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Pulmonary Recovery 12 Months after Non-Severe and Severe COVID-19: The Prospective Swiss COVID-19 Lung Study

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Keywords
SARS-CoV-2 · Long COVID · COVID-19 sequelae · SARS-CoV-2 radiological sequelae · SARS-CoV-2 lung functional sequelae

Abstract

Background: Lung function impairment persists in some patients for months after acute coronavirus disease 2019 (COVID-19). Long-term lung function, radiological features, and their association remain to be clarified. Objectives: We aimed to prospectively investigate lung function and radiological abnormalities over 12 months after severe and non-severe COVID-19. ***Methods:*** 584 patients were included in the Swiss COVID-19 lung study. We assessed lung function at 3, 6, and 12 months after acute COVID-19 and compared chest computed tomography (CT) imaging to lung functional abnormalities. ***Results:*** At 12 months, diffusion capacity for carbon monoxide ($DLCO_{corr}$) was lower after severe COVID-19 compared to non-severe COVID-19 (74.9% vs. 85.2% predicted, *p*

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< 0.001). Similarly, minimal oxygen saturation on 6-min walk test and total lung capacity were lower after severe COVID-19 (89.6% vs. 92.2%, $p = 0.004$, respectively, 88.2% vs. 95.1% predicted, $p = 0.011$). The difference for forced vital capacity (91.6% vs. 96.3% predicted, $p = 0.082$) was not statistically significant. Between 3 and 12 months, lung function improved in both groups and differences in DLCO between non-severe and severe COVID-19 patients decreased. In patients with chest CT scans at 12 months, we observed a correlation between radiological abnormalities and reduced lung function. While the overall extent of radiological abnormalities diminished over time, the frequency of mosaic attenuation and curvilinear patterns increased. ***Conclusions:*** In this prospective cohort study, patients who had severe COVID-19 had diminished lung function over the first year compared to those after non-severe COVID-19, albeit with a greater extent of recovery in the severe disease group.

Introduction

Acute manifestations and treatments for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been extensively studied, but reports on the long-term outcomes after SARS-CoV-2 infection only begin to emerge [1], and evaluation of different patients' cohorts are of interest to improve our understanding of pulmonary long-term impairment after coronavirus disease 2019 (COVID-19). At the time of hospital discharge following COVID-19, the most frequent lung functional abnormalities are impairment of diffusion capacity for carbon monoxide (DLCO) and a restrictive ventilatory pattern [2, 3]. We recently reported the association of the initial severity of COVID-19 with lower DLCO and increased mosaic attenuation pattern with hypoattenuated areas on chest computed tomography (CT) 4 months after acute infection [4]. Other studies confirmed that reduced DLCO and oxygenation impairment four to 6 months after COVID-19 infection depend on initial disease severity [5–9].

Data on long-term respiratory sequelae beyond 6 months after COVID-19 infections are only beginning to emerge. Although most survivors eventually recover, dyspnea and reduced DLCO persist in a subgroup of patients between 6 and 12 months after the acute phase of the disease [1, 10]. Fibrotic-like changes (e.g., parenchymal bands, irregular interfaces, traction bronchiectasis, honeycombing) were observed on chest CT at 6 months in roughly one-third of patients and ground glass opacities (GGO) and interstitial thickening in about one quarter [7]. However, the relationship between radiological abnormalities and lung functional impairment remains unclear [11]. We aimed to compare respiratory impairment 12 months after acute COVID-19 in patients who initially suffered from severe disease (admission to intensive care unit [ICU] and/or acute respiratory distress syndrome [ARDS]) with those who had milder disease and to determine the relationship between functional and radiological abnormalities.

Materials and Methods

Study Population and Follow-Up

Patients included in the current analyses were participants of the prospective multicentre observational Swiss COVID-19 lung cohort study (Swiss COVID lung study). Patients were prospectively recruited in 9 centres from May 1, 2020 to December 31, 2021, following acute SARS-CoV-2 infection. Initial findings of this study and details on participating centres have been previously published [4]. Severe COVID-19 was defined as admission to an ICU and/or a diagnosis of ARDS. This approach considered that ARDS patients were taken care of depending on their severity degree and comorbidities not only in ICU, but also in intermediate care or general wards. Non-severe COVID-19 excluded both ICU admission and ARDS. Patient visits took place at 3, 6, and 12 (+/−2) months after initial COVID-19 symptoms, with dropouts of participants who recovered and no longer required respiratory follow-up. All participants provided written informed consent, and the study was approved by the Central Ethics Committee and the respective Local Cantonal Ethics Committees (KEK 2020-00799). The study is registered at clinicaltrial.gov (NCT04581135).

