



# Prospective longitudinal evaluation of hospitalised COVID-19 survivors 3 and 12 months after discharge

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Shareable abstract (@ERSpublications)

Most hospitalised #COVID19 survivors show promising recovery 1 year after discharge, although mild symptoms may linger. Severe impairments are rare, but this study suggests an evaluation of the individual care needs after discharge. <https://bit.ly/3sZK45x>

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## Abstract

**Background** Long-term outcome data of coronavirus disease 2019 (COVID-19) survivors are needed to understand their recovery trajectory and additional care needs.

**Methods** A prospective observational multicentre cohort study was carried out of adults hospitalised with COVID-19 from March through May 2020. Workup at 3 and 12 months following admission consisted of clinical review, pulmonary function testing, 6-min walk distance (6MWD), muscle strength, chest computed tomography (CT) and quality of life questionnaires. We evaluated factors correlating with recovery by linear mixed effects modelling.

**Results** Of 695 patients admitted, 299 and 226 returned at 3 and 12 months, respectively (median age 59 years, 69% male, 31% severe disease). About half and a third of the patients reported fatigue, dyspnoea and/or cognitive impairment at 3 and 12 months, respectively. Reduced 6MWD and quadriceps strength were present in 20% and 60% at 3 months *versus* 7% and 30% at 12 months. A high anxiety score and body mass index correlated with poor functional recovery. At 3 months, diffusing capacity for carbon monoxide ( $D_{LCO}$ ) and total lung capacity were below the lower limit of normal in 35% and 18%, decreasing to 21% and 16% at 12 months; predictors of poor  $D_{LCO}$  recovery were female sex, pre-existing lung disease, smoking and disease severity. Chest CT improved over time; 10% presented non-progressive fibrotic changes at 1 year.

**Conclusion** Many COVID-19 survivors, especially those with severe disease, experienced limitations at 3 months. At 1 year, the majority showed improvement to almost complete recovery. To identify additional care or rehabilitation needs, we recommend a timely multidisciplinary follow-up visit following COVID-19 admission.



## Introduction

Since early 2020, the coronavirus disease 2019 (COVID-19) pandemic has been raging on relentlessly with over 270 million confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and over 5.3 million reported deaths as of 16 December 2021 [1]. Despite a relatively high mortality rate, the majority of patients recover from the acute phase, but long-term sequelae are not yet well understood. Experience from previous coronavirus outbreaks [2] has taught us that despite the lungs being the most affected organ [3], the impact goes well beyond the pulmonary system. Functional, cognitive and psychological impairment as well as poor general health status have been documented [2]. Several cohort studies on COVID-19, with varying sample size, disease severity and time to follow-up, report on 3- to 6-month outcomes [4–7] with to date only few reporting on 12-month outcome [8–13]. Despite the majority of patients recovering well, a significant proportion – including mild cases – still experience symptoms of fatigue and exertional dyspnoea with persistent absenteeism from work up to 6 and even 12 months after infection. Residual limitations on pulmonary function testing (PFT), physical capacity and chest computed tomography (CT) sequelae are not uncommon, particularly in patients surviving severe disease [5, 7, 8, 12–14]. Initial recommendations for follow-up of COVID-19 patients relied largely on expert opinion and observations from earlier coronavirus outbreaks (severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)) but are now available as living guidelines and updated as new information arises [15, 16].

We aimed to document the medium- and long-term clinical, functional and radiological implications of COVID-19, in order to better understand their recovery trajectory and to inform follow-up of hospitalised COVID-19 patients. Therefore, we present outcome data at 3 and 12 months of a cohort of hospitalised patients with moderate to severe COVID-19 during the first COVID-19 wave (March through May 2020) in Belgium. To our knowledge this is the first and largest European cohort to date with an elaborate follow-up and reporting on sequelae up to 12 months.

## Methods

### *Study design and patient population*

We conducted a multicentric prospective observational cohort study of consecutive adult patients ( $\geq 18$  years), who were admitted to either University Hospitals Leuven (UZL) or Ghent University Hospital (UZG) with COVID-19 between 1 March and 31 May 2020, and were seen in the outpatient clinic at 3 and 12 months after discharge. The study was approved by the institutional ethics committees of UZL (S64081/S65411) and UZG (BC-07831/BC-10247). Written informed consent was obtained from all participating patients.

Diagnosis of SARS-CoV-2 infection was defined as either a positive reverse transcription polymerase chain reaction (RT-PCR) assay on nasopharyngeal swab or bronchoalveolar lavage fluid, or radiological findings compatible with COVID-19 in the absence of other plausible diagnoses [17].

All eligible subjects admitted to a COVID intensive care unit (ICU) or a conventional COVID ward were invited for follow-up. Residents of a medical care facility, patients with cognitive impairment or those with a geriatric profile (clinical frailty scale  $>4$ ) [18] were excluded. For these patients further care was pursued as needed. Patients admitted with incidental finding of SARS-CoV-2 infection without respiratory symptoms were also excluded from follow-up.

### *General COVID-19 management*

Medical treatment involved hydroxychloroquine unless contraindicated, in line with national guidelines at that time. The administration of remdesivir, itraconazole (EU Clinical Trials Registry: 2020-001243-15), azithromycin (EU Clinical Trials 2020-001614-38), interleukin inhibitors (tocilizumab, siltuximab, anakinra; ClinicalTrials.gov: NCT04330638), inhaled granulocyte-macrophage colony-stimulating factor (sargramostim, ClinicalTrials.gov: NCT04326920) or convalescent plasma (ClinicalTrials.gov: NCT04429854) was considered either in compassionate use or in the context of a clinical trial. Treatment with corticosteroids was given at the physician's discretion. All severe COVID-19 patients received anti-Xa-guided intermediate to high doses of low-molecular-weight heparin; routine thrombosis prophylaxis was prescribed on low-care units. Respiratory management involved oxygen administration based on severity in line with international guidance [19]. Patients with rapidly increasing oxygen need were transferred to a medium/ICU for high-flow oxygen therapy (HFOT) and/or mechanical ventilation. Lung-protective ventilation, including prone positioning, was performed according to guidelines [20]. Both centres had extracorporeal membrane oxygenation (ECMO) available if required.

### Procedures and definitions

Follow-up criteria and procedures were aligned prior to implementation in both centres; some minor differences relate to organisational purposes. We used a standardised data collection tool to gather information from the patient's electronic hospital records on demographics, comorbidities, smoking history, severity of illness, maximum respiratory support requirements and length of hospital (and, if applicable, ICU) stay. At follow-up, patients were offered a comprehensive medical assessment with detailed history and physical examination. Follow-up data were collected prospectively and included: residual symptoms (based on patient's history; for dyspnoea we used the modified Medical Research Council score); blood sampling including full blood count, renal and liver function tests, and SARS-CoV-2 antibody titre; chest CT; PFT including (but not exclusively) forced vital capacity (FVC), forced expiratory volume in 1 s (FEV<sub>1</sub>), total lung capacity (TLC) and diffusing capacity for carbon monoxide ( $D_{LCO}$ ). Values are reported according to European Respiratory Society/American Thoracic Society Guidelines [21–23]; z-scores below  $-1.64$  were considered under the lower limit of normal (LLN). Peripheral muscle strength was measured by hand grip strength (HGS), using a Jamar Hydraulic Hand Dynamometer (JA Preston Corporation, Jackson, MI, USA), and by quadriceps strength (QS), using a fixed handheld dynamometer (Microfet; Biometrics, Amere, The Netherlands) (QS) (in UZG only) according to a standardised protocol as previously described [24, 25]. Measurements were performed by a team of four experienced physiotherapists. The measured values were compared to normative values (percentile 50 value) according to age and sex and expressed as a percentage [26, 27]. We assessed functional exercise capacity by 6-min walk distance (6MWD), following European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines [28]. We considered as impaired values below 80, 70 and 70% predicted for hand grip strength, quadriceps strength and 6-min walk distance, respectively [26, 27, 29]. The presence of SARS-CoV-2 antibodies was determined using the IgG anti-nucleocapsid-based Abbott Architect immunoassay.

