One-fourth of COVID-19 patients have an impaired pulmonary function after 12 months of illness onset

Hugo D.G. van Willigen[1] (MD), Elke Wynberg[1,2#] (MBBS MSc), Anouk Verveen[3#], Maartje Dijkstra[2,4] (MD PhD), Bas J. Verkaik[4] (MD), Orlane J.A. Figaroa[4] (MD), Marianne C. de Jong[2], Annelou L.I.P. van der Veen[4], Agata Makowska[2], Nelleke Koedoot[2], Pythia T Nieuwkerk[3] (PhD), Anders Boyd[2,6], Maria Prins[2,4] (PhD), Godelieve J. de Bree[4] (MD PhD), Menno D. de Jong[1] (MD PhD), Joost G. van den Aardweg[5] (MD PhD), and the RECoVERED Study Group.

Affiliations:

[1] Department of Medical Microbiology & Infection prevention, Amsterdam UMC, University of Amsterdam, Amsterdam Institute for Infection and Immunity, Amsterdam, the Netherlands.

[2] Department of Infectious Diseases, Public Health Service of Amsterdam, GGD, Amsterdam, the Netherlands.

[3] Department of Medical Psychology, Amsterdam UMC, Amsterdam Public Health Research Institute, University of Amsterdam, Amsterdam, the Netherlands.

[4] Department of Internal Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam Institute for Infection and Immunity, Amsterdam, the Netherlands.

[5] Department of Pulmonary Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands.

[6] Stichting HIV monitoring, Amsterdam, the Netherlands

[#] Contributed equally

Corresponding author:

H.D.G. van Willigen, Department of Medical Microbiology & Infection prevention, Amsterdam UMC location AMC, room L1-105, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands, email: h.d.vanwilligen@amsterdamumc.nl, tel: 020 73 20 882.

Word count:

Abstract: 247

Manuscript: 2802

Summary (words: 247)

Background: This longitudinal study evaluates the extent of impaired pulmonary function over time after SARS-CoV-2 infection across the full spectrum of COVID-19 severity.

M**ethods:** Pulmonary function was measured by diffusing capacity for carbon monoxide (DLCO) at one, six, and twelve months after illness onset. Additionally, data on sociodemographics, clinical characteristics, symptoms, and health-related quality of life (HRQL) were collected. Pulmonary function and determinants were modelled over time using mixed-effect linear regression. Determinants of pulmonary impairment at 12 months since illness onset were identified using logistic regression.

Findings: Between May 2020 and December 2021, 301 of 349 participants underwent at least one pulmonary function test. After one year of follow-up, 25% of the participants had an impaired pulmonary function which translates in 11%, 22%, and 48% of the participants with mild, moderate and severe/critical COVID-19. Improvement in DLCO among the participants continued over the period across one, six and twelve months. Having more than three comorbidities ($p<0{\cdot}001$) and initial severe/critical illness ($p<0{\cdot}001$) were associated with slower improvement of pulmonary function over time, adjusted for age and sex. HRQL improved over time and was not different to those without impaired pulmonary function.

Interpretation: The prevalence of impaired pulmonary function after twelve months of follow-up, was still significant among those with initially moderate or severe/critical COVID-19. However, those who continued to have impaired pulmonary function after one year did not have impaired HRQL.

Funding: This work was supported by the Netherlands Organization for Health Research and Development (ZonMw) and the Public Health Service of Amsterdam.

Background

As the SARS-CoV-2 pandemic continues, there is an increasing focus on the long-term consequences of infection. Previous coronavirus outbreaks with post-viral sequelae have been well documented. Patients who recovered from Middle East Respiratory Syndrome (MERS) or Severe Acute Respiratory Syndrome (SARS) pneumonia reported experiencing significant negative effects on pulmonary function lasting from months to years.[1] Post-Acute Sequelae of SARS-CoV-2 (PASC) or 'long COVID' includes a wide range of ongoing symptoms, mental disorders, pulmonary sequelae, and functional impairments. Data collected from the RECoVERED cohort study showed fatigue, dyspnoea, and myalgia were the most commonly reported symptoms across different disease severities at illness onset onward and many individuals reported still having these symptoms at one year from illness onset.[2] This raises the question whether individuals are able to fully recover from reduced pulmonary function due to COVID-19.

The current literature shows the most important lung function abnormality upon SARS-COV2 infection is reduced DLCO in association with reduced alveolar volume (VA). The severity of this abnormality typically depends on the severity of the illness during the acute phase of infection, yet this finding is based on mainly hospitalised patients, whether or not admitted to the intensive care unit (ICU). Patients with severe illness, prolonged hospital stay, mechanical ventilation, or ICU admission have a higher risk for persisting impaired pulmonary function after infection. As in previous coronavirus outbreaks, pulmonary function abnormalities still persist months after discharge.[3-6] However, there is evidence from longitudinal studies indicating that improvement in pulmonary function can occur between eight and twelve months of follow-up.[7-9] Furthermore, it is unclear to what extent the observed impact of COVID-19 on pulmonary function relates to decreased quality of life or to other post COVID-19 symptoms. Reductions in DLCO have been associated with reduced exercise tolerance, although this finding is inconsistent[10-12].