Clinical Outcomes

All tests were systematically performed at the first visit, then during follow-up based on clinical indication, and according to international and national recommendations for pulmonary long COVID [12]. Lung function tests included measurement of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and DLCO adjusted for haemoglobin level ($DLCO_{corr}$), performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards [13, 14]. Six-minute walk tests (6MWTs) [15] and arterial blood gas analysis were performed if clinically indicated. Minimal and maximal transcutaneous oxygen during 6MWT were reported as SpO_2 (max) and SpO_2 (min). Oxygen desaturation (ΔSpO_2) during 6MWT was calculated as follows: (SpO_2 [max] – SpO_2 [min]).

Baseline demographics and comorbidities before COVID-19 were collected retrospectively from medical records and based on clinical history. Respiratory symptoms and new diagnoses were documented during each visit using standardised questionnaires.

Chest CT Acquisition, Post-Processing, and Image Analysis

Chest CT images were collected from the participating radiology centres, Bern and Lausanne. Chest CT images were pseudo-

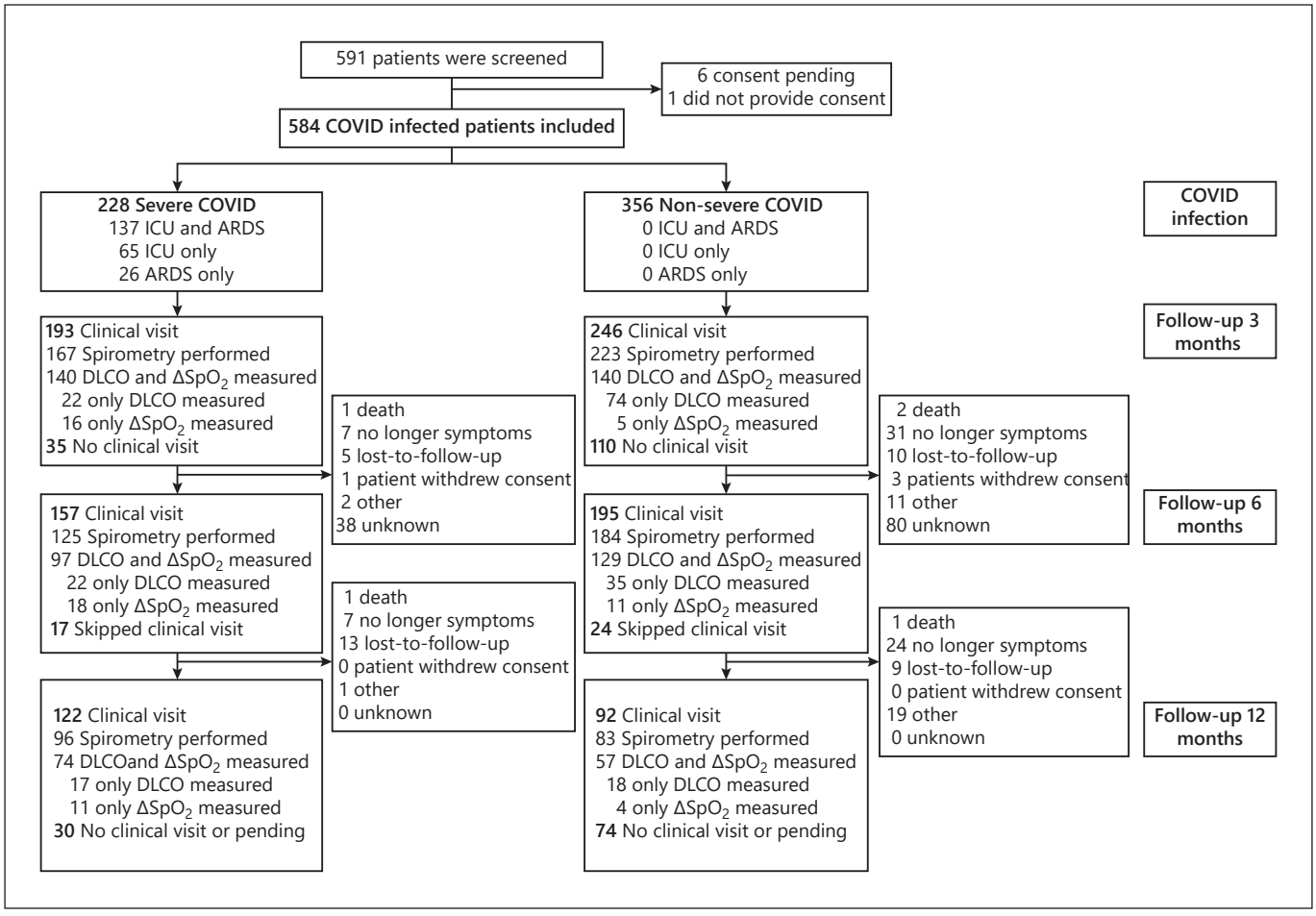

Fig. 1. Flow chart of available clinical and lung function data for all study visits from the prospective Swiss COVID-19 lung study are shown. ARDS, acute respiratory distress syndrome; COVID, coronavirus disease; DLCO, diffusion capacity for carbon monoxide; ICU, intensive care unit; SpO_2, oxygen saturation.

anonymized in the local picture archiving and communication system. Two subspecialized chest radiologists (LE, CB) from tertiary care centres performed a consensus read-out, blinded to the clinical status of the patients. Disagreement between the two readers was solved by discussion. Details on the exact procedure have been previously reported [4].

