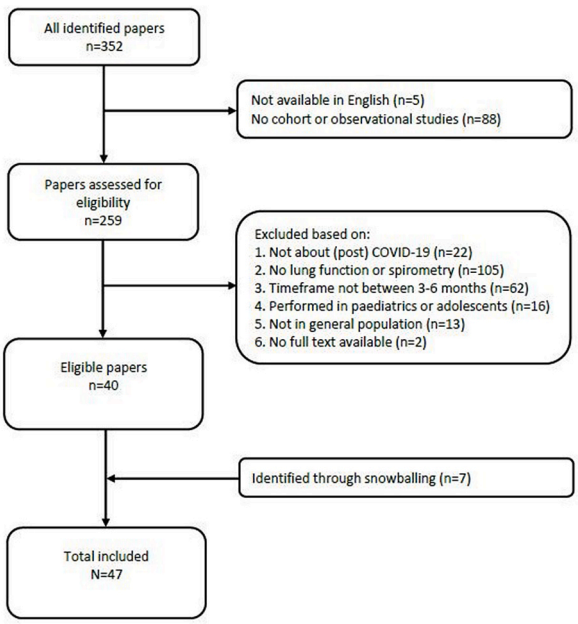


Fig. 1. Flow chart of the number of studies screened and included in the review.

First, univariable linear regression analyses between the potential predictors and pulmonary outcomes were conducted, adjusted for time since positive PCR for SARS-CoV-2. For the outcome pulmonary restriction (yes vs. no), logistic regression analyses were performed. Before conducting the regression analyses, assumptions were checked [34].

Variables that had a significance of $p < 0.20$ in univariable regression analyses were included in a multivariable model. BMI and time since positive PCR for SARS-CoV-2 were included in the model as confounders. We included a product interaction term between severity of acute infection and pulmonary embolism during acute infection in the adjusted model to evaluate effect modification. Finally, a sensitivity analysis was performed by excluding cases with pulmonary comorbidities and VTE, since these patients are likely to have a lower lung function (prior to COVID-19).

To check whether PFT improved after 9–12 months, lung function of participants that had a DLCO < LLN at visit 1 were compared using a paired *t*-test with their lung function at visit 2.

Analyses were performed with R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Systematic review

With the literature search, a total of 352 papers were found. Fourty papers fulfilled our inclusion criteria. By snowballing we found an additional seven papers, therefore 47 studies were included in this review (Fig. 1). Of the 19 studies which were scored with the JBI checklist (Table S2), none of the studies scored all eight points and seven studies scored ≤4. The other 12 studies scored between the 5 and 7 points. The studies that had a low score did not identify confounding factors and did not clearly defined their inclusion criteria. Furthermore, all studies clearly described the study subjects and setting and almost all of them described the statistical analysis they used.

Results of all included studies can be found in Table S1. All studies included a population with a mean or median age between 47

Table 1
Characteristics of the population (n = 90).

	n (%), mean ± SD or median (25th-75th percentiles)
Age in years	53.9 ± 6.0
Sex, male	46 (51.1)
Ethnicity	
Caucasian	64 (71.1)
African	6 (6.7)
Asian	3 (3.3)
Latin-American	2 (2.2)
Other/unknown	15 (16.7)
BMI in kg/m^2	30.4 ± 5.4
Smoking status	
Current	3 (3.3)
Ex-smoker	48 (53.3)
Never	39 (43.3)
Hospitalized	81 (90.0)
Hospital duration in days	8.0 (4.0–16.0)
Admitted to ICU	26 (28.9)
Oxygen supplementation	
None	13 (14.4)
Non-rebreathing mask	15 (16.3)
High flow nasal cannula	39 (42.4)
Non-invasive ventilation	5 (5.4)
Invasive ventilation	18 (19.6)
Acute COVID-19 Severity[a]	
Mild	9 (10.0)
Moderate	58 (64.4)
Severe	23 (25.6)
Pulmonary embolism during COVID-19	15/87 (17.2)
Pulmonary comorbidities	19/89 (21.3)
Asthma	15/89 (16.9)
COPD	4/89 (4.5)
fILD	2/89 (2.2)
VTE	9 (10.1)
Dominant virus type[b]	
Beta	25 (27.8)
Delta	38 (42.2)
Gamma	14 (15.6)
Omicron	13 (14.4)

[a] According to the WHO Clinical Progression Scale.
[b] Virus type which was dominant in the Netherlands at the date of positive PCR or serology test.

and 66 years and most studies had an equal distribution of males and females.The majority of the studies were conducted in Europe (n = 26) [3,4,35–58],49,51,56,60,62,65,66,67,69,70,74,76,77,79,80,81,83,84], six were conducted in North America [59–64], four in South America [65–68] and eleven in Asia [16,17,69–77]. The population of the studies varied between 17 and 1733 with a mean of 177 participants. Twenty-two studies included only hospitalized patients. Although most studies did report the percentage of participants having persistent symptoms, only one study included specifically long COVID patients [35]. Most studies found a FEV_1 and FVC <80% predicted in approximately 10–20% of the population and a DLCO <80% predicted in approximately 40–50% (Fig. S2).

Seventeen studies also examined factors associated with decreased lung function 3–6 months after acute COVID-19. Factors that were found to be associated with impaired DLCO were: days on oxygen supplementation (coefficient [95% confidence interval (CI)]: −0.44 [−0.77,−0.11]) [59], female sex (odds ratio (OR) [95%CI]: 6.00 [1.26,28.55] [69] and 6.22 [2.77,15.04] [36]), longer length of hospital stay ($r = -0.518$; $p < 0.0001$ [37] and $r = -0.378$; $p = 0.002$ [38]), obesity ($r = -0.25$; $p = 0.042$ [38]), and higher age ($r = -0.41$; $p < 0.01$ [60] and OR [95%CI]: 1.04 [1.00,1.07] [36]).