In the present study, we investigated the kinetics of pulmonary function over time in a well characterized, prospective cohort of both hospitalised and non-hospitalised individuals with SARS-CoV-2 infection. We additionally aimed to evaluate impaired pulmonary function and its relationship to HRQL and ongoing COVID-sequelae across different initial COVID-19 severities.

Methods

Study design

The RECoVERED cohort study aims to describe the immunological, clinical and psychosocial sequelae of a SARS-CoV-2 infection. Inclusion criteria were an age from 16 to 85 years and a laboratory confirmed SARS-CoV-2 infection. Participants were enrolled in the municipal region of Amsterdam, the Netherlands, from May 2020 until the end of June 2021. The COVID-19 diagnosis was based on positive polymerase chain reaction (PCR). Non-hospitalised participants were identified from notification data at the Public Health Service of Amsterdam (PHSA) and enrolled within seven days of diagnosis. Additionally, participants who were hospitalised were approached on the COVID-19 wards of two academic hospitals in Amsterdam. Between 11 May 2020 and 30 June 2020, a limited number of hospitalised patients were included retrospectively within three months following SARS-CoV-2 diagnosis. The study design, enrolment and follow-up of participants have been described in detail elsewhere.[2] RECoVERED was approved by the medical ethical review board of the Amsterdam University Medical Centres (NL73759.018.20). All participants provided written informed consent.

In the present study, we included all participants who had at least one pulmonary function measurement during follow-up as of December 2021.

Study procedures

Data regarding socio-demographic characteristics and past medical history were collected by patient interview and reviewing medical records. A symptom questionnaire on the presence and duration of symptoms was collected through participant interview in the first month of follow-up, based on the World Health Organisation [WHO] Case Report Form. Thereafter, the questionnaire was administered monthly online, to be completed by participants.

Physical signs during the acute phase of the infection, including heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO_2), were measured or retrieved from hospital records at enrolment (D0), seven days (D7) and one month (M1) after enrolment.

Pulmonary function testing

Pulmonary function was measured according to the American Thoracic Society (ATS)–European Respiratory Society guidelines.[13] At 28 days, six months, and twelve months after enrolment participants underwent standard pulmonary function testing (PFT). The following parameters were measured: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), vital capacity (VC), pulmonary diffusion capacity, and alveolar volume. DLCO is the single-breath diffusing capacity (or transfer capacity) of the lung. Before each PFT, haemoglobin was measured and used to correct for DLCO. Alveolar volume was derived from dilution of methane during the manoeuvre. These PFTs were conducted at the Amsterdam UMC (location AMC) using CareFusion MasterScreen® PFT with SentrySuite software (Vyaire, Wuerzburg, Germany).

On the day of PFT the spirometer was calibrated, including registration of barometric pressure and temperature. During the PFT trained members of the study staff coached the participant, while routinely being supervised by a pulmonary technician. Pulmonologists within the study group were responsible for test validation and interpretation. In the analysis, the highest value of the three attempts was used and differences to the PFT predicted values and lower limit of normal values were calculated. To ensure measurement quality, the maximum inspiration during spirometry and during the single-breath CO technique were not allowed to differ by more than 5%. Lung function tests performed under similar methods before COVID-19 diagnosis were gathered, if available.

Health-related quality of life

Participants were asked to complete the Medical Outcomes Studies Short Form 36-item Health Survey (SF-36), a self-administered questionnaire containing 36 items to assess health-related quality of life, at one and twelve months of follow-up.[14] The questionnaire measures health on eight multi-item dimensions, covering functional status, well-being, and overall evaluation. Participants were asked to rate their responses on three- or six-point scales in six of the eight dimensions. Item scores were coded, summed, and transformed for each dimension, resulting in a scale ranging from 0 (i.e., worst health) to 100 (i.e., best health).

Definitions

Based on the WHO COVID-19 disease severity criteria, clinical severity groups were defined as: mild disease, having an RR <20/min, and SpO2>94% on room air on D0, D7, and/or M1; moderate disease, having an RR 20-30/min or SpO2 90-94%, or receiving oxygen therapy at D0, D7, or M1; severe disease, having an RR>30/min or SpO2<90%, or receiving oxygen therapy at D0, D7, or M1; critical disease, ICU admission due to

COVID-19 at any timepoint. Illness onset was defined as the first day of symptom onset in symptomatic patients or the day of diagnosis in asymptomatic patients. BMI (kg/m^2) was categorised as: <25, underweight or normal weight; 25-30, overweight; >30, obese. Symptoms reported in the first month after overall illness onset were defined as acute symptoms due to COVID-19. The predicted lung function was regarded as impaired if a measured pulmonary value was below the lower limit of normal (LLN), which was already based according to pre-defined factors (e.g. age, sex, height).