CT scans were read by two radiologists, focusing primarily on ground glass opacities, inter/intralobular and irregular lines (reticulations), bronchiectasis, consolidations and fibrosis (12 months). At baseline and 3 months, CT scans were scored based on the percentage of affected parenchyma (0–25) as described by PAN *et al.*, 2020 [30]. Patients without significant radiological abnormalities at 3 months were not scheduled for repeat CT at 12 months.

Health-related quality of life (HRQoL) (Short Form-36 health survey version 1, SF-36) [31] as well as anxiety and depression questionnaires (Hospital Anxiety and Depression Scale, HADS) [32] were completed at follow-up. For the HADS, a cut-off of 8 or more for both depression and anxiety subscales was used. The SF-36 consists of eight domains: physical functioning (PF), physical role functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role functioning (RE), and mental health (MH), with higher scores indicating better health status. The physical component summary (PCS) and mental component summary (MCS) scores were calculated using oblique scoring algorithms [33]. All scores were calculated as norm-based (NB) scores, based on the well-studied USA normative scores (mean score of 50 with 47–53 considered normal and a difference of 10 clinically significant) [31].

Disease severity was defined as per World Health Organisation (WHO) clinical progression scale [34].

### Statistical analysis

Descriptive statistics for continuous variables are presented as median and interquartile ranges (IQR), and as numbers and percentages for categorical variables. Comparisons of numerical data are evaluated using the non-parametric Mann–Whitney U test or paired samples Wilcoxon test, and categorical variables with the Pearson Chi-square test or the Fisher's exact when appropriate. A two-sided p-value of  $<0.05$  was considered statistically significant. Analysis was done using STATA v15 (StataCorp 2017, College Station, TX, USA) and IBM SPSS statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA).

Linear mixed effects models (LME) were used to assess changes over time for repeated measurements of symptoms, functional and pulmonary function tests at 3- and 12-month follow-up. LME account for variability between subjects and variability between repeated measurements in the same subject simultaneously. To assess different trajectories for patients with severe and moderate disease, we included the intercept slope effect as random effects, baseline characteristics, time, group, interaction term of group and time as fixed effects. The variance–covariance structure was fixed to an unstructured matrix, and the random effects and error terms were assumed to have a normal distribution. The nlme package of R software (version 4.0.3) was used to estimate these regression models. Multicollinearity was checked by using variance inflation factors.

To evaluate residual CT abnormalities at 1 year, we have used last observation carried forward (LCOF) in the patients with normal CT at 3 months. We performed a logistic regression model to explore possible predictors for residual CT abnormalities at 12 months.

We adhered to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) recommendations to present our work.

## Results

### Study population

From March through May 2020, 695 patients with COVID-19 were hospitalised in both centres. The patient flow is presented in figure 1. We reviewed 299 patients at a first follow-up at a median 82 days (IQR 60–115) from initial admission; 222 (74%) of whom returned at 1 year (70% of moderate, 84% of severe patients) at a median of 387 days (IQR 363–419).

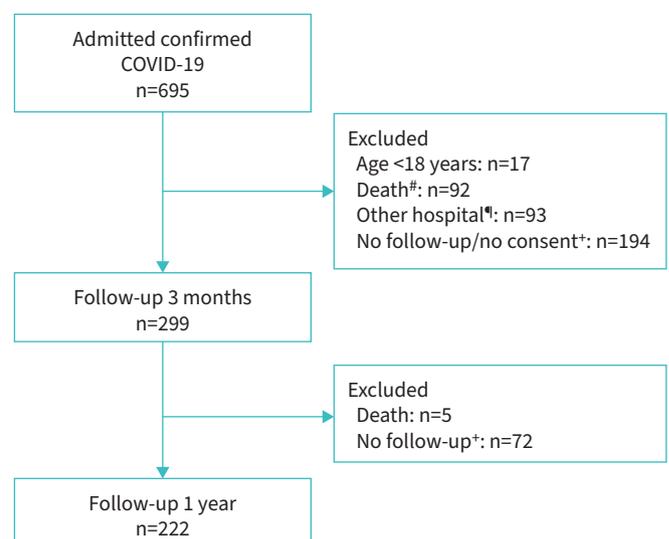
The large majority (91%) had confirmed SARS-CoV-2 infection by RT-PCR on admission; 26 had suggestive chest CTs with no alternative diagnosis and positive SARS-CoV-2 anti-N IgG at follow-up.

Baseline characteristics of the 299 patients are listed in table 1; median age was 59 years, 69% were male, median body mass index (BMI) was 27.4 kg m<sup>-2</sup>, 49% had two or more comorbidities and median length of hospital stay (LOS) was 10 days. Disease severity was moderate in 205 (69%) and severe in 94 (31%) patients. Supplemental oxygen was given to 270 patients (90.3%), including 22 (7.8%) that were treated with HFOT and 72 (24%) mechanically ventilated, 16.6% of whom required ECMO. Thirty-seven (12.4%) (mostly severe) patients received systemic corticosteroids.

A significantly higher proportion of severe patients were male, had a BMI of 30 or more, had two or more comorbidities, and suffered from arterial hypertension or diabetes. Patients with severe COVID-19 had a significantly longer hospital LOS (30 versus 7 days,  $p<0.001$ ). Following discharge from the COVID ward, 31% of patients were referred for rehabilitation, particularly those recovering from severe COVID-19 (62%).

### Clinical data

Results of clinical, respiratory, functional and laboratory assessments at 3 and 12 months are shown in table 2. At 3 and 12 months, respectively, 77.9% and 51.8% reported persisting symptoms: most commonly fatigue (50% and 41%), dyspnoea (47% and 32%) and cognitive symptoms (23% and 28%), more so in severe disease. Smell and taste impairment recovered in most: 7 out of 54 patients reported this at 12 months. Of professionally active patients, 59% had resumed work by 3 months; at 1 year, this had increased to 91%. In LME, a higher BMI ( $p=0.003$ ) correlated with persistent dyspnoea at 1 year; higher BMI ( $p<0.001$ ), corticosteroid therapy ( $p<0.001$ ) and a higher HADS score for anxiety ( $p=0.002$ ) were



**FIGURE 1** Flow chart of COVID-19 patients. Enrolment in follow-up cohort started at 3 months follow-up. #: death prior to discharge; ¶: follow-up at referring hospital or discharge to care home; \*: patients who did not attend or refused follow-up or refused consent for enrolment.