3.2. Cohort study

3.2.1. General demographics

The mean ± SD (standard deviation) age of our study participants was 53.9 ± 6.0 years, 46 (51.1%) patients were male and their mean ± SD BMI was 30.4 ± 5.4 kg/m^2 (Table 1). Nineteen patients (21.3%) had a pulmonary comorbidity, of which 14 had asthma, two had COPD, one had fILD, one had COPD and asthma, one had COPD and fILD and nine (10.1%) patients had a VTE before infection. The majority of patients was hospitalized during the acute infection (90.0%), with a median (25th-75th percentiles) duration of hospitalization of 8.0 (4.0–16.0) days and 26 (28.9%) of the patients were admitted to the ICU. Nine (10.2%) patients had a mild acute disease, 58 (64.4%) had a moderate disease, and 23 (25.6%) had a severe disease (Table 1).

3.2.2. Pulmonary function 3–6 months after COVID-19

The mean ± SD FEV_1 % predicted was 91.5 ± 17.1% and 13 (14.4%) patients had a FEV_1 z-score < LLN 3–6 months after acute COVID-19 (Table 2). The mean ± SD FVC % predicted was 89.8 ± 18.1% and 22 (24.4%) patients had a FVC z-score < LLN. A total of 22 (24.4%) patients had a restrictive PFT, defined as FVC z-score < LLN and FEV_1/FVC z-score > LLN. Mean FEV_1/FVC ratio was 80.1 ± 8.0% and seven (7.8%) patients had an obstruction in their PFT, defined as FEV_1/FVC z-score < LLN.

Transfer factor was measured in 89 patients. The mean ± SD DLCO % predicted was 79.9 ± 20.0% and 35 (40.2%) patients had a DLCO z-score < LLN. The mean ± SD KCO % predicted (n = 88) was 95.7 ± 16.6% and 10 (11.5%) patients had a KCO z-score < LLN.

3.2.3. Regression analyses

Differences are found between DLCO < LLN and DLCO ≥ LLN for age, total hospital duration, severity of acute COVID-19 and pulmonary embolism (Table 3). In the univariable regression analysis, associations were found between decreased DLCO and age (adjusted difference [95% CI]: −0.08 [−0.14,-0.03] per year increase), severe acute COVID-19 (−1.05 [−1.80,-0.30]), pulmonary embolism during acute COVID-19 (−0.94 [−1.84,-0.04]), and male sex (−0.57 [−1.24,0.09]) (Table 4).

Table 2
Pulmonary function 3–6 months after SARS-CoV-2 infection (n = 90).

	n (%) or mean ± SD
FEV_1	
% predicted	91.5 ± 17.1
z-score < LLN	13 (14.4)
FVC	
% predicted	89.8 ± 18.1
z-score < LLN	22 (24.4)
Restriction (FVC < LLN + FEV_1/FVC > LLN)	22 (24.4)
FEV_1/FVC	
ratio	80.1 ± 8.0
z-score < LLN (obstruction)	7 (7.8)
DLCO, n = 89	
% predicted	79.9 ± 20.0
z-score < LLN	35/87 (40.2)
KCO, n = 88	
% predicted	95.7 ± 16.6
z-score < LLN	10/87 (11.5)
V_A, n = 88	
% predicted	83.1 ± 17.1
z-score < LLN	37/87 (42.5)

LLN = z-score −1.645. Abbreviations: DLCO = diffusing capacity for carbon monoxide, FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, KCO = carbon monoxide transfer coefficient, LLN = lower limit of normal, SD = standard deviation, V_A = alveolar volume.

In the multivariable regression analysis, age (−0.07 [−0.13,-0.02] per year increase) and severe acute COVID-19 (−0.80 [−1.54,-0.05]) were independently associated with decreased DLCO, while pulmonary embolism and male sex were not (Table 5). Furthermore, we observed an interaction of pulmonary embolism with severe acute COVID-19 in relation to the DLCO z-score (interaction term: $\beta = -1.52$, $p = 0.09$), meaning if a patient had both a severe acute SARS-CoV-2 infection and pulmonary embolism, the DLCO z-score was even lower (Table S3). A sensitivity analysis was performed by excluding cases with pulmonary comorbidities and VTE ($n = 26$). Of the patients without pulmonary comorbidities and VTE, 36.1% had a DLCO z-score < LLN. There was no difference found between the univariable analyses with and without these cases. (Table S4).

We observed no associations between decreased FEV_1/FVC and the predictors (Table S5). When conducting a univariable logistic regression analysis for the outcome restrictive PFT, there was a significant association found with pulmonary embolism (OR [95%CI] = 7.15 [2.03,27.59]) (Table S6).

3.2.4. DLCO 12–18 months after COVID-19

Eighteen participants had a DLCO < LLN at visit 1 and had performed PFT at visit 2. Overall, patients' DLCO z-scores did improve over time (Fig. 2) from mean ± SD -3.1 ± 1.5 at visit 1 to −2.2 ± 1.4 at visit 2 ($p = 0.09$). Of these 18 patients, nine patients still have a DLCO z-score < LLN.