Statistical analysis

Clinical and sociodemographic characteristics were compared between moderate/severe and mild disease severity groups. Continuous variables were given as medians and interquartile ranges, compared using the Mann-Whitney test. Categorical variables were given as frequencies and percentages, compared using the Pearson χ^2 or Fisher exact test, when appropriate.

Lung function was modelled overtime using mixed-effects linear regression. The kinetics (per 6 months) of lung function was obtained by including a fixed-effect for time, while adding a random intercept to account for between-patient variation at enrolment.[15,16] In multivariable analysis, we produced increasingly complex multivariable models where variables were grouped as follows: model 1, clinical and sociodemographic characteristics; Model 2, addition of acute phase COVID-19 symptoms; and model 3, addition of COVID-19 clinical severity. At each model, variables were selected using a backwards stepwise approach in which variables with a p-value <0·20 from a Wald χ^2 test were retained. Age, sex, and time since illness onset were forced in all models.

Abnormal pulmonary function that persisted after 12 months of illness onset was modelled as an outcome using logistic regression. The same procedure as described above was used to construct the multivariable models for these analyses. Adjusted odds ratios (ORs) and their 95% CIs are presented.

In post-hoc analysis, we determined whether severe lung impairment affected HRQL over time. We modelled continuous HRQL using mixed-effects linear regression. We included time points (i.e., month one and month twelve), lung function severity (i.e., severe or not severe) and the interaction between the two as fixed covariates, while adding a random intercept across patients. This model was adjusted for age and sex. We tested the difference between severity groups at each time point using Wald χ^2 test. *P*-values were two-sided and a *P*-value

of <0·05 was considered statistically significant. Data were analysed using Stata statistical software (v15.1, College Station, TX, USA).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing of this article or in the decision to submit the paper for publication.

Results

Characteristics of study participants

In total, 349 participants were enrolled in the RECoVERED cohort study. By December 2021, 301 (86%) participants underwent at least one PFT during follow-up. Participant flow is described in Supplementary figure S2. Of the 301 participants, 89 (30%) experienced mild, 133 (44%) moderate, and 79 (26%) severe/critical disease severity. The median age was 51 year (IQR, 36-62 year) and 170 (56%) were men (Table 1). Older age (p<0·001), higher BMI (p<0·001), number of comorbidities in general (p<0·001), cardiovascular disease (CVD) (p<0·001), diabetes (DM) (p<0·001), and chronic pulmonary diseases other than asthma or COPD (p=0·02) appeared more often in the severe/critical compared to mild severity group. Among the 301 evaluated participants, 141 (47%) were hospitalized. 133 (44%) participants required supplementary oxygen, while 30 participants (10%) received mechanical ventilation during the first month following illness onset. A total of 39 participants (13%) were admitted to the ICU, with a median stay of 6 (IQR 4-13) days. Overall, 70 participants (23%) received dexamethasone and 14 participants (10%) received tocilizumab.

Lung function over time

When evaluating pulmonary involvement, abnormal DLCO was present in six (26%) participants with mild, 21 (23%) with moderate and 25 (74%) with severe/critical disease severity at one month after illness onset (Table 1). No statistically significant improvement in lung function was observed among participants with mild disease. Among those with moderate disease, improvement was observed between one and six months, but no further improvement occurred after six months. Among participants with severe disease, improvement in DLCO and VA continued over the period across one, six and 12 months. In the first linear mixed-effects regression model, female sex (β=-3·94, 95%CI: -7·23, -0·66) p=0·019), higher BMI (β -3·05, 95%CI: -5·16- -0·94) p = 0·005), and higher number of comorbidities (β -4·43, 95%CI: -6·34- -2·53) p<0·001) were associated with

DLCO over time (Figure 3a). In model 2, a higher BMI was no longer statistically significant when adjusting for clinical symptoms in the first month. While wheezing in the first month after illness onset was significantly associated with reduced DLCO over time in univariable analysis, this symptom did not remain statistically significantly associated with the outcome in multivariable model 2 (Figure 3b). When including clinical severity in model 3, female sex (β -3·62, 95%CI: -7·08- -0·15) p=0·041), higher number of comorbidities (β -4·04, 95%CI: -6·07- -2·01) p<0·001), and more severe clinical severity (β -5·62, 95%CI: -8·04- -3·21) p<0·001) were significantly associated with DLCO over time (Figure 3c).