**TABLE 1** Baseline characteristics of all patients included in the follow-up at 3 and 12 months following admission, by initial COVID-19 severity

Characteristics	All	Moderate	Severe	p-value
<b>Participants</b>	299 (100)	205 (68.6) <sup>#</sup>	94 (31.4) <sup>#</sup>	
<b>Age years</b>	59 (52–68)	59 (52–67)	60 (52–70)	0.44
<b>Male sex</b>	205 (69)	127 (62)	78 (83)	<0.001
<b>Ethnicity</b>				0.4
White	281 (94)	190 (92.7)	91 (96.8)	
Arab	11 (3.7)	9 (4.4)	2 (2.1)	
Asian	2 (0.7)	1 (0.5)	1 (1.1)	
Black	5 (1.7)	5 (2.4)	0	
<b>BMI kg m<sup>-2</sup></b>	27.4 (25.0–31.6)	27.0 (25.0–31.0)	28.2 (25.0–32.4)	0.22
BMI >30	99 (33)	61 (30)	38 (40)	0.069
<b>Comorbidities</b>				0.021
Number:				
0	80 (27)	64 (31)	16 (17)	
1	72 (24)	43 (21)	29 (31)	
≥2	147 (49)	97 (47)	50 (53)	
Arterial hypertension	143 (48)	86 (42)	57 (61)	0.003
Hyperlipidaemia	113 (38)	72 (35)	41 (44)	0.16
Diabetes	75 (25)	43 (21)	32 (34)	0.016
Ischaemic heart disease	36 (12)	25 (12)	11 (12)	0.90
Active malignancy	57 (19)	41 (20)	16 (17)	0.54
Chronic lung disease	52 (17)	40 (20)	12 (13)	0.15
OSAS	32 (11)	22 (11)	10 (11)	0.98
Immune suppression	32 (11)	24 (12)	8 (8.5)	0.41
Chronic renal disease	45 (15)	28 (14)	17 (18)	0.32
Heart failure	15 (5)	9 (4.4)	6 (6.4)	0.57
Transplant (organ/other)	9 (3)	9 (4.4)	-	
<b>Acute COVID-19 characteristics</b>				
Diagnosis				
Positive RT-PCR	273 (91)	183 (89)	90 (96)	0.065
Suggestive CT scan	212/234 (91)	140/156 (90)	72/78 (92)	0.41
Oxygen supplementation				
No oxygen	29 (9.7)	29 (14)	-	<0.001
Oxygen by nasal prongs/mask	176 (59)	176 (86)	-	<0.001
HFOT	22 (7.3)	-	22 (23)	<0.001
Invasive mechanical ventilation	72 (24)	-	72 (77)	<0.001
ECMO	12 (4.0)	-	12 (13)	<0.001
Corticotherapy	37 (12)	4 (2.0)	33 (35)	<0.001
Length of hospital stay, days	10 (6–21)	7 (5–11)	30 (18–44)	<0.001
Admission to ICU	108 (36)	16 (7.8)	92 (98)	<0.001
Length of stay at ICU days	14 (7–25)	3 (2–6)	18 (9–28)	<0.001
Referral for rehabilitation				
In-hospital	32 (10.7)	2 (0.1)	30 (31.9)	<0.001
Ambulatory private	38 (12.7)	12 (5.9)	26 (27.7)	<0.001
Ambulatory multidisciplinary	28 (9.3)	7 (3.4)	21 (22.3)	<0.001

Moderate COVID-19 disease severity refers to WHO category 4–5 according to the WHO progression scale (30); severe COVID-19 disease refers to WHO category 6–9. Continuous variables are depicted as median (IQR), dichotomous variables as number of patients (percentage of column total). p-values refer to the statistical significance of the difference between the moderate COVID-19 disease survivors and the survivors of severe disease. BMI: body mass index; OSAS: obstructive sleep apnoea syndrome; RT-PCR: reverse transcription polymerase chain reaction; CT: computed tomography; HFOT: high-flow oxygen therapy; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit. #: number of patients (percentage of row total).

associated with persistence of fatigue; anxiety (p=0.002) and female sex (p=0.035) correlated with persistent cognitive impairment.

### Pulmonary function and functional assessment

PFT and functional assessments and their evolution over time by disease severity are shown in table 2 and figure 2. Spirometry volumes were impaired at 3 months in less than 10%; by 1 year, results had improved

TABLE 2 Clinical, pulmonary, functional and laboratory assessments at 3 and 12 months, by initial COVID-19 severity