4. Discussion

We reviewed literature for the effect of COVID-19 on pulmonary function tests. Most commonly found in literature was a DLCO <80% predicted in approximately 40–50% of the participants, measured between 3 and 6 months after acute COVID-19. Obstructive airway disease was only found in a small proportion of the patients. These results are in line with our findings within the P4O2 COVID-19 cohort, where we assessed pulmonary function at 3–6 months following acute COVID-19. The mean FEV_1 and FVC were slightly decreased compared to the predicted scores, however the ratio FEV_1/FVC was <LLN in only seven participants. DLCO was impaired in almost half of the patients in the cohort. However, after 9–12 months there is some improvement found within the patients with impaired DLCO.

In our literature review we found DLCO <80% predicted in almost half of the participants. Previously published systematic reviews and meta-analysis reported impaired diffusion capacity in 30–50% of the participants [19,78–81], which is in line with the results we found. The predictors for impaired DLCO that we found with our literature review were older age, female sex, length of hospital stay, COVID-19 severity, BMI and d-dimer. Zhi et al. [79] reported female sex, older age, higher d-dimer and urea nitrogen to be risk factors for impaired DLCO.

Although DLCO was decreased in this cohort, KCO was relatively normal compared to predicted values. Alveolar volume was decreased in a large proportion of patients. A low DLCO with low V_A and relatively normal KCO compared to predicted values leads to interpretation consistent with loss of alveolar capillary structure [25]. We did not find an association between BMI and decreased DLCO through univariable regression analysis and other studies also did not find this association [37]. Known from literature is that obesity does not lead to a lower lung capacity [82].

This study showed that age and severe acute COVID-19 were independently associated with a decrease in DLCO at 3–6 months following COVID-19. Other studies [16,17,39,40] confirm the association of severe acute COVID-19 and decreased DLCO at follow up, although Fortini et al. [41] and Diaz-Fuentes [61] did not find an association between severe acute COVID-19 and decreased DLCO. This might be explained by the patient selection since no patients who were admitted to the ICU were included in the cohort of Fortini et al. and 20.7% of the included patients were asymptomatic at 3 months post COVID-19 in the cohort of Diaz-Fuentes et al.

Table 3
Characteristics of participants with DLCO ≥ LLN and DLCO < LLN.

	DLCO ≥ LLN (n = 52)	DLCO < LLN (n = 35)	P value
Age (years), mean ± SD	52.5 ± 5.7	55.9 ± 5.4	**0.006**
Sex, male, n (%)	23.0 (44.2)	20 (57.1)	0.238
BMI (kg/m^2), mean ± SD	31.1 ± 5.1	29.9 ± 5.6	0.305
Smoking status, n (%)			0.696[a]
Current	1 (1.9)	2 (5.7)	
Ex-smoker	28 (53.8)	19 (54.3)	
Never	23 (44.2)	14 (40.0)	
Pulmonary comorbidities, n (%)	9/51 (17.6)	10 (28.6)	0.212
Total hospital duration in days, median (25th-75th percentiles)	7.0 (3.0–9.5) (n = 51)	16.0 (7.0–52.0)	**<0.001**
Severity of acute COVID-19, n (%)			**0.006**[b]
Mild	9 (17.3)	0 (0.0)	
Moderate	34 (65.4)	21 (60.0)	
Severe	9 (17.3)	14 (40.0)	
Pulmonary embolism during COVID-19, n (%)	4/49 (8.2)	11 (31.4)	**0.008**

LLN = z-score −1.645. Variables with $p < 0.05$ are marked bold. Abbreviations: BMI = body mass index, DLCO = diffusion capacity for carbon monoxide, LLN = lower limit of normal, SD = standard deviation.

[a] Current + ex-smokers compared to never smokers.

[b] Severe cases compared to mild + moderate cases.

Table 4
Univariable associations between potential predictors and DLCO z-score 3–6 months after SARS-CoV-2 infection.

Predictors	β (95%CI)	
	Unadjusted	Adjusted[a]
Age (years)	**−0.08 (-0.14, -0.03)**	**−0.08 (-0.14, -0.03)**
Male sex	**−0.58 (-1.24, 0.09)**	**−0.57 (-1.24, 0.09)**
BMI (kg/m^2)	0.02 (−0.04, 0.09)	0.02 (−0.04, 0.09)
Smoking (current + ex)[b]	−0.01 (−0.70, 0.67)	−0.01 (−0.70, 0.68)
Pulmonary comorbidities[b]	−0.46 (−1.27, 0.35)	−0.51 (−1.33, 0.32)
Severe acute COVID-19[b]	**−1.00 (-1.74, -0.27)**	**−1.05 (-1.80, -0.30)**
Pulmonary embolism during COVID-19[b]	**−0.94 (-1.81, -0.06)**	**−0.94 (-1.84, -0.04)**

For this analysis, univariable linear regression was performed. Predictors with $p < 0.20$ are marked bold. Abbreviations: BMI = body mass index, CI = confidence interval, DLCO = diffusion capacity for carbon monoxide, PCR = polymerase chain reaction.
[a] Adjusted for time since positive PCR test (in days).
[b] Additionally adjusted for BMI.

Table 5
Multivariable association between potential predictors and DLCO z-score 3–6 months after SARS-CoV-2 infection.

Predictors	β (95%CI)[a]
Age (years)	**−0.07 (-0.13, -0.02)**
Male sex	−0.27 (−0.98, 0.44)
Severe acute COVID-19	**−0.80 (-1.54, -0.05)**
Pulmonary embolism during COVID-19	−0.60 (−1.47, 0.28)

For this analysis, multivariable linear regression was performed. Predictors with $p < 0.05$ are marked bold. Abbreviations: BMI = body mass index, CI = confidence interval, DLCO = diffusion capacity for carbon monoxide, PCR = polymerase chain reaction.
[a] Adjusted for time since positive PCR test (in days) and BMI.