Factors associated with impaired pulmonary function at 12 months after illness onset

During the spirometry 11/128 (9%) had an FVC below the LLN at 12 months, while 7/128 participants with an impaired FEV1/FVC had a medical history of pulmonary origin. The prevalence of reduced DLCO at 12 months after illness onset was 11%, 22%, and 48% for mild, moderate, and severe/critical disease severity, respectively. Significant differences in DLCO between the disease severity groups continued to be present up to 12 months of follow-up (Supplementary table S1). The backwards stepwise approach is shown in supplementary table S3. In multivariable analysis, risk factors associated with an abnormal DLCO at 12 months were having initial severe COVID-19 (OR=2·69, 95%CI: 1·25-5·78) and having more comorbidities overall (OR=3·02, 95%CI: 1·71-5·34).

Association between pulmonary function and HRQL

When adjusting for age and sex, participants with a DLCO below LLN in the first month after illness onset scored significantly lower on the physical functioning (β -20·27, 95%CI: -27·91- -12·63) and general health (β -10·34, 95%CI: -17·21- -3·47) dimensions of the SF-36. This association was also seen between an abnormal FVC, physical functioning (β -39·38, 95%CI: -48·87- -29·89) and general health (β -15·34, 95%CI: -24·04- -6·64). In addition, abnormal FEV_1 was associated with a lower physical functioning dimension score (β -20·75, 95%CI: -30·76- -10·73). In individuals with impaired pulmonary function at 12 months after illness onset, HRQL improved over time and was no different to those without impaired pulmonary function.

Discussion

Using data from a large prospective study including participants with a varying degree of disease severity, our findings indicate that one-fourth of patients still have impaired the single-breath diffusing capacity 12 months after SARS-CoV-2 infection. Nevertheless, significant increases in DLCO, VA, and FVC were observed among

those with an initially moderate or severe/critical COVID-19, suggesting an extent of reversibility of COVID-19-associated lung damage. Reassuringly, these individuals were also able to achieve a level of HRQL that was not different from those without impaired pulmonary function.

The impaired pulmonary function observed in our study was mainly driven by an abnormal diffusion capacity and persisted up to 12 months of illness onset. Abnormalities in DLCO were mostly found in patients in the moderate and severe disease severity groups, which was in accordance with other studies[7-9,11]. These findings are more suggestive of restrictive lung function origin, as opposed to volume-adjusted diffusion capacity. The association between severity of COVID-19 and restrictive pulmonary function has also been observed in previous studies with follow-up of up to one year[9,17]. Within 12 months of follow-up, a continuous improvement in pulmonary function was observed in the severe/critical disease severity group, whereas such improvements began to wane after the first 6 months for those in the moderate disease severity group. The rather strong differences in single-breath diffusing capacity between disease severities is unique and insightful. These trajectories are also observed by Zhang et al[18], and even describe a decline in lung function after one year of follow-up. Chronic weakness in the severe COVID-19 illness group may be present due circulatory limitation, muscle weakness, critical illness neuropathy and myopathy, and deconditioning, as described by Ong et al[19] in SARS patients.

Radiological abnormalities, such as pulmonary fibrosis, can be associated with restrictive lung function. Pulmonary fibrosis been found to persist months and even years after COVID-19 infection[20]. In this study, most participants were admitted to the ICU at the time of infection, yet underwent a CT-scan weeks following their discharge. Hence, the proportion of participants with pulmonary fibrosis in this study is unclear due to limited data.

It is known that, following acute lung injury, muscle weakness developed during ICU admission has been associated with substantial impairments in physical function, restrictive pulmonary function, and quality of life[21]. When comparing HRQL at one and twelve month(s) after illness onset, there was an increase in HRQL in the patient group with impaired pulmonary function, while the mean HRQL at the end of follow-up was not significantly different compared to that of individuals without impaired function. This observation supports the effect of rehabilitation or coping of impaired pulmonary function[22]. However, this result is in contrast to another study in which patients who were experiencing persistent symptoms one year after illness onset reported poorer HRQL[23].

This study has several limitations. Retrospective enrolment of ICU patients obviously allowed only individuals who remained alive at a certain timepoint to be included, which might have introduced survival bias. In addition, patients who were in a life-threatening situation were unlikely to have been enrolled in the study. Hence, our findings might not be generalizable to the larger group of COVID-19 patients with severe/critical disease severity. Furthermore, during the pandemic, newly developed or integrated treatments e.g., the use of dexamethasone and tocilizumab, became available during follow-up, raising the possibility that accelerated recovery from COVID-19 disease could have occurred during the study. As a result, impairment of pulmonary function might have been lessened compared to what would have been expected during the natural course of infection. Nevertheless, our results clearly demonstrate that impaired lung function is a common problem after 12 months of infection. Due to the lack of pre-COVID-19 PFT measurements, we were unable to assess what proportion of impaired lung function was directly attributable to SARS-CoV-2 infection as compared to previous pulmonary comorbidities.