Characteristics	3 months outcome				12 months outcome			
	All	Moderate	Severe	p-value	All	Moderate	Severe	p-value
<b>Participants</b>	299 (100)	205 (69) <sup>#</sup>	94 (31) <sup>#</sup>		222 (100)	143 (64) <sup>#</sup>	79 (36) <sup>#</sup>	
<b>Days since admission</b>	82 (60–115)	74 (49–115)	84 (71–116)	0.001	387 (363–419)	389 (366–420)	380 (352–414)	0.26
<b>Days since discharge</b>	58 (43–100)	66 (41–102)	52 (44–76)	0.019	371 (346–400)	379 (358–410)	353 (324–376)	<0.001
<b>Persistent symptoms, any</b>	233 (77.9)	158 (77.1)	75 (79.8)	0.599	155 (51.8)	93 (45.4)	62 (66.0)	0.001
Dyspnoea	140 (47)	89 (43)	51 (44)	0.081	72 (32)	40 (28)	32 (40)	0.065
Fatigue	149 (50)	113 (55)	36 (38)	0.007	90 (41)	52 (36)	38 (47)	0.10
Ageusia/dysgeusia <sup>¶</sup>	19 (26)	17 (28)	2 (15)	0.33	7 (12)	7 (15)	0 (0)	0.58
Cognitive impairment	70 (23)	53 (26)	17 (18)	0.14	64 (28)	47 (32)	17 (21)	0.068
Sleep disturbance	62 (21)	41 (20)	21 (22)	0.66	47 (21)	31 (21)	16 (20)	0.81
Chest pain	38 (13)	29 (14)	9 (9.6)	0.26	2 (2.0)	1 (1.3)	1 (4.5)	0.40
Cough	47 (16)	31 (15)	16 (17)	0.68	28 (12)	14 (9.7)	14 (18)	0.088
Headache	25 (8.4)	20 (9.8)	5 (5.3)	0.19	31 (14)	20 (14)	11 (14)	0.96
Palpitations	19 (6.4)	15 (7.4)	4 (4.3)	0.31	16 (7.1)	10 (6.9)	6 (7.4)	0.89
Sputum production	12 (4.0)	6 (2.9)	6 (6.4)	0.20	6 (2.7)	2 (1.4)	4 (4.9)	0.19
<b>mMRC</b>				0.52				0.078
0	128 (43)	89 (44)	39 (41)		114 (60)	82 (65)	32 (51)	
1	101 (34)	71 (35)	30 (32)		55 (29)	36 (28)	19 (30)	
2	43 (14)	30 (15)	13 (14)		14 (7.4)	7 (5.5)	7 (11)	
3	24 (8.1)	13 (6.4)	11 (12)		4 (2.1)	1 (0.8)	3 (4.8)	
4	2 (0.7)	1 (0.5)	1 (1.1)		3 (1.6)	1 (0.8)	2 (3.2)	
<b>Work resumption</b>	101/171 (59)	84/117 (72)	17/54 (31)	<0.001	139/153 (91)	97/105 (92)	45/51 (88)	0.37
<b>Pulmonary function testing</b>								
% pred FVC, median (IQR)	99 (87–109)	102 (89–112)	90 (83–104)	<0.001	106 (92–114)	107 (96–115)	99 (88–110)	0.022
FVC <80% pred, n (%)	35 (12)	18 (8.9)	17 (18)	0.023	17 (7.6)	10 (6.9)	7 (8.8)	0.61
FVC z-score, median (IQR)	-0.06 (-0.89–0.6)	0.13 (-0.72–0.75)	-0.63 (-1.21–0.3)	<0.001	0.40 (-0.59–0.95)	0.5 (-0.29–1.03)	-0.09 (-0.73–0.77)	0.016
FVC z-score <-1.64	23 (7.8)	11 (5.5)	12 (13)	0.028	11 (4.9)	7 (4.8)	4 (5.1)	>0.99
% pred FEV <sub>1</sub>	98 (87–111)	101 (90–113)	94 (83–106)	0.005	103 (93–115)	104 (93–116)	102 (92–111)	0.21
FEV <sub>1</sub> <80% pred	40 (14)	22 (11)	18 (19)	0.053	19 (8.4)	11 (7.6)	8 (10)	0.53
FEV <sub>1</sub> z-score, median (IQR)	-0.13 (-0.86–0.75)	0.06 (-0.68–0.82)	-0.48 (-1.08–0.4)	0.004	0.2 (-0.52–1.07)	0.28 (-0.45–1.17)	0.13 (-0.71–0.82)	0.22
FEV <sub>1</sub> z-score <-1.64	33 (11)	19 (9.5)	14 (15)	0.17	16 (7.1)	9 (6.2)	7 (8.9)	0.46
% pred TLC	95 (86–106)	100 (89–108)	89 (80–95)	<0.001	97 (89–107)	100 (91–109)	93 (84–100)	<0.001
TLC <80% pred	37 (13)	14 (7.0)	23 (25)	<0.001	23 (11)	10 (7.1)	13 (17)	0.021
TLC z-score, median (IQR)	-0.42 (-1.34–0.56)	0.01 (-0.98–0.78)	-1.06 (-2.05–0.30)	<0.001	-0.29 (-1.1–0.63)	0.05 (-0.92–0.82)	-0.66 (-1.6–0.02)	<0.001
TLC z-score <-1.64	53 (18)	21 (11)	32 (34)	<0.001	34 (16)	16 (11)	18 (24)	0.014
% pred D <sub>LCO</sub>	85 (69–96)	88 (78–98)	71 (56–87)	<0.001	90 (79–99)	93 (84–101)	84 (68–94)	<0.001
D <sub>LCO</sub> <80% pred	117 (39.8)	60 (29.9)	57 (61.3)	<0.001	56 (26.1)	24 (17.3)	32 (42.1)	<0.001
D <sub>LCO</sub> z-score, median (IQR)	-0.99 (-2.16–0.28)	-0.76 (-1.51–0.11)	-2.02 (-3.52–0.87)	<0.001	-0.60 (-1.25–0.07)	-0.46 (-1.06–0.10)	-1.05 (-2.16–0.28)	<0.001
D <sub>LCO</sub> z-score <-1.64	101 (35)	46 (23)	55 (59)	<0.001	45 (21)	19 (14)	26 (35)	<0.001
% pred K <sub>CO</sub>	90 (79–99)	92 (83–101)	84 (70–96)	<0.001	94 (84–105)	96 (87–104)	92 (78–104)	0.068
K <sub>CO</sub> <80% pred	76 (26)	38 (19)	38 (41)	<0.001	36 (17)	15 (11)	21 (28)	0.002
K <sub>CO</sub> z-score, median (IQR)	-0.67 (-1.42–0.01)	-0.56 (-1.19–0.07)	-1.07 (-1.99–0.27)	<0.001	-0.36 (-1.03–0.32)	-0.3 (-0.84,0.31)	-0.50 (-1.46,0.37)	0.12
K <sub>CO</sub> z-score <-1.64	56 (19)	26 (13)	30 (32)	<0.001	23 (11)	11 (8.0)	12 (16)	0.074
<b>Functional assessment</b>								

Continued

TABLE 2 Continued

Characteristics	3 months outcome				12 months outcome			
	All	Moderate	Severe	p-value	All	Moderate	Severe	p-value
6MWD m	557 (466–630)	578 (476–645)	525 (442–600)	0.004	606 (515–666)	614 (516–675)	583 (503–652)	0.092
% pred 6MWD	83 (73–92)	86 (75–94)	77 (68–88)	<0.001	89 (81–98)	90 (82–98)	88 (80–96)	0.26
6MWD <70% pred	57 (20)	31 (16)	26 (29)	0.012	16 (7.5)	10 (7.1)	6 (8.1)	0.80
% pred HS	100 (83–116)	104 (90–122)	88 (74–104)	<0.001	117 (100–134)	118 (100–135)	112 (96–134)	0.21
HGS <80% pred	63 (22)	25 (13)	38 (42)	<0.001	14 (6.6)	10 (7.1)	4 (5.6)	0.78
% pred QS	66 (56–79)	69 (58–83)	59 (49–67)	0.003	74 (68–88)	75 (65–91)	73 (69–78)	0.62
QS <70% pred	77 (60.2)	50 (52.1)	27 (84.4)	0.001	31 (32.0)	25 (32.5)	6 (30)	x
<b>HADS</b>								
Anxiety ≥8	53 (21)	41 (24)	12 (14)	0.070	40 (19)	29 (20)	11 (15)	0.39
Depression ≥8	31 (12)	26 (15)	5 (6.0)	0.032	32 (15)	25 (17)	7 (9.7)	0.14
<b>Laboratory results</b>								
C-reactive protein	1.7 (1.0–3.8)	1.6 (1.0–3.4)	1.7 (1.0–4.8)	0.34	1.7 (1.0–3.3)	1.4 (1.0–3.2)	2.0 (1.0–4.0)	0.11
CRP >6 mg mL <sup>-1</sup>	46 (15)	30 (15)	16 (21)	0.62	33 (15)	17 (12)	16 (21)	0.095
Haemoglobin g dL <sup>-1</sup>	14 (12.9–15.1)	14.1 (13.4–15.1)	13.7 (12.4–14.6)	0.012	14.6 (13.6–15.6)	14.6 (13.7–15.6)	14.6 (13.5–15.7)	0.98
Haemoglobin <10 mg dL <sup>-1</sup>	3 (1.6)	1 (0.8)	2 (2.8)	0.56	–	–	–	
HbA1c %	5.7 (5.4–6.0)	5.7 (5.5–6.0)	5.7 (5.2–6.0)	0.18	–	–	–	
eGFRs mL/min/1.73m <sup>2</sup>	85 (71–90)	85 (71–90)	81 (71–96)	0.39	81 (69–90)	84 (72–90)	76 (65–88)	0.015
eGFR <60 mL/min/1.73m <sup>2</sup>	26 (14)	16 (14)	10 (14)	>0.99	35 (16)	21 (15)	14 (19)	0.52
SARS-CoV-2 anti-N antibody	166 (87)	95 (81)	71 (97)	0.001	117 (64)	73 (62)	44 (69)	0.35

Moderate COVID-19 disease severity refers to WHO category 4–5 according to the WHO progression scale (30); severe COVID-19 disease refers to WHO category 6–9. Continuous variables are depicted as medians (IQR), dichotomous variables as number of patients (percentage of column total). p-values refer to the statistical significance of the difference between moderate COVID-19 disease and severe disease. mMRC: modified Medical Research Council; FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in 1 s; TLC: total lung capacity; D<sub>LCO</sub>: diffusing capacity for carbon monoxide; K<sub>CO</sub>: transfer coefficient of the lung for carbon monoxide; pp: per cent predicted; 6MWD: 6 min walk distance; HGS: hand grip strength; QS: quadriceps strength; HADS: hospital anxiety and depression score; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate.<sup>#</sup>: number of patients (percentage of row total); <sup>\*</sup>: only 73 patients at 3 months with known problems of dysosmia/dysgeusia in the acute phase, only 56 patients at 1 year.