Chest CT scans were acquired at the end of full inspiration according to local protocols in Bern and Lausanne. All available chest CT scans were reconstructed with 1 mm slice thickness with lung- and soft tissue kernels. Iodine contrast agents were only applied if pulmonary embolism was clinically suspected. Multi-planar reconstructions were used in axial, coronal, and sagittal planes, along with maximum-intensity projections and minimum-intensity projections (minIP) post-processing with soft kernel. Lung analysis employed a regular as well as an adapted windowing in width and level to optimize differences in contrast. All images were stored in the local picture archiving and communication system.

To assess the spread of a pattern, the radiological observers used a semiquantitative CT score calculated per each of the six lobes (with the left upper lobe and lingula counted separately) based on the extent of radiological involvement (0: 0%; 1: <5%; 2: 5–25%; 3: 26–50%; 4: 51–75%; 5: >75%; range 0–5; global score 0–25) [16]. The severity score was normalized to a volume score (score 1 grouped with score 2) leading to four categories: <25%, 26–50%, 51–75%, and ≥75% of affected volume. The number of lobes affected multiplied with the individual volume score led to a maximum of 24 points per patient (6 lobes *x* 4 scores, according to radiological standards).

Statistical Analysis

Baseline characteristics were compared between patients with initial severe and non-severe disease. Differences were assessed using χ^2 and Fisher's exact tests for categorical and two-sample *t* test and Wilcoxon rank sum tests for continuous variables. Distribution of continuous variables was verified for normality through visual inspection of histograms and qq-plots on the residuals of the models described below.