In conclusion, one-fourth of COVID-19 patients in our study still had impaired pulmonary function after 12 months of illness onset. Nevertheless, this impairment did not appear to substantially affect HRQL after 12 months of follow-up. Single-breath diffusing capacity improvement after SARS-CoV-2 infection is noticeably different between the disease severities, while prolonged recovery of pulmonary function is observed in patients who had severe/critical COVID-19.

Declaration of interests

All authors declare no competing interests.

Patient consent statement:

Written informed consent was obtained from each study participant. The study design was approved by the local ethics committee of the Amsterdam UMC (Medisch Ethische Toetsingscommissie [METC]; NL73759.018.20).

Acknowledgments

This work was supported by the Netherlands Organization for Health Research and Development (ZonMw) [10150062010002 to M.D.d.J.] and the Public Health Service of Amsterdam [R&D in 2021 and 2022 to M.P.].

The authors wish to thank all RECoVERED study participants. In addition, we wish to thank all members of the RECoVERED Study Group, listed below.

RECoVERED Study Group:

Public Health Service of Amsterdam: Ivette Agard, Jane Ayal, Floor Cavdar, Annemarieke Deuring, Annelies van Dijk, Ertan Ersan, Laura del Grande, Joost Hartman, Tjalling Leenstra, Romy Lebbink, Dominique Loomans, Tom du Maine, Ilja de Man, Amy Matser, Lizenka van der Meij, Marleen van Polanen, Maria Oud, Clark Reid, Leeann Storey, Marc van Wijk.

Amsterdam University Medical Centres: Joyce van Assem, Marijne van Beek, Thyra Blankert, Leah Frenkel, Marit van Gils, Jelle van Haga, Xiaochuan (Alvin) Han, Agnes Harskamp-Holwerda, Mette Hazenberg, Soemeja Hidad, Neeltje Kootstra, Lara Kuijt, Colin Russell, Karlijn van der Straten, Gerben-Rienk Visser.

Data availability

Data supporting the findings in this manuscript are available from the corresponding author upon request.

Patient consent statement

Written informed consent was obtained from each study participant. The study design was approved by the local ethics committee of the Amsterdam UMC (Medisch Ethische Toetsingscommissie [METC]; NL73759.018.20).

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Tables

Tables

Table 1. Socio-demographic, clinical (baseline and COVID-19-related) and study characteristics of RECoVERED study participants who conducted a pulmonary function test between May 2020-December 2021, in Amsterdam, the Netherlands.

	Total	Mild	Moderate	Severe/Critical	p-value
	N=301	N=89	N=133	N=79	
Sex					0.32
Male	170 (56%)	45 (51%)	76 (57%)	49 (62%)	
Female	131 (44%)	44 (49%)	57 (43%)	30 (38%)	
Age, years	51 (36-62)	40.0 (27.0-53.0)	49.0 (34.0-61.0)	60.0 (50.0-66.0)	<0.001
BMI, kg/m2[†]	25.8 (23.2-29.4)	24.4 (22.8-27.3)	25.7 (23.2-29.4)	27.5 (25.1-33.3)	<0.001
BMI category					<0.001
Normal weight	126 (42%)	52 (58%)	55 (41%)	19 (24%)	
Overweight	102 (34%)	23 (26%)	46 (35%)	33 (42%)	
Obese	68 (23%)	13 (15%)	30 (23%)	25 (32%)	
Missing	5 (2%)	1 (1%)	2 (2%)	2 (3%)	
Smoking					0.12
Non-smoker	187 (62%)	55 (62%)	76 (57%)	56 (71%)	
Smoker	20 (7%)	8 (9%)	11 (8%)	1 (1%)	
Ex-smoker	88 (29%)	23 (26%)	44 (33%)	21 (27%)	
Missing	6 (2%)	3 (3%)	2 (2%)	1 (1%)	
Number of comorbidities[*]					<0.001
0	140 (47%)	56 (63%)	63 (47%)	21 (27%)	
1	87 (29%)	23 (26%)	34 (26%)	30 (38%)	
2	31 (10%)	5 (6%)	15 (11%)	11 (14%)	
3 or more	43 (14%)	5 (6%)	21 (16%)	17 (22%)	
Cardiovascular disease	77 (26%)	11 (12%)	32 (24%)	34 (44%)	<0.001
Diabetes	34 (11%)	4 (4%)	10 (8%)	20 (26%)	<0.001
Asthma and/or COPD	34 (11%)	8 (9%)	17 (13%)	9 (12%)	0.68
Other chronic pulmonary disease	12 (4%)	1 (1%)	4 (3%)	7 (10%)	0.020
Cancer	18 (6%)	6 (7%)	8 (6%)	4 (5%)	0.91
Other comorbidities	67 (22%)	12 (14%)	35 (27%)	20 (26%)	0.060