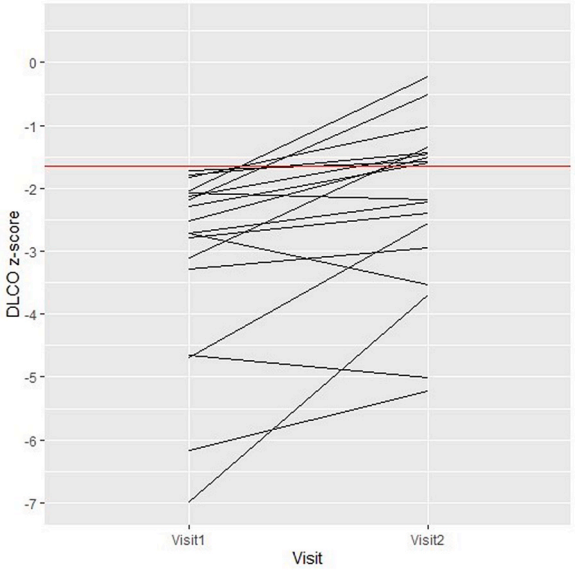


Fig. 2. Plot of visit 1 and visit 2 of patients (n = 18) who had a DLCO < LLN at visit 1. The red line represents the LLN of z = −1.645. Abbreviations: DLCO = diffusion capacity of carbon monoxide, LLN = lower limit of normal. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

We did not find an independent association between DLCO and sex, however, many studies did find this association [69,36,42,65]. The discrepancy between the findings from our study and findings from previous studies could be due to differences in study population. Salem et al. [69] found an association between decreased DLCO and female sex, but they excluded severe cases. Safont et al. [42] found an association between decreased DLCO and male sex, but they only studied hospitalized cases with pneumonia. Our cohort

consists of both hospitalized and non-hospitalized cases and consists of patients with different grades of severity of the acute infection.

The results of this study add to the understanding of pulmonary function test changes that exist 3–6 months after acute COVID-19. Underlying mechanisms, such as immunological [83], cardiac [84] and metabolic alterations [85] following COVID-19 could also explain decreased physical functioning. Because of this, it is necessary to further improve our understanding of persisting alterations following COVID-19 in a multidisciplinary way. Further research is warranted to establish the role of decreased pulmonary function in persisting morbidity following SARS-CoV-2 infection and to identify other underlying mechanisms that may be treatable.

When looking at 12–18 months after SARS-CoV-2 infection, patients with impaired DLCO in our cohort show some improvement. This is in line with existing literature investigating DLCO one year after SARS-CoV-2 infection. Tarraso et al. [36] reported that 53.8% of patients had diffusion impairment (<80% of predicted DLCO) at 60 days and one year later this percentage decreased to 39.8%. Steinbeis et al. [43] observed improvement in DLCO up to one year among patients with impaired pulmonary function at six weeks (defined as TLC, FVC and/or DLCO < LLN). Notably, literature with a two-year follow-up indicated an initial recovery from six months to one year after infection, with no further improvement beyond one year [86]. However, due to the limited studies assessing pulmonary function at least one year after SARS-CoV-2 infection, more research is needed to determine the long lasting consequences of SARS-CoV-2 infection on pulmonary function in post COVID-19 patients.

4.1. Strengths and limitations

This study has several limitations. First, because of the studies prospective nature, lung function of the participants was not measured prior to COVID-19. There was also no control group available to use in this study. Therefore, it cannot be ruled out that alterations in pulmonary function already existed before SARS-CoV-2 infection or if they were due to other factors. However, we did conduct a sensitivity analysis where we excluded cases which already had a pulmonary comorbidity or VTE and there was no difference in predictors compared to the whole cohort. The findings in the literature review on pulmonary function are in the same direction as ours, which strengthens our findings. Furthermore, two studies included in the review did include a control group of healthy individuals (one study included non-smokers with no history of pulmonary disease and the other study included age and gender-matched healthy individuals without any acute diseases) and found that DLCO, FVC and FEV1 at 3–6 months after infection were significantly lower in post COVID-19 patients compared to the controls [69,70]. Second, a selection bias is presumable present because patients with a high burden of persisting symptoms were more likely to participate in this study than patients who recovered more quickly. Since there might have been selected patients with a high burden of disease in the cohort, alterations in pulmonary function following acute COVID-19 might be more prevalent than in other populations. Another limitation is that we were not able to measure the variant of SARS-CoV-2 infection our patients had. The variant could affect the severity of the acute infection and therewith affect the transfer factor. However, we do know which variant was most dominant per time period, but the numbers per variant were too small to use in the regression analysis.

This study also has multiple strengths. First, we made use of the lower limit of normal values and z-scores. It has recently been advised in the European Respiratory Journal to make use of these values, as the lower limit of normal can better predict alterations in transfer factor than predicted values [25]. Another strength is that we made use of multivariable regression analysis to assess potential predictors for decreased pulmonary function test. This enabled us to evaluate individual risk factors for pulmonary dysfunction, taking into account that several risk factors were strongly related to one another and could act as confounders. Finally, in contrast to many other studies on long COVID in which all post COVID-19 patients were included, the current study focuses on patients that experience persisting symptoms, which can lead to valuable new insights on long COVID patients specifically.

5. Conclusions

In the P4O2 COVID-19 cohort, diffusion capacity for carbon monoxide was decreased at 3–6 months following acute COVID-19. However, half of the patients show an improvement in their diffusion capacity over time. Severe acute COVID-19 and higher age were independently associated with a decreased DLCO at 3–6 months following acute COVID-19. This is in line with the results of the studies included in the review.