Table 1. Baseline characteristics of all participants at first follow-up visit

	All patients	Non-severe COVID-19	Severe COVID-19*
	N = 584	*N* = 356	*N* = 228
Age, *N* (years±SD)	584 (58.0±14.1)	356 (55.5±15.1)	228 (61.8±11.3)
Gender (male), *N* (%)	332 (57)	168 (47)	164 (72)
BMI (kg/m^2±SD)	27.9 (±5.6)	26.9 (±5.7)	29.5 (±5.1)
Smoking status, *N* (%)			
Never	238 (46)	151 (49)	86 (40)
Previous stopped	210 (40)	104 (34)	106 (50)
Current	28 (5)	21 (7)	7 (3)
Unknown	45 (9)	31 (10)	14 (7)
Comorbidities, *N* (%)			
ILD	8 (2)	5 (2)	3 (1)
Asthma	74 (15)	49 (17)	25 (12)
COPD	17 (3)	7 (2)	10 (5)
Coronary artery disease	46 (9)	25 (9)	21 (11)
Arterial hypertension	207 (40)	92 (30)	115 (55)
Pulmonary hypertension	9 (2)	6 (2)	3 (2)
Heart failure	29 (6)	14 (5)	15 (8)
Pulmonary embolism/DVT	20 (4)	9 (3)	11 (6)
GERD with PPI	45 (9)	27 (10)	18 (9)
GERD without PPI	11 (2)	7 (3)	4 (2)
Sleep apnoea	68 (14)	40 (14)	28 (14)
Lung cancer	4 (1)	2 (1)	2 (1)
Other cancer	46 (9)	21 (7)	25 (12)
Connective tissue disease or vasculitis	4 (1)	3 (1)	1 (1)
Depression/anxiety	49 (11)	32 (12)	17 (9)
Diabetes	94 (18)	45 (15)	49 (24)
Chronic renal failure	31 (7)	18 (7)	13 (7)
Solid organ transplant	5 (1)	1 (0)	4 (2)
Other comorbidities	224 (47)	126 (46)	97 (49)

Majority of items were reported at first contact; if not available, this was updated at the next contact with the patient. ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DVT, deep venous thrombosis; GERD, gastro-esophageal reflux disease; ICU, intensive care unit; ILD, interstitial lung disease; PPI, proton pump inhibitor; SD, standard deviation. *Evidence for ICU admission or ARDS.

For the cross-sectional analyses, FVC, $DLCO_{corr}$, SpO_2 (min), and 6MWT distance at each study visit after initial COVID-19 symptoms were summarised and then severe versus non-severe patients were compared using Fisher's tests and *t* tests. For the longitudinal analyses, linear mixed-effect models with a random intercept for patient were utilised, thus accounting for the repeated measurements per patient. The unadjusted model contained the fixed effects severe COVID-19 (yes/no) and visit (3, 6, or 12 months) and their interaction. Marginal differences from these mixed models were reported comparing severe and non-severe patients at the various study visits. The adjusted model contained in addition predefined potential confounders of the relationship between COVID-19 severity and outcomes: age, body mass index, COPD, coronary artery disease, heart failure, arterial hypertension, and diabetes at baseline.

To compare the radiological pattern prevalence and extent of the 3 months post-COVID-19 versus the 12 months post-COVID-19 chest CT, the CT pattern prevalence (yes/no) of the occurring 10 patterns (consolidation, reticulation, cysts, bronchiectasis, focal GGO, diffuse GGO, mosaic GGO, arcades, curvilinear, plugging) was compared by the McNemar test in a per patient analysis. The mean spread per affected lung was calculated in percentages separately for each pattern and overall. The Z test of proportions was applied to compare the mean spread between 3 and 12 months post-COVID-19 chest CT. In addition, Fisher's exact test was employed to compare the individual volume scores during the CT follow-up (prevalence and spread). The lobes were compared regarding their overall pattern distribution using Fisher's exact test.

To assess the relationship between CT patterns and lung function tests, Pearson's correlation coefficient (r) and its 95% confidence interval (95% CI) were calculated. According to the number of CT patterns analysed ($n = 10$), a Bonferroni correction factor of 10 was used. A significance level of $\alpha < 0.05$ was applied. All analyses were performed using Stata version 17.0 (StataCorp, TX, USA).

Table 2. Lung function results at 12 months after severe versus non-severe COVID-19