Tables

	Total	Mild	Moderate	Severe/critical	p-value
	N=301	N=89	N=133	N=79	
Clinical features of SARS-CoV-2 infection					
Symptom status at baseline					0.45
Symptomatic	299 (99%)	88 (99%)	133 (100%)	78 (99%)	
Asymptomatic	2 (1%)	1 (1%)	0 (0%)	1 (1%)	
Hospital admission	141 (47%)	4 (4%)	61 (46%)	76 (96%)	<0.001
Duration of hospital admission	6 (4-10)	3 (2-6)	5 (4-8)	9 (4-14)	<0.001
ICU admission	39 (13%)	0 (0%)	0 (0%)	39 (49%)	<0.001
Duration of ICU admission[#]	6 (4-13)			6 (4-13)	
Received suppl. oxygen therapy	133 (47%)	0 (0%)	59 (47%)	74 (95%)	<0.001
Received mechanical ventilation	30 (10%)	0 (0%)	0 (0%)	30 (38%)	<0.001
Received Dexamethason	70 (25%)	0 (0%)	34 (27%)	36 (46%)	<0.001
Received Tocilluzimab	14 (10%)	0 (0%)	2 (3%)	12 (16%)	0.022
Days from illness onset to COVID-19 diagnosis	4 (2-9)	3 (1-8)	4 (2-9)	7 (2-10)	0.26
Time from start illness to hospitalisation	9 (7-13)	49 (16-85)	9 (8-14)	9 (7-12)	0.11
Time from start illness to ICU admission[#]	10 (7-12)			10 (7-12)	
Time from hospitalisation to ICU admission[#]	1 (0-3)			1 (0-3)	
Acute presence (<28 days from illness onset) of symptom:					
Dyspnoea	138 (61%)	31 (39%)	76 (72%)	31 (78%)	<0.001
Cough	167 (75%)	49 (61%)	85 (81%)	33 (87%)	0.002
Fever	140 (64%)	42 (53%)	73 (70%)	25 (68%)	0.052
Myalgia	143 (64%)	53 (66%)	71 (68%)	19 (49%)	0.095
Wheezing	59 (26%)	8 (10%)	31 (29%)	20 (53%)	<0.001
Fatigue	193 (87%)	68 (84%)	92 (88%)	33 (92%)	0.50

BMI=Body mass index; ICU= Intensive Care Unit; forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), vital capacity (VC), corrected pulmonary diffusion capacity (DLCOc) and alveolar volume (VA)

[†] Normal BMI group includes 3 individuals with BMI between 18.0 and 18.5 kg/m2.

[#] Only those admitted to the Intensive Care Unit

* COVID-related comorbidities are based on WHO Clinical Management Guidelines[16] and include: cardiovascular disease (including hypertension), chronic pulmonary disease (excluding asthma), renal disease, liver disease, cancer, immunosuppression (excluding HIV, including previous organ transplantation), previous psychiatric illness and dementia.

Tables

Table 2. Pulmonary function per time point of different severity groups from illness onset.

Spirometry					
	Total	**Mild**	**Moderate**	**Severe/critical**	**p-value**
	N=301	**N=89**	**N=133**	**N=79**	
Days from illness onset to month 1	42 (36-51)	39 (34-49)	42 (36-51)	48 (41-53)	0.004
Days from illness onset to month 6	198 (188-209)	197 (186-207)	199 (189-213)	198 (190-206)	0.46
Days from illness onset to month 12	382 (369-396)	384 (372-398)	382 (367-396)	380 (368-394)	0.72
Abnormal FVC month 1	30/213 (14%)	3/74 (4%)	12/101 (12%)	15/38 (39%)	<0.001
Abnormal FVC month 6	20/224 (9%)	2/70 (3%)	12/104 (12%)	6/50 (12%)	0.077
Abnormal FVC month 12	11/128 (9%)	2/33 (6%)	4/66 (6%)	5/29 (17%)	0.23
Abnormal FEV_1 month 1	28/213 (13%)	3/74 (4%)	13/101 (13%)	12/38 (32%)	<0.001
Abnormal FEV_1 month 6	27/224 (12%)	5/70 (7%)	12/104 (12%)	10/50 (20%)	0.12
Abnormal FEV_1 month 12	20/128 (16%)	3/33 (9%)	10/66 (15%)	7/29 (24%)	0.26
Single-breath carbon monoxide uptake in the lung					
Abnormal VC month 1	26/213 (12%)	3/74 (4%)	8/101 (8%)	15/38 (39%)	<0.001
Abnormal VC month 6	18/224 (8%)	2/70 (3%)	10/104 (10%)	6/50 (12%)	0.12
Abnormal VC month 12	10/128 (8%)	2/33 (6%)	3/66 (5%)	5/29 (17%)	0.14
Abnormal DLCO month 1	52/197 (26%)	6/70 (9%)	21/93 (23%)	25/34 (74%)	<0.001
Abnormal DLCO month 6	51/195 (26%)	4/54 (7%)	22/90 (24%)	25/51 (49%)	<0.001
Abnormal DLCO month 12	31/122 (25%)	3/28 (11%)	14/65 (22%)	14/29 (48%)	0.004
Abnormal VA month 1	61/199 (31%)	10/71 (14%)	28/94 (30%)	23/34 (68%)	<0.001
Abnormal VA month 6	3/195 (2%)	0/55 (0%)	2/90 (2%)	1/50 (2%)	0.62
Abnormal VA month 12	23/104 (22%)	2/24 (8%)	14/54 (26%)	7/26 (27%)	0.18