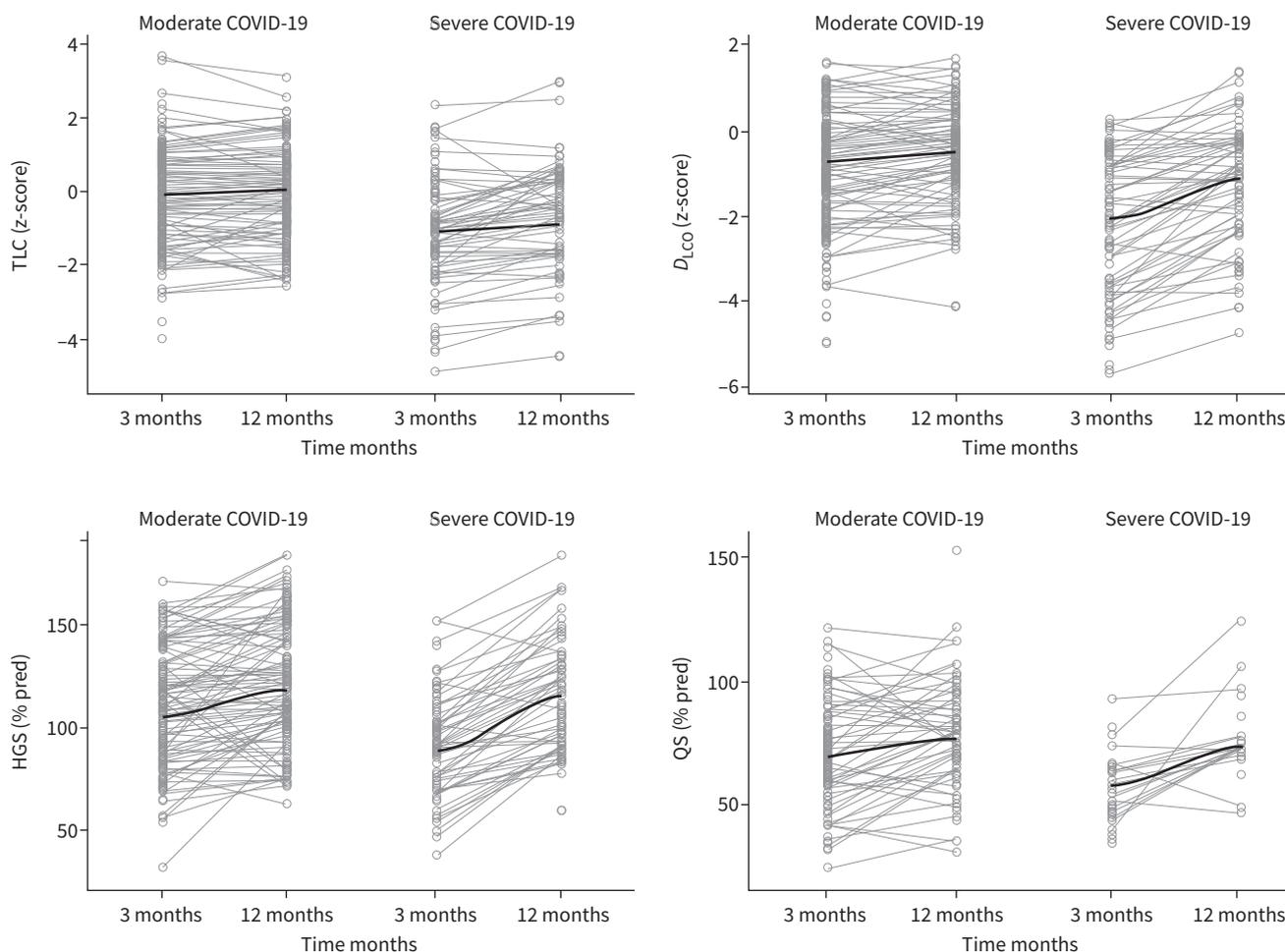
across the whole range: FVC from 7.8% to 4.5% and FEV<sub>1</sub> from 11% to 7.1% of patients with values below LLN (table 2).

PFT results most frequently impaired were  $D_{LCO}$  and TLC. At 3 months,  $D_{LCO}$  and TLC were below the LLN in 35% and 18%, decreasing to 21% and 16% at 1 year. In patients with severe disease,  $D_{LCO}$  and TLC were below the LLN at 3 and 12 months in 59% and 34%, and 35% and 24%, respectively (figure 2). Impaired TLC at 12 months correlated mainly with severe disease. Factors contributing to poor recovery of  $D_{LCO}$  over time were, besides disease severity, female sex, longer hospital stay, pre-existing chronic lung disease and smoking (table 3).

Overall, functional assessments through 6MWD, HGS and QS were impaired in 20% or more at 3 months. A significantly higher proportion of severely diseased patients (29%, 42%, 84% versus 16%, 13%, 52% of moderate) had reduced 6MWD, HGS and QS at 3 months. A significant recovery was noted between 3 and 12 months for all, although the recovery potential seemed higher after severe disease for all three measurements (figure 3). Additional predictors (table 3) for poor 6MWD recovery were higher BMI ( $p < 0.001$ ) and anxiety ( $p = 0.004$ ). Higher BMI had a similar effect on QS recovery ( $p < 0.001$ ).

### Computed tomography assessment

Chest CTs improved gradually over time as reflected in a significant reduction in CT severity scores between baseline and 3-month follow-up (table 4). Overall, 139 (47%) had a normal chest CT at 3 months;



**FIGURE 2** Longitudinal trajectories of total lung capacity (TLC), diffusing capacity for carbon monoxide ( $D_{LCO}$ ), 6-min walk distance (6MWD), hand grip strength (HGS) and quadriceps strength (QS) at 3 and 12 months by disease severity. Moderate and severe cases with their corresponding trajectory plot are presented. The figure shows mean $\pm$ SD of each time point. For TLC and  $D_{LCO}$  the x-axis depicts the z-score, lower than  $-1.64$  being considered abnormal. For 6MWD, QS and HGS, the x-axis depicts the % predicted values with respectively below 70, 70 and 80% being considered abnormal. The effect plot illustrates the evolution of the values between 3 and 12 months.