	Non-severe COVID-19 *N* = 92	Severe COVID-19 *N* = 122	Difference (95% CI)	*p* value
Spirometry, *N* (%)	83 (90)	96 (79)		
FVC (litres±SD)	3.6±1.0	3.6±1.0	0.1 (−0.2; 0.4)	0.635
FVC (%±SD)	96.3±16.9	91.6±18.3	4.6 (−0.6; 9.9)	0.082
DLCO available, *N* (%)	75 (82)	95 (78)		
$DLCO_{corr}$ (%predicted±SD)	85.2±21.0	74.9±15.4	10.3 (4.7; 15.8)	<0.001
$DLCO_{corr}$ ≤80%, *N* (%)	28 (37)	62 (68)	−31% (−45%; −16%)	<0.001
Plethysmography, *N* (%)*	68 (74)	82 (67)		
RV (%±SD)	94.2±26.8	82.9±23.6	11.3 (2.8; 19.8)	0.009
TLC (litres±SD)	5.6±1.3	5.5±1.3	0.1 (−0.3; 0.5)	0.647
TLC (%±SD)	95.1±17.3	88.2±15.6	7.0 (1.7; 12.3)	0.011
RV/TLC (%±SD)	98.5±22.3	93.8±22.8	4.7 (−2.9; 12.3)	0.225
6MWT, N (%)	61 (70)	86 (72)		
Walk distance (m±SD)	519.6±138.4	523.0±109.3	−3.5 (−43.8; 36.9)	0.866
Max. SpO_2 (%±SD)	97.1±2.0	96.0±2.1	1.1 (0.4; 1.8)	0.002
Min. SpO_2 (%±SD)	92.2±5.0	89.6±5.7	2.6 (0.8; 4.4)	0.004
ΔSpO_2 (% [max-min]±SD)	4.9±4.5	6.5±4.9	−1.6 (−3.1; 0.0)	0.052
ΔSpO_2 ≥4%, *N* (%)	33 (54)	53 (62)	−8% (−25%; 8%)	0.394

COVID-19, coronavirus disease 2019; DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity; RV, residual volume; SD, standard deviation; SpO_2, oxygen saturation; TLC, total lung capacity; 6MWT, 6-min walk test. *RV and RV/TLC only available for *N* = 65 and *N* = 73 for severe and non-severe COVID-19 patients, respectively.

Results

Patient Characteristics and Cross-Sectional Results at 12 Months

Numbers of participants with available clinical and lung function data for the three study visits are illustrated in Figure 1. One year after initial COVID-19 symptoms, data from 584 patients were available. 228 (39%) patients initially had severe disease, according to ICU admission and/or ARDS diagnosis. Patient characteristics are shown in Table 1. Body mass index was significantly higher in the severe disease group ($p < 0.001$). Predominantly male and older patients suffered severe disease (both $p < 0.001$). Arterial hypertension and diabetes were both more common in severe patients than in non-severe ($p < 0.001$ and $p = 0.014$, respectively), with arterial hypertension being the most common comorbidity in both groups (30% in non-severe and 55% in severe disease patients).

Table 2 shows results of the cross-sectional analysis of lung function parameters at 12 months after COVID-19. In 92 patients with non-severe and 122 patients with severe disease, lung function and/or 6MWT were available. 83 patients with non-severe and 96 patients with severe disease had spirometry. Plethysmography was available from 68 and 82 patients, respectively. In the severe COVID-19 disease group, total lung capacity (TLC) was 7.0% predicted lower ($p = 0.011$) and RV was 11.3% lower ($p = 0.009$) compared to the non-severe group. There was no difference between the two groups for FVC at 12 months after the acute infection. $DLCO_{corr}$ was 10.3% predicted lower compared to the non-severe group ($p < 0.001$). Significantly more patients from the severe COVID-19 group had a $DLCO_{corr}$ below 80% predicted compared to the non-severe group (68 vs. 37%, $p < 0.001$). Patients in the severe COVID-19 group had a lower minimal and maximal saturation during 6MWT compared to patients who had non-severe disease ($p = 0.002$ and 0.004, respectively). Although ΔSpO_2 on 6MWT was higher in the severe disease group, this difference did not reach statistical significance ($p = 0.052$).

Change of Functional Parameters over Time

Trajectories of $DLCO_{corr}$, FVC (% predicted), and SpO_2 (min) on 6MWT at 3, 6, and at 12 months after the first COVID-19 symptoms in non-severe and severe patients are shown in Figures 2, 3, 4. The difference (95% CI) for $DLCO_{corr}$ between patients with severe and non-severe COVID-19 decreased over time (−18.8%, 95% CI −22.4% to −15.1% at 3 months; −15.0%, 95% CI −18.9% to −11.1% at 6 months; −10.2%, 95% CI −14.6% to −5.7% at 12 months) (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000528611).