Funding

Partners in the Precision Medicine for more Oxygen (P4O2) consortium are the Amsterdam UMC, Leiden University Medical Center, Maastricht UMC+, Maastricht University, UMC Groningen, UMC Utrecht, Utrecht University, TNO, Aparito, Boehringer Ingelheim, Breathomix, Clear, Danone Nutricia Research, Fluidda, MonitAir, Ncardia, Ortec Logiqcare, Philips, Proefdiervrij, Quantib-U, RespiQ, Roche, Smartfish, SODAQ, Thirona, TopMD, Lung Alliance Netherlands (LAN) and the Lung Foundation Netherlands (Longfonds). The consortium is additionally funded by the PPP Allowance made available by Health~Holland, Netherlands, Top Sector Life Sciences & Health, Netherlands (LSHM20104; LSHM20068), to stimulate public-private partnerships and by Novartis, Netherlands.

Ethical statement

This study was approved by the ethical board of the Amsterdam University Medical Center (UMC), reference number NL74701.018.20.

Data availability statement

The data presented in this study are available on request to the corresponding author. The data are not publicly available due to agreements made by the consortium, that only allow access by each consortium partner to specific data that answers their pre-specified research questions. A request for access to data by organizations outside of the consortium can be submitted to the P4O2 Data Committee (via p4o2@amsterdamumc.nl) and the research will need to be performed in collaboration with one of the P4O2 consortium partners.

CRediT authorship contribution statement

Merel E.B. Cornelissen: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Asabi Leliveld:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Nadia Baalbaki:** Writing – review & editing, Investigation. **Debbie Gach:** Writing – review & editing. **Ivo van der Lee:** Writing – review & editing. **Esther J. Nossent:** Writing – review & editing. **Lizan D. Bloemsma:** Writing – review & editing, Supervision. **Anke H. Maitland-van der Zee:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.E.B. Cornelissen reports financial support was provided by Health Holland. N. Baalbaki reports financial support was provided by Health Holland. D. Gach reports financial support was provided by Health Holland. E.J. Nossent reports financial support was provided by Health Holland. L.D. Bloemsma reports financial support was provided by Health Holland. A.H. Maitland-van der Zee reports financial support was provided by Health Holland. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Acknowledgements are given to all the patients and healthcare professionals, specifically the pulmonary function analysts, who contributed to the P4O2 COVID-19 study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27964.

References

[1] W.J. Wiersinga, A. Rhodes, A.C. Cheng, S.J. Peacock, H.C. Prescott, Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review, JAMA 324 (8) (2020) 782–793.
[2] World Health Organization, WHO Coronavirus (COVID-19) Dashboard, 2022. https://covid19.who.int/.
[3] T. Sonnweber, S. Sahanic, A. Pizzini, A. Luger, C. Schwabl, et al., Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial, Eur. Respir. J. 57 (4) (2021).
[4] B. van den Borst, J.B. Peters, M. Brink, Y. Schoon, C.P. Bleeker-Rovers, et al., Comprehensive health assessment 3 Months after recovery from acute coronavirus disease 2019 (COVID-19), Clin. Infect. Dis. 73 (5) (2021) e1089–e1098.
[5] D. Groff, A. Sun, A.E. Ssentongo, D.M. Ba, N. Parsons, et al., Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review, JAMA Netw. Open 4 (10) (2021) e2128568.
[6] M.C. Nurchis, D. Pascucci, M. Sapienza, L. Villani, F. D'Ambrosio, et al., Impact of the burden of COVID-19 in Italy: results of disability-adjusted life years (DALYs) and productivity loss, Int. J. Environ. Res. Publ. Health 17 (12) (2020).
[7] T. Nasserie, M. Hittle, S.N. Goodman, Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review, JAMA Netw. Open 4 (5) (2021) e2111417.
[8] A.M. Baig, Chronic COVID syndrome: need for an appropriate medical terminology for long-COVID and COVID long-haulers, J. Med. Virol. 93 (5) (2021) 2555–2556.
[9] V. Soriano, P. Ganado-Pinilla, M. Sanchez-Santos, P. Barreiro, Unveiling long COVID-19 disease, AIDS Rev. 22 (4) (2020) 227–228.
[10] World Health Organization, A Clinical Case Definition of Post COVID-19 Condition by a Delphi Consensus, 6 October 2021, World Health Organization, 2021.
[11] B. Raman, M.P. Cassar, E.M. Tunnicliffe, N. Filippini, L. Griffanti, et al., Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge, EClinicalMedicine 31 (2021) 100683.
[12] K.B. Jacobson, M. Rao, H. Bonilla, A. Subramanian, I. Hack, et al., Patients with uncomplicated coronavirus disease 2019 (COVID-19) have long-term persistent symptoms and functional impairment similar to patients with severe COVID-19: a cautionary tale during a global pandemic, Clin. Infect. Dis. 73 (3) (2021) e826–e829.
[13] Coronavirus (COVID-19): evidence relevant to acute and critical care - Cochrane special collections https://www.cochranelibrary.com/collections/doi/SC000039/full: Cochrane library; [updated 6-July-2022.
[14] C. Del Rio, L.F. Collins, P. Malani, Long-term health consequences of COVID-19, JAMA 324 (17) (2020) 1723–1724.
[15] J.E. Cotes, D.J. Chinn, P.H. Quanjer, J. Roca, J.C. Yernault, Standardization of the measurement of transfer factor (diffusing capacity). Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European respiratory society, Eur. Respir. J. Suppl. 16 (1993) 41–52.