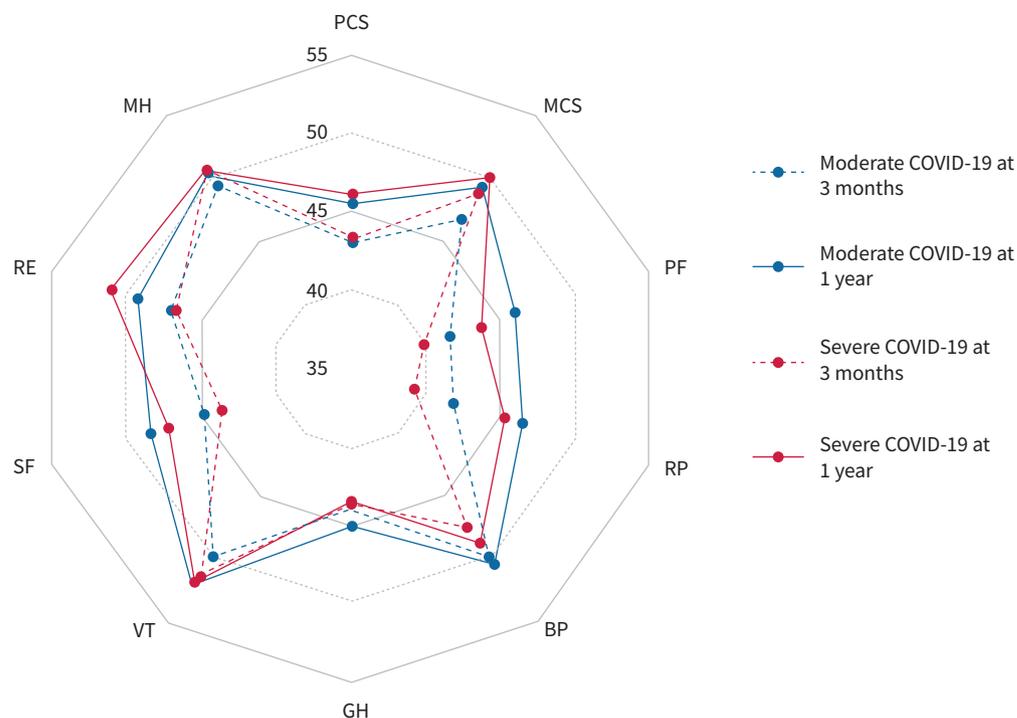
**TABLE 3** Results of multivariable linear mixed effects models for total lung capacity (TLC), diffusing capacity for carbon monoxide ( $D_{LCO}$ ), 6-min walk distance (6MWD), quadriceps and handgrip strength

Predictors	Pulmonary functions								
	$D_{LCO}$			TLC			$K_{CO}$		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value	Estimate	95% CI	p-value
(Intercept)	-1.99	-2.74--1.23	<b>&lt;0.001</b>	0.48	-0.30--1.27	0.227	-2.14	-2.77--1.51	<b>&lt;0.001</b>
Time	0.25	0.09--0.41	<b>0.002</b>	0.04	-0.06--0.14	0.445	0.13	0.04--0.23	<b>0.005</b>
Severe disease	-0.94	-1.36--0.51	<b>&lt;0.001</b>	-0.72	-1.16--0.29	<b>0.001</b>	-0.38	-0.73--0.02	<b>0.037</b>
Female sex	-0.48	-0.79--0.17	<b>0.003</b>	0.32	-0.01--0.64	0.054	-0.20	-0.46--0.06	0.137
Chronic lung disease	-0.59	-0.97--0.22	<b>0.002</b>	-0.09	-0.47--0.30	0.661	-0.46	-0.77--0.15	<b>0.004</b>
BMI	0.06	0.03--0.08	<b>&lt;0.001</b>	-0.02	-0.05--0.00	0.098	0.07	0.05--0.09	<b>&lt;0.001</b>
Smoking	-0.32	-0.61--0.03	<b>0.030</b>	0.05	-0.25--0.34	0.762	-0.41	-0.65--0.18	<b>0.001</b>
Referral rehabilitation	0.00	-0.36--0.36	0.987	0.29	-0.09--0.66	0.133	-0.20	-0.50--0.10	0.188
Corticosteroids	-0.22	-0.73--0.29	0.392	-0.29	-0.82--0.24	0.287	-0.20	-0.62--0.23	0.363
Length of stay	-0.02	-0.03--0.00	<b>0.011</b>	-0.01	-0.03--0.00	0.065	-0.01	-0.02--0.00	0.193
Time * severe disease	0.67	0.41--0.94	<b>&lt;0.001</b>	0.27	0.09--0.44	<b>0.003</b>	0.31	0.15--0.47	<b>&lt;0.001</b>
sd (intercept)	1.19			1.25			1.02		
sd (slope)	0.77			0.44			0.42		
Cor (intercept slope)	-0.34			-0.33			-0.43		
sd (observations)	0.63			0.55			0.52		

Predictors	Functional tests								
	6MWD			HGS			Qceps		
	Estimates	95% CI	p-value	Estimates	95% CI	p-value	Estimates	95% CI	p-value
(Intercept)	105.79	96.56--115.02	<b>&lt;0.001</b>	104.13	88.22--120.05	<b>&lt;0.001</b>	105.88	89.12--122.63	<b>&lt;0.001</b>
Time	4.58	2.75--6.41	<b>&lt;0.001</b>	11.76	7.56--15.96	<b>&lt;0.001</b>	7.42	3.36--11.49	<b>&lt;0.001</b>
Severe disease	-4.59	-9.88--0.70	0.089	-15.23	-23.76--6.69	<b>0.001</b>	-4.49	-15.26--6.28	0.411
Female sex	0.09	-3.85--4.04	0.963	2.59	-4.18--9.36	0.452	5.53	-1.41--12.48	0.117
HADS Anxiety	-0.67	-1.13--0.22	<b>0.004</b>	-0.90	-1.69--0.11	<b>0.026</b>	-0.41	-1.20--0.39	0.315
BMI	-0.56	-0.85--0.26	<b>&lt;0.001</b>	0.11	-0.40--0.63	0.663	-1.10	-1.66--0.54	<b>&lt;0.001</b>
Smoking	-1.06	-4.34--2.22	0.524	7.98	2.25--13.71	<b>0.007</b>	-1.51	-7.20--4.18	0.601
Referral rehabilitation	-3.13	-7.22--0.96	0.133	1.48	-5.73--8.70	0.686	-9.78	-16.78--2.78	<b>0.007</b>
Corticosteroids	-3.54	-9.32--2.24	0.229	-21.84	-32.05--11.64	<b>&lt;0.001</b>	-7.35	-17.48--2.79	0.154
Length of stay	-0.05	-0.19--0.10	0.510	0.12	-0.12--0.37	0.324	0.05	-0.17--0.27	0.659
Time * severe disease	6.07	2.97--9.18	<b>&lt;0.001</b>	14.39	7.24--21.55	<b>&lt;0.001</b>	8.14	-1.12--17.41	0.084
sd (intercept)	14.64			21.48			16.32		
sd (slope)	8.54			20.07			15.67		
Cor (intercept slope)	-0.64			-0.21			-0.42		
sd (observations)	2.09			2.91			2.51		

The linear mixed effects models include coefficient estimations, confidence intervals and p-values reflecting the effect of the risk factors on the change of each variable over time from 3 to 12 months following admission. Statistically significant values are presented in bold.  $K_{CO}$ : transfer coefficient of the lung for carbon monoxide; BMI: body mass index; Corticosteroids: treatment with corticosteroids during hospitalisation; sd: standard deviation; Cor: correlation; HADS Anxiety: anxiety score of the Hospital Anxiety and Depression Score.