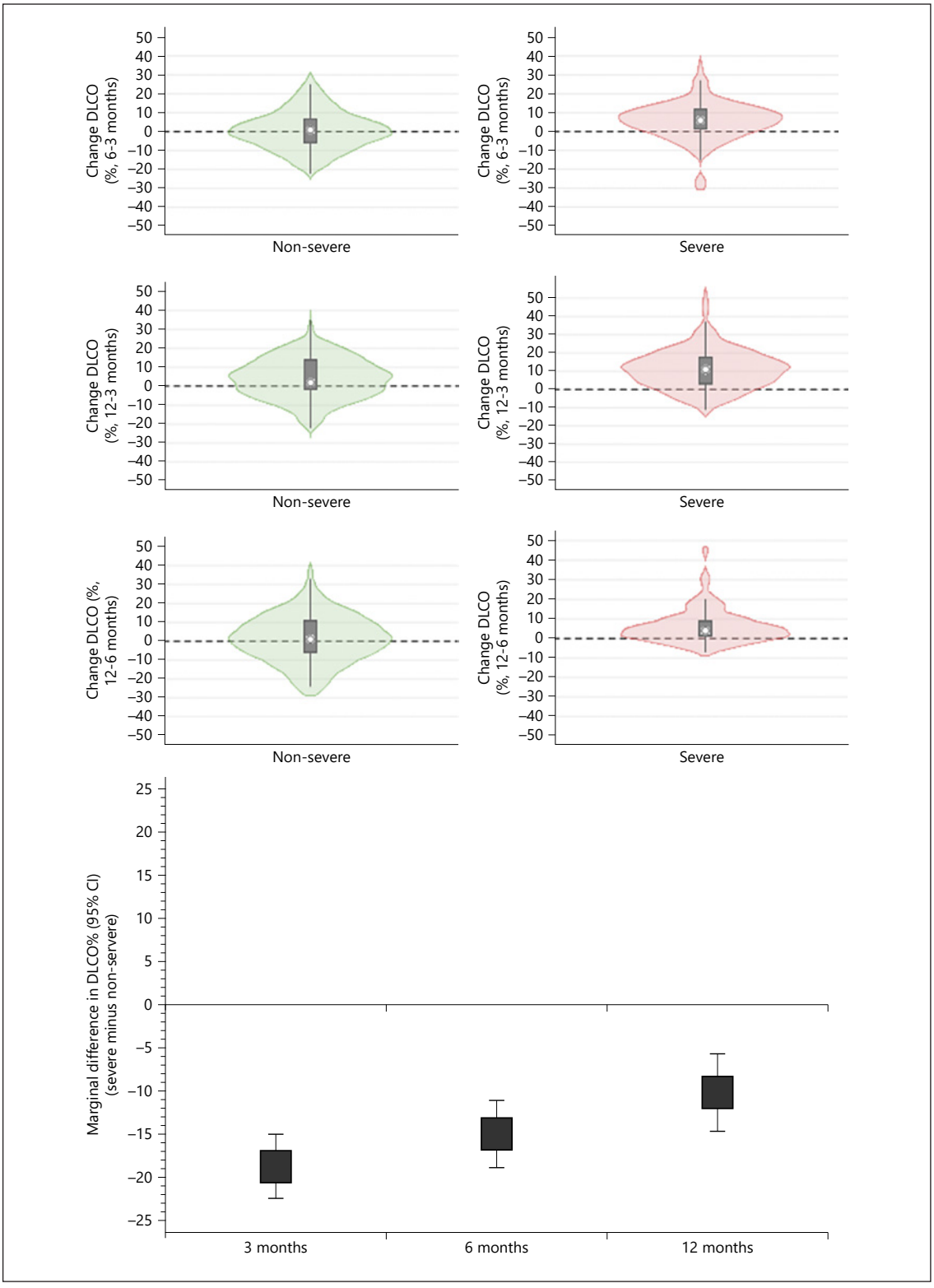

Fig. 2. Differences in $DLCO_{corr}$ between patients with non-severe and severe COVID-19 at 3, 6, and 12 months. Post-COVID-19 change and marginal differences with 95% CI from simple full-factorial general linear mixed models in $DLCO_{corr}$(%) comparing severe versus non-severe COVID-19 patients. DLCO, diffusion capacity for carbon monoxide.