[16] C. Huang, L. Huang, Y. Wang, X. Li, L. Ren, et al., 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study, Lancet 397 (10270) (2021) 220–232.
[17] W. Qin, S. Chen, Y. Zhang, F. Dong, Z. Zhang, et al., Diffusion capacity abnormalities for carbon monoxide in patients with COVID-19 at 3-month follow-up, Eur. Respir. J. 58 (1) (2021).
[18] K. Liu, W. Zhang, Y. Yang, J. Zhang, Y. Li, Y. Chen, Respiratory rehabilitation in elderly patients with COVID-19: a randomized controlled study, Compl. Ther. Clin. Pract. 39 (2020) 101166.
[19] Q. Long, J. Li, X. Hu, Y. Bai, Y. Zheng, Z. Gao, Follow-ups on persistent symptoms and pulmonary function among post-acute COVID-19 patients: a systematic review and meta-analysis, Front. Med. 8 (2021) 702635.
[20] M.P. Cassar, E.M. Tunnicliffe, N. Petousi, A.J. Lewandowski, C. Xie, et al., Symptom persistence despite improvement in cardiopulmonary health - insights from longitudinal CMR, CPET and lung function testing post-COVID-19, EClinicalMedicine 41 (2021) 101159.
[21] N. Mumoli, A. Bonaventura, A. Colombo, A. Vecchie, M. Cei, et al., Lung function and symptoms in post-COVID-19 patients: a single-center experience, Mayo Clin Proc Innov Qual Outcomes 5 (5) (2021) 907–915.
[22] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (2021) n71.
[23] Joanna Briggs Institute, Checklist for Analytical Cross Sectional Studies, 2017 [Available from: https://joannabriggs.org/ebp/critical_appraisal_tools.
[24] N. Baalbaki, J. Blankestijn, M. Abdel-Aziz, J.D. Backer, S. Bazdar, et al., First study results of the P4O2 long COVID cohort, ERJ Open Research 9 (suppl 10) (2023) 68.
[25] S. Stanojevic, D.A. Kaminsky, M.R. Miller, B. Thompson, A. Aliverti, et al., ERS/ATS technical standard on interpretive strategies for routine lung function tests, Eur. Respir. J. 60 (1) (2022).
[26] R.J. Knudson, M.D. Lebowitz, Maximal mid-expiratory flow (FEF25-75%): normal limits and assessment of sensitivity, Am. Rev. Respir. Dis. 117 (3) (1978) 609–610.
[27] B.L. Graham, V. Brusasco, F. Burgos, B.G. Cooper, R. Jensen, et al., ERS/ATS standards for single-breath carbon monoxide uptake in the lung, Eur. Respir. J. 49 (1) (2017), 2017.
[28] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, et al., Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur. Respir. J. 40 (6) (2012) 1324–1343.
[29] P. Modi, M. Cascella, Diffusing Capacity of the Lungs for Carbon Monoxide, StatPearls. Treasure Island (FL, 2022.
[30] E.J. Heckman, G.T. O'Connor, Pulmonary function tests for diagnosing lung disease, JAMA 313 (22) (2015) 2278–2279.
[31] R.H. Sansores, P.D. Pare, R.T. Abboud, Acute effect of cigarette smoking on the carbon monoxide diffusing capacity of the lung, Am. Rev. Respir. Dis. 146 (4) (1992) 951–958.
[32] WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection, A minimal common outcome measure set for COVID-19 clinical research, Lancet Infect. Dis. 20 (8) (2020) e192–e197.
[33] J. Textor, B. Van der Zander, M.S. Gilthorpe, M. Liskiewicz, G.T. Ellison, Robust causal inference using directed acyclic graphs: the R package 'dagitty', Int. J. Epidemiol. 45 (6) (2016) 1887–1894.
[34] E.C. Alexopoulos, Introduction to multivariate regression analysis, Hippokratia 14 (Suppl 1) (2010) 23–28.
[35] J. Kersten, A. Wolf, L. Hoyo, E. Hull, M. Tadic, et al., Symptom burden correlates to impairment of diffusion capacity and exercise intolerance in long COVID patients, Sci. Rep. 12 (1) (2022) 8801.
[36] J. Tarraso, B. Safont, J.A. Carbonell-Asins, E. Fernandez-Fabrellas, J.N. Sancho-Chust, et al., Lung function and radiological findings 1 year after COVID-19: a prospective follow-up, Respir. Res. 23 (1) (2022) 242.
[37] R.C. Robey, K. Kemp, P. Hayton, D. Mudawi, R. Wang, et al., Pulmonary sequelae at 4 Months after COVID-19 infection: a single-centre experience of a COVID follow-up service, Adv. Ther. 38 (8) (2021) 4505–4519.
[38] D. Munker, T. Veit, J. Barton, P. Mertsch, C. Mummler, et al., Pulmonary function impairment of asymptomatic and persistently symptomatic patients 4 months after COVID-19 according to disease severity, Infection 50 (1) (2022) 157–168.