**FIGURE 3** Results of Short Form-36 health survey—component scores (physical (PCS) and mental (MCS)) and mean domain scores represented as norm-based values based on the USA normal values, with mean 50 (47–53) as normal and  $1_{SD}$  (difference of 10), is deemed as clinically significant. Represented according to disease severity and time point of measurement, including only the patients with two measurements (3 months and 1 year;  $n=197$  (of whom moderate  $n=128$  and severe  $n=69$ )). PF: physical functioning; RP: physical role functioning; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: emotional role functioning; MH: mental health.

at 1 year, this increased to 55%. Commonest abnormalities at 3 months were multifocal ground glass opacities and reticulations. Residual CT changes at 1 year were mostly mild; hence, CT severity score was no longer deemed applicable. CT findings consistent with fibrosis were present in 23 (10%) at 1 year, 19 (24%) of whom with severe disease; none were suggestive of disease progression.

Disease severity, age, longer hospital stay and a high CT severity score at baseline (all  $p \leq 0.001$ ) predicted persistent CT changes at 1 year. In univariate analysis, residual CT anomalies did not correlate with symptoms such as dyspnoea or fatigue at 3 and 12 months ( $p=0.155$ ;  $p=0.206$ ); they did inversely correlate with  $D_{LCO}$  ( $p < 0.001$ ;  $p=0.015$ ) and 6MWD ( $p=0.021$ ;  $p=0.014$ ) at both time points.

#### Health-related quality of life

Figure 3 shows the HRQoL data measured by the SF-36. At 3 months, we noted lower mean NB scores for all domains, especially in the physical domains (mean NB score PCS of 43) with an NB score of 40 in both PF and RP; at 12 months these improved to 46, 45 and 46, respectively. The MCS was not significantly reduced (47 and 49 at 3 and 12 months, respectively). There was a positive evolution in HRQoL (PCS  $p < 0.001$  and MCS  $p=0.001$  respectively with related samples Wilcoxon statistic) between 3 and 12 months, irrespective of disease severity. People who participated in rehabilitation significantly improved their HRQoL (PCS  $p=0.008$  and MCS  $p=0.024$  with Mann–Whitney U statistic) compared to those who did not. Generally, women experienced more limitations than men (at 3 months for PCS, MCS and all domains  $p \leq 0.005$ ; at 1 year this difference persisted except for RP and RE), but with similar subjective recovery trajectories between 3 and 12 months.

#### Laboratory data

At 3 months, 87% had positive anti-N SARS-CoV-2 antibodies, which reduced to 64% at 1 year. C-reactive protein had normalised in the majority (85%), as did complete blood count, renal and liver

TABLE 4 Temporal evolution of computed tomography at baseline, 3 and 12 months, by COVID-19 severity

Characteristics	Baseline				3 months post-discharge				12 months post-discharge			
	All	Moderate	Severe	p-value	All	Moderate	Severe	p-value	All	Moderate	Severe	p-value
CT available <sup>#</sup>	234 (78)	156 (76)	78 (83)	0.18	297 (99)	203 (99.5)	94 (99)		105 (47.3)	48 (33.5)	57 (72.2)	
CT severity score	11 (7–14)	9 (6–13)	14 (10–17)	<0.001	4 (1–8)	3 (0–6)	7 (3–12)	<0.001	–	–	–	
<b>Anomalies</b>												
Normal findings	1 (0.3)	1 (0.5)	0 (0)	0.41	139 (46.8)	113 (55.7)	26 (27.6)	<0.001	37 (35.2)	20 (41.7)	17 (35.2)	0.21
GGO	215 (91)	139 (89)	76 (96)	0.065	137 (46.1)	76 (37.4)	61 (64.9)	<0.001	39 (37.1)	18 (37.5)	21 (36.8)	0.94
Crazy paving	35 (15)	24 (15)	11 (14)	0.77	2 (0.7)	1 (0.5)	1 (1.1)	0.57	–	–	–	
Consolidation	123 (52)	76 (49)	47 (59)	0.12	19 (6.4)	9 (4.4)	10 (11)	0.042	1 (1)	1 (2)	0 (0)	0.46
Reticulations	122 (52)	80 (51)	42 (53)	0.78	107 (36)	56 (27.6)	51 (54.3)	<0.001	58 (55.2)	22 (45.8)	36 (63.2)	0.08
Bronchiectasis	85 (36)	47 (30)	38 (48)	0.007	49 (16.5)	20 (9.8)	29 (30.8)	<0.001	21 (20)	7 (14.6)	14 (24.6)	0.2
									221 <sup>¶</sup>	142 <sup>¶</sup>	79 <sup>¶</sup>	
Normal at 1 year follow-up <sup>+</sup>	–	–	–		–	–	–		121 (54.7)	92 (64.7)	29 (36.7)	<0.001
Fibrosis at 1 year follow-up <sup>§</sup>	–	–	–		–	–	–		23 (10.4)	4 (2.8)	19 (24.1)	0.002

At baseline 234 patients had chest CT, 297 at 3 months follow-up and only 105 at 1 year. Patients with normal CT or minor radiological abnormalities at 3 months did not undergo repeat imaging at 1 year. We also included an estimation of normalised chest CTs including patients returning at 1 year who already had a normal CT at 3 months. It is possible for a single patient to have multiple residual radiological anomalies. Continuous variables are depicted as medians (IQR), dichotomous variables as number of patients (percentage of column total). p-values refer to the statistical significance of the difference between moderate and severe COVID-19 disease survivors. At 12 months, the CT severity score was deemed irrelevant by the radiologists and no longer scored. CT: computed tomography; GGO: ground glass opacities. <sup>¶</sup>: number of scanned patients (percentage of total patients in this group); <sup>¶</sup>: we also included the number of patients who had a CT at 1 year or 3 months; <sup>+</sup>: including normal chest CT of patients returning at 1 year who already had a normal CT at 3 months; <sup>§</sup>: percentage calculated on total of individuals who got chest CT at 3 months or 1 year.

function tests and HbA1c. At 3 months, 26 (14%) patients had an eGFR below 60 mL min<sup>-1</sup>/1.73 m<sup>2</sup>; this increased to 35 (16%) at 1 year unrelated to disease severity.

## Discussion

To the best of our knowledge, this is the first prospective multicentre European study comprehensively reporting on clinical, radiological, functional and HRQoL outcomes of hospitalised, moderate and severe, COVID-19 patients up to 12 months following discharge. Although a considerable proportion of patients report symptoms of fatigue, dyspnoea and cognitive dysfunction at 1 year, self-reported quality of life did not indicate major limitations. A minority had measurable functional impairment at 1 year. A higher anxiety score and BMI were predictors of poor clinical and functional recovery. Pulmonary function recovered over time for most, but in one out of four,  $D_{LCO}$  remained below the LLN at 1 year. CT abnormalities improved remarkably in the first 3 months; residual changes suggestive of non-progressive fibrosis were nevertheless present in 10% by 12 months. Initial disease severity was a major predictor.

Recovery was slower than observed after community-acquired pneumonia [35] but not unexpected as previously described following viral outbreaks of H1N1 influenza virus and SARS-coronavirus [2]. Symptoms such as fatigue, dyspnoea and cognitive impairment were the commonest to persist, even up to 12 months, in agreement with prior reports [5–12]. The frequency of ongoing symptoms varies in the literature, but in several studies almost 50% of COVID-19 patients report at least one persisting symptom after 12 months (irrespective of disease severity) [8, 11, 12].