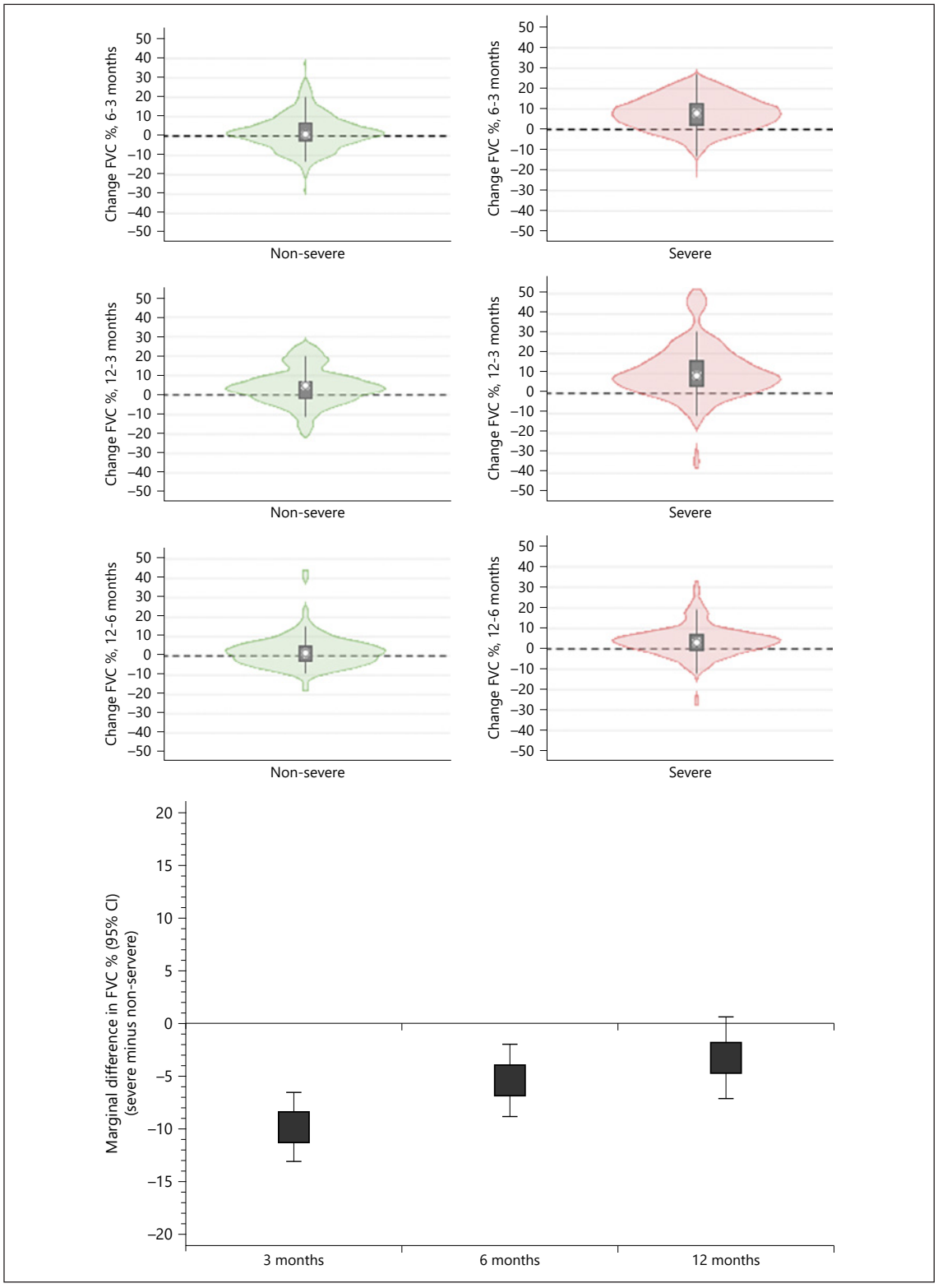

Fig. 3. Differences in FVC (%predicted) between patients with non-severe and severe COVID-19 at 3, 6, and 12 months. Post-COVID-19 change and marginal differences with 95% CI from simple full-factorial general linear mixed models in FVC (%predicted) comparing severe versus non-severe COVID-19 patients. FVC, forced vital capacity.