[39] T. Bjorsell, J. Sundh, A. Lange, C. Ahlm, M.N.E. Forsell, et al., Risk factors for impaired respiratory function post COVID-19: a prospective cohort study of nonhospitalized and hospitalized patients, J. Intern. Med. 293 (5) (2023) 600–614.
[40] S.A. Guler, L. Ebner, C. Aubry-Beigelman, P.O. Bridevaux, M. Brutsche, et al., Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study, Eur. Respir. J. 57 (4) (2021).
[41] A. Fortini, A. Torrigiani, S. Sbaragli, A. Lo Forte, A. Crociani, et al., COVID-19: persistence of symptoms and lung alterations after 3-6 months from hospital discharge, Infection 49 (5) (2021) 1007–1015.
[42] B. Safont, J. Tarraso, E. Rodriguez-Borja, E. Fernandez-Fabrellas, J.N. Sancho-Chust, et al., Lung function, radiological findings and biomarkers of fibrogenesis in a cohort of COVID-19 patients six months after hospital discharge, Arch. Bronconeumol. 58 (2) (2022) 142–149.
[43] F. Steinbeis, C. Thibeault, F. Doellinger, R.M. Ring, M. Mittermaier, 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. 191 (2022) 106709.
[44] M. Vejen, E.F. Hansen, B.N.I. Al-Jarah, C. Jensen, P. Thaning, et al., Hospital admission for COVID-19 pneumonitis - long-term impairment in quality of life and lung function, Eur Clin Respir J 9 (1) (2022) 2024735.
[45] L. Spicuzza, R. Campisi, S. Alia, S. Prestifilippo, M.L. Giuffrida, et al., Female sex affects respiratory function and exercise ability in patients recovered from COVID-19 pneumonia, J Womens Health (Larchmt) 32 (1) (2023) 18–23.
[46] D.T. Arnold, F.W. Hamilton, A. Milne, A.J. Morley, J. Viner, et al., Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort, Thorax 76 (4) (2021) 399–401.
[47] D. Stylemans, J. Smet, S. Hanon, D. Schuermans, B. Ilsen, et al., Evolution of lung function and chest CT 6 months after COVID-19 pneumonia: real-life data from a Belgian University Hospital, Respir. Med. 182 (2021) 106421.
[48] J. Frija-Masson, M.P. Debray, S. Boussouar, A. Khalil, C. Bancal, et al., Residual ground glass opacities three months after Covid-19 pneumonia correlate to alteration of respiratory function: the post Covid M3 study, Respir. Med. 184 (2021) 106435.
[49] G. Darcis, A. Bouquegneau, N. Maes, M. Thys, M. Henket, et al., Long-term clinical follow-up of patients suffering from moderate-to-severe COVID-19 infection: a monocentric prospective observational cohort study, Int. J. Infect. Dis. 109 (2021) 209–216.
[50] S. Johnsen, S.M. Sattler, K.W. Miskowiak, K. Kunalan, A. Victor, et al., Descriptive analysis of long COVID sequelae identified in a multidisciplinary clinic serving hospitalised and non-hospitalised patients, ERJ Open Res 7 (3) (2021).
[51] G. Vagheggini, F. Marzetti, M. Miniati, L. Bernardeschi, M. Miccoli, et al., Pulmonary function and psychological burden three months after COVID-19: proposal of a comprehensive multidimensional assessment protocol, Healthcare 10 (4) (2022).
[52] S. Sperling, A. Floe, S. Leth, C. Hyldgaard, T. Gissel, et al., Fatigue is a major symptom at COVID-19 hospitalization follow-up, J. Clin. Med. 11 (9) (2022).
[53] A. Lehmann, M. Gysan, D. Bernitzky, C. Bal, H. Prosch, et al., Comparison of pulmonary function test, diffusion capacity, blood gas analysis and CT scan in patients with and without persistent respiratory symptoms following COVID-19, BMC Pulm. Med. 22 (1) (2022) 196.
[54] L. Pini, R. Montori, J. Giordani, M. Guerini, N. Orzes, et al., Assessment of respiratory function and exercise tolerance at 4-6 months after COVID-19 infection in patients with pneumonia of different severity, Intern. Med. J. 53 (2) (2023) 202–208.
[55] M.P. de Roos, S. Siegerink, N.G. Dijkstra, B.F. Broekman, K. Brinkman, et al., Pulmonary function and Quality of Life in a prospective cohort of (non-) hospitalized COVID-19 pneumonia survivors up to six months, Chron. Respir. Dis. 19 (2022) 14799731221114271.
[56] K. Guziejko, A. Moniuszko-Malinowska, P. Czupryna, M. Dubatowka, M. Lapinska, et al., Assessment of pulmonary function tests in COVID-19 convalescents six months after infection, J. Clin. Med. 11 (23) (2022).