PFT abnormalities, particularly impaired  $D_{LCO}$  and TLC, have been reported in other coronavirus-induced syndromes such as SARS and MERS [2]. Although recovery occurs, impaired  $D_{LCO}$  could last for months, even years after discharge with little functional repercussions [36]. In accordance with HUANG *et al.*, our findings confirm recovery of pulmonary function over time; however, reduced TLC and  $D_{LCO}$  are noted up to 12 months. Although of unclear clinical significance, they correlate with disease severity and length of stay [6, 13, 37–39] after correction for smoking, sex and pre-existing respiratory diseases. The underlying pathophysiological mechanism remains elusive; inflammatory interstitial lung disease and pulmonary (micro)vascular damage have been hypothesised [40].

We documented functional impairment (reduced 6MWD and muscle strength) in a substantial proportion of patients at 3 months but to much less extent at 1 year, in line with SARS outcomes [2]. The prolonged hospital stay in strict isolation conditions with little exercise and the use of neuromuscular blocking agents

in critical cases may all contribute to profound muscle weakness and deconditioning at discharge [7, 41, 42]. Increased anxiety levels, as documented by HADS scores, also impacted functional recovery, in keeping with other cohorts [7, 8]. When left unaddressed, these symptoms considerably interfere with activities of daily living, reflected in a poor general health score and prolonged absenteeism. In our study we opted to do a first evaluation at 6–12 weeks after discharge based on consensus, limited literature [15, 43] and our own experience in pulmonary rehabilitation. The early recommendation for timely referral to multidisciplinary rehabilitation services [15, 16] remains relevant: as our data show, even beyond 3 months following acute disease, substantial recovery is possible, especially in severe disease patients. The benefits of multidisciplinary rehabilitation in physical and emotional well-being have been documented particularly for those who suffered severe to critical COVID-19 [44] and is also apparent in our HRQoL results. Milder cases may also benefit from a multidisciplinary rehabilitation intervention, but this remains to be ascertained [11, 14].

Studies examining temporal evolution of pulmonary CT changes of COVID-19 have revealed rapid resolution of ground glass opacities in the majority of cases [5, 8, 13]. Residual interstitial changes have been reported in 26–100% at 3-month follow-up and in 24–55% at 1-year follow-up, particularly in the mechanically ventilated, which suggests some ventilation-associated lung injury [5, 8, 13, 37, 38] and has raised concern about post-COVID lung fibrosis. Consistent with current and previous SARS-CoV infections, we observed persistent interstitial changes suggestive of fibrosis – although mostly subtle – in 10% of COVID-19 survivors at 1 year of follow-up, particularly in severe disease and in older age [2]. It remains an unresolved matter whether fibrosis can be prevented by treatment early in the course of disease. Radiological abnormalities correlated with PFT impairment but not with respiratory symptoms.

HRQoL questionnaires, such as the SF-36, complement symptom reporting. Results surprisingly seemed unrelated to initial disease severity. In line with the COMEBAC study and LATRONICO *et al.* [9], scores in our cohort were lowest in the physical domains, specifically PF and RP, at 3 months but improved significantly at 12 months [45].

The major strength of our study is that it provides a comprehensive and detailed insight into the evolution of post-acute sequelae in a representative cohort of COVID-19 patients admitted to hospital during the first wave of the pandemic in Europe, over the period of 1 year following discharge. The cohort is multicentric, sizeable and covers a wide variety of severities of disease. It enabled us to answer some priority research questions as to exploring the correlation between WHO COVID severity score on admission and long-term symptoms, and correlations between imaging abnormalities and long-term symptoms.

Our study also has some limitations. We did not capture data on premorbid status, which may influence the interpretation of post-COVID functional outcome (possible recall bias). To mitigate, we thoroughly reviewed medical files of admitted patients, which enabled us to record comorbidities and adjust for these when analysing outcomes. The study setup introduced a selection bias since not all COVID-19 survivors were either invited or returned for follow-up (reasons outlined in the flow chart); however, more than two-thirds of the ICU-patients did. Assuming the latter had worse pre-COVID performance status, it could have resulted in an overestimation of the prevalence of medium to long-term sequelae after COVID-19. Additionally, survival bias was inevitable: the limited number of patients showing radiographic hallmarks of pulmonary fibrosis does not preclude the occurrence of irreversible pulmonary damage in non-survivors. Furthermore, the patients of this study experienced their COVID-19 episode in the pre-dexamethasone era: only a minority of (mostly critically ill) patients were treated with corticosteroids upon the treating physician's discretion. The potential influence of corticosteroid treatment on medium- to long-term patient's functionality, therefore, remains to be assessed. Third, only part of the study population had quadriceps strength measurements, as this was exclusively done in one centre (UZG) for logistical matters. We believe these results are representative given similar patient population and disease characteristics in both centres. Testing was not necessarily performed by the same physiotherapists on different occasions. However, the team performing the tests has extensive experience in voluntary muscle strength measurement in the pulmonary rehabilitation programme. Limb muscle strength measurements have shown good to very good inter- and intra-observer reliability provided strict adherence to test procedures and positions are followed, implying that a meaningful effect on our outcomes is unlikely [46].

Based on our comprehensive assessment of the clinical, functional and radiological outcome of both moderate and severe COVID-19 survivors, we conclude that a substantial proportion of patients experience physical limitations at 3 months. However, our disease-specific outcome data strengthen our belief that physical recovery at 12 months after COVID-19 is reassuring in most cases. Hence, we would recommend timely follow-up to identify those in need of additional care and rehabilitation. Nevertheless, we

acknowledge the potential risk of prolonged disability due to – not routinely measurable, largely unexplained – long-term post-acute COVID sequelae, which deserves further research into mechanisms and management.

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Availability of data and materials: The dataset used and/analysed during the current study is available from the corresponding author on reasonable request.

Author contributions: Y. Vande Weygaerde, N. Lorent and E. Claeys contributed equally to this work. Y. Vande Weygaerde, N. Lorent, I.G. Caamano Fajardo, E. Van Braeckel, W. Janssens, R. Gosselink, G. Hermans, B. Salhi and E. Dorem conceived and designed the study, and took responsibility for the integrity of data and the accuracy of the data analysis. All authors had full access to all the data in the study. Y. Vande Weygaerde, N. Lorent, E. Claeys and E. Van Braeckel drafted the manuscript; all co-authors contributed to reviewing and editing the manuscript. Y. Vande Weygaerde, N. Lorent, I.G. Caamano Fajardo, E. Claeys and H. Demeyer performed the analysis. Y. Vande Weygaerde, N. Lorent, I.G. Caamano Fajardo and E. Claeys designed the figures. Y. Vande Weygaerde, N. Lorent, E. Van Braeckel, C. Bosteels, L. Godinas, L. Dupont, P. Van Bleyenbergh, W. Janssens, A. Heyns, N. De Vos, W. De Wever, B. Salhi, C. Schepers, I. Gyselinck and S. Everaerts completed the follow-up work. Y. Vande Weygaerde, E. Claeys, N. Lorent, A. Heyns, S. Everaerts, B. Salhi, C. Bosteels, E. Van Braeckel and S. Verschraegen collected the data. All authors critically revised the manuscript for important intellectual content and gave final approval for this version to be published.

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