Tables

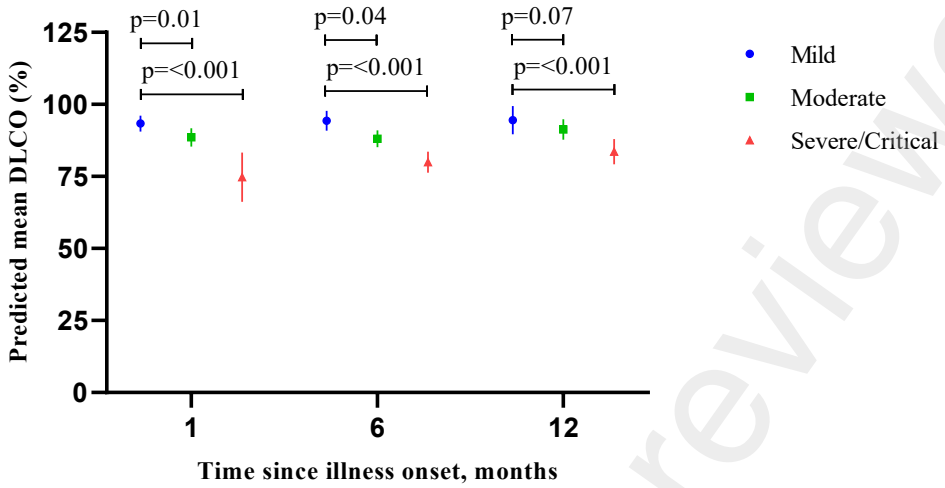
Table 3. Health-related quality of life per time point of different severity groups from illness onset.

Health-related quality of life item scores					
	Total	**Mild**	**Moderate**	**Severe/critical**	**p-value**
	N=301	**N=89**	**N=133**	**N=79**	
Physical Functioning month 1	80 (50-95)	95 (80-100)	73 (45-95)	55 (30-70)	<0.001
Physical Functioning month 12	95 (75-100)	100 (93-100)	90 (70-100)	80 (65-100)	0.004
Role Functioning-Physical month 1	25 (0-100)	50 (0-100)	25 (0-50)	0 (0-75)	0.002
Role Functioning-Physical month 12	100 (75-100)	100 (100-100)	100 (75-100)	100 (25-100)	0.14
Bodily Pain month 1	72 (41-100)	84 (62-100)	62 (41-80)	62 (41-100)	<0.001
Bodily Pain month 12	84 (62-100)	100 (84-100)	100 (72-100)	74 (51-100)	0.007
Social Functioning month 1	63 (38-88)	75 (50-100)	50 (38-63)	50 (38-88)	<0.001
Social Functioning month 12	88 (75-100)	100 (88-100)	88 (63-100)	88 (63-100)	0.027
Mental Health month 1	76 (60-88)	78 (62-88)	72 (56-84)	80 (68-92)	0.016
Mental Health month 12	84 (72-92)	88 (80-96)	76 (64-92)	84 (76-96)	0.053
Role Functioning-Emotional month 1	100 (33-100)	100 (33-100)	67 (0-100)	67 (0-100)	0.11
Role Functioning-Emotional month 12	100 (67-100)	100 (100-100)	100 (67-100)	100 (67-100)	0.051
Vitality month 1	50 (35-65)	60 (45-78)	43 (30-60)	40 (35-55)	<0.001
Vitality month 12	75 (55-85)	80 (70-85)	65 (55-80)	70 (55-80)	0.008
General Health Perceptions month 1	65 (50-80)	80 (65-90)	63 (50-75)	55 (35-70)	<0.001
General Health Perceptions month 12	70 (50-85)	80 (63-90)	65 (45-80)	65 (45-80)	0.014

Figures

Figures

Figure 1. Diffusing capacity for CO for different severity groups as a function of time.