[57] M. Berger, D. Daubin, J. Charriot, K. Klouche, V. Le Moing, et al., Mid-term sequelae of surviving patients hospitalized in intensive care unit for COVID-19 infection: the REHCOVER study, J. Clin. Med. 12 (3) (2023).
[58] T.V. Lerum, T.M. Aalokken, E. Bronstad, B. Aarli, E. Ikdahl, et al., Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19, Eur. Respir. J. 57 (4) (2021).
[59] A.S. Shah, A.W. Wong, C.J. Hague, D.T. Murphy, J.C. Johnston, et al., A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations, Thorax 76 (4) (2021) 402–404.
[60] K.L. Lewis, S.A. Helgeson, M.M. Tatari, J.M. Mallea, H.Z. Baig, N.M. Patel, COVID-19 and the effects on pulmonary function following infection: a retrospective analysis, EClinicalMedicine 39 (2021) 101079.
[61] G. Diaz-Fuentes, G. Roa-Gomez, O. Reyes, R. Singhal, S. Venkatram, Coronavirus pneumonia: outcomes and characteristics of patients in an inner-city area after 3 Months of infection, J. Clin. Med. 10 (15) (2021).
[62] A. Cortes-Telles, S. Lopez-Romero, E. Figueroa-Hurtado, Y.N. Pou-Aguilar, A.W. Wong, et al., Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnoea, Respir. Physiol. Neurobiol. 288 (2021) 103644.
[63] A.S. Shah, M.H. Ryu, C.J. Hague, D.T. Murphy, J.C. Johnston, et al., Changes in pulmonary function and patient-reported outcomes during COVID-19 recovery: a longitudinal, prospective cohort study, ERJ Open Res 7 (3) (2021).
[64] A. Eligulashvili, M. Darrell, C. Miller, J. Lee, S. Congdon, et al., COVID-19 patients in the COVID-19 recovery and engagement (CORE) clinics in the bronx, Diagnostics 13 (1) (2022).
[65] G.D.S. Prestes, C.S. Simon, R. Walz, C. Ritter, F. Dal-Pizzol, Respiratory outcomes after 6 Months of hospital discharge in patients affected by COVID-19: a prospective cohort, Front. Med. 9 (2022) 795074.
[66] G. Labarca, M. Henriquez-Beltran, J. Lastra, D. Enos, F. Llerena, et al., Analysis of clinical symptoms, radiological changes and pulmonary function data 4 months after COVID-19, Clin. Res. J 15 (9) (2021) 992–1002.
[67] D.C. Bretas, A.S. Leite, E.V. Mancuzo, T.A. Prata, B.H. Andrade, et al., Lung function six months after severe COVID-19: does time, in fact, heal all wounds? Braz. J. Infect. Dis. 26 (3) (2022) 102352.
[68] I. Cherrez-Ojeda, E. Sanchez-Angarita, E. Vanegas, M.J. Farfan Bajana, K. Robles-Velasco, et al., Pulmonary evaluation of post-COVID-19 patients: an Ecuadorian experience, J. Community Hosp. Intern. Med. Perspect. 12 (2) (2022) 30–34.
[69] A.M. Salem, N. Al Khathlan, A.F. Alharbi, T. Alghamdi, S. AlDuilej, et al., The long-term impact of COVID-19 pneumonia on the pulmonary function of survivors, Int. J. Gen. Med. 14 (2021) 3271–3280.
[70] U. Sirayder, D. Inal-Ince, B. Kepenek-Varol, C. Acik, Long-term characteristics of severe COVID-19: respiratory function, functional capacity, and quality of life, Int. J. Environ. Res. Publ. Health 19 (10) (2022).
[71] E. Afsin, M.E. Demirkol, Post-COVID pulmonary function test evaluation, Turk Thorac J 23 (6) (2022) 387–394.
[72] A.S. Nirmal, R. Venkitakrishnan, J. Augustine, R. Divya, M. Cleetus, et al., Delayed lung function testing after COVID-19 to detect persistent lung function abnormalities - the DELTA - COVID-19 lung function study, J. Fam. Med. Prim. Care 11 (11) (2022) 7351–7356.
[73] X. Liao, Y. Wang, Z. He, Y. Yun, M. Hu, et al., Three-Month pulmonary function and radiological outcomes in COVID-19 survivors: a longitudinal patient cohort study, Open Forum Infect. Dis. 8 (9) (2021) ofaa540.
[74] B. Kerget, E. Celik, F. Kerget, A. Aksakal, E.Y. Ucar, et al., Evaluation of 3-month follow-up of patients with postacute COVID-19 syndrome, J. Med. Virol. 94 (5) (2022) 2026–2034.
[75] F. Darawshy, A. Abu Rmeileh, R. Kuint, D. Padawer, K. Karim, et al., Residual symptoms, lung function, and imaging findings in patients recovering from SARS-CoV-2 infection, Intern Emerg Med 17 (5) (2022) 1491–1501.
[76] L. Liang, B. Yang, N. Jiang, W. Fu, X. He, et al., Three-month follow-up study of survivors of coronavirus disease 2019 after discharge, J. Kor. Med. Sci. 35 (47) (2020) e418.
[77] M. Miwa, M. Nakajima, R.H. Kaszynski, S. Hamada, H. Ando, et al., Abnormal pulmonary function and imaging studies in critical COVID-19 survivors at 100 days after the onset of symptoms, Respir Investig 59 (5) (2021) 614–621.
[78] Y. Ma, J. Deng, Q. Liu, M. Du, M. Liu, J. Liu, Long-term consequences of asymptomatic SARS-CoV-2 infection: a systematic review and meta-analysis, Int. J. Environ. Res. Publ. Health 20 (2) (2023).
[79] H. Zhi, X. Ji, Z. Zhao, H. Liang, S. Zhong, et al., Risk factors for impaired pulmonary diffusion function in convalescent COVID-19 patients: a systematic review and meta-analysis, EClinicalMedicine 49 (2022) 101473.
[80] R. Torres-Castro, L. Vasconcello-Castillo, X. Alsina-Restoy, L. Solis-Navarro, F. Burgos, et al., Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis, Pulmonology 27 (4) (2021) 328–337.
[81] D.C. Sanchez-Ramirez, K. Normand, Y. Zhaoyun, R. Torres-Castro, Long-term impact of COVID-19: a systematic review of the literature and meta-analysis, Biomedicines 9 (8) (2021).
[82] G.L. Ruppel, What is the clinical value of lung volumes? Respir. Care 57 (1) (2012) 26–35, discussion -8.
[83] A.D. Proal, M.B. VanElzakker, Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms, Front. Microbiol. 12 (2021) 698169.
[84] I. Basu-Ray, N.K. Almaddah, A. Adeboye, M.P. Soos, Cardiac Manifestations of Coronavirus (COVID-19), StatPearls. Treasure Island (FL, 2023.
[85] P.E. Scherer, J.P. Kirwan, C.J. Rosen, Post-acute sequelae of COVID-19: a metabolic perspective, Elife (2022) 11.
[86] H. Zhang, X. Li, L. Huang, X. Gu, Y. Wang, et al., Lung-function trajectories in COVID-19 survivors after discharge: a two-year longitudinal cohort study, EClinicalMedicine 54 (2022) 101668.