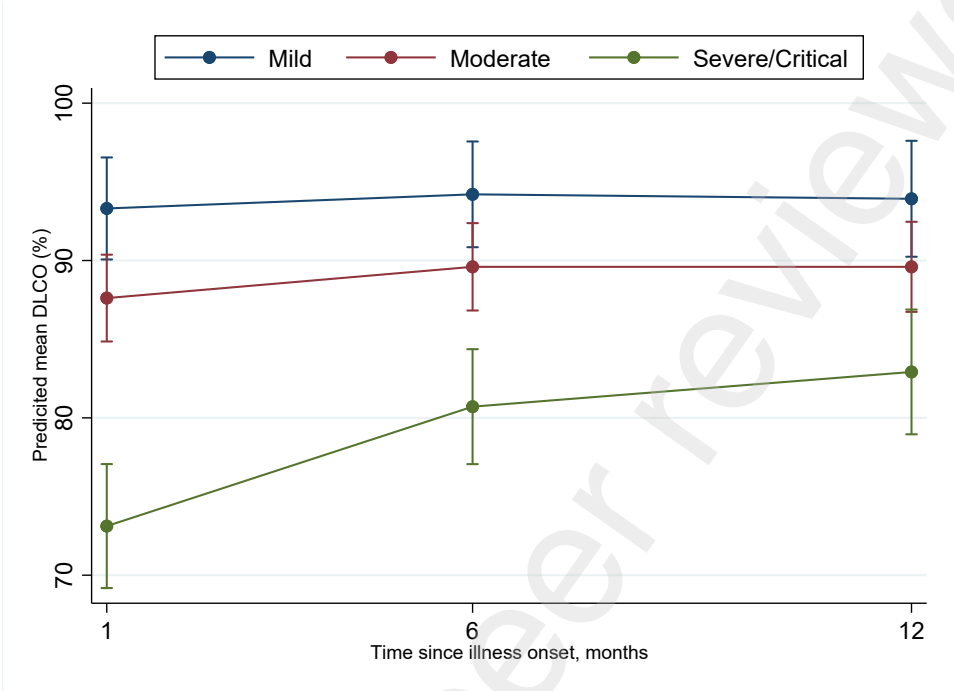


Dots represent mean predicted values of pulmonary diffusion capacity among included individuals; vertical bars are 95% confidence intervals.

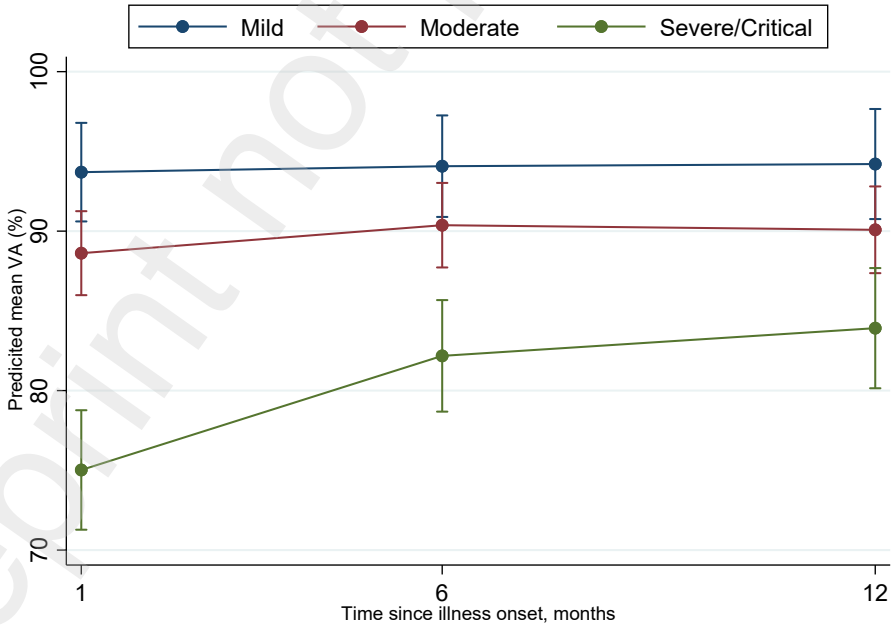
Figures

Figure 2. Diffusing capacity and alveolar volume for CO from 1 to 12 months for different severity groups.

A. Predicted mean of DLCO in percentages



B. Predicted mean of VA for CO in percentages



Dots represent mean predicted pulmonary function levels of included individuals; vertical bars are 95% confidence intervals; modelled in a linear mixed-effects regression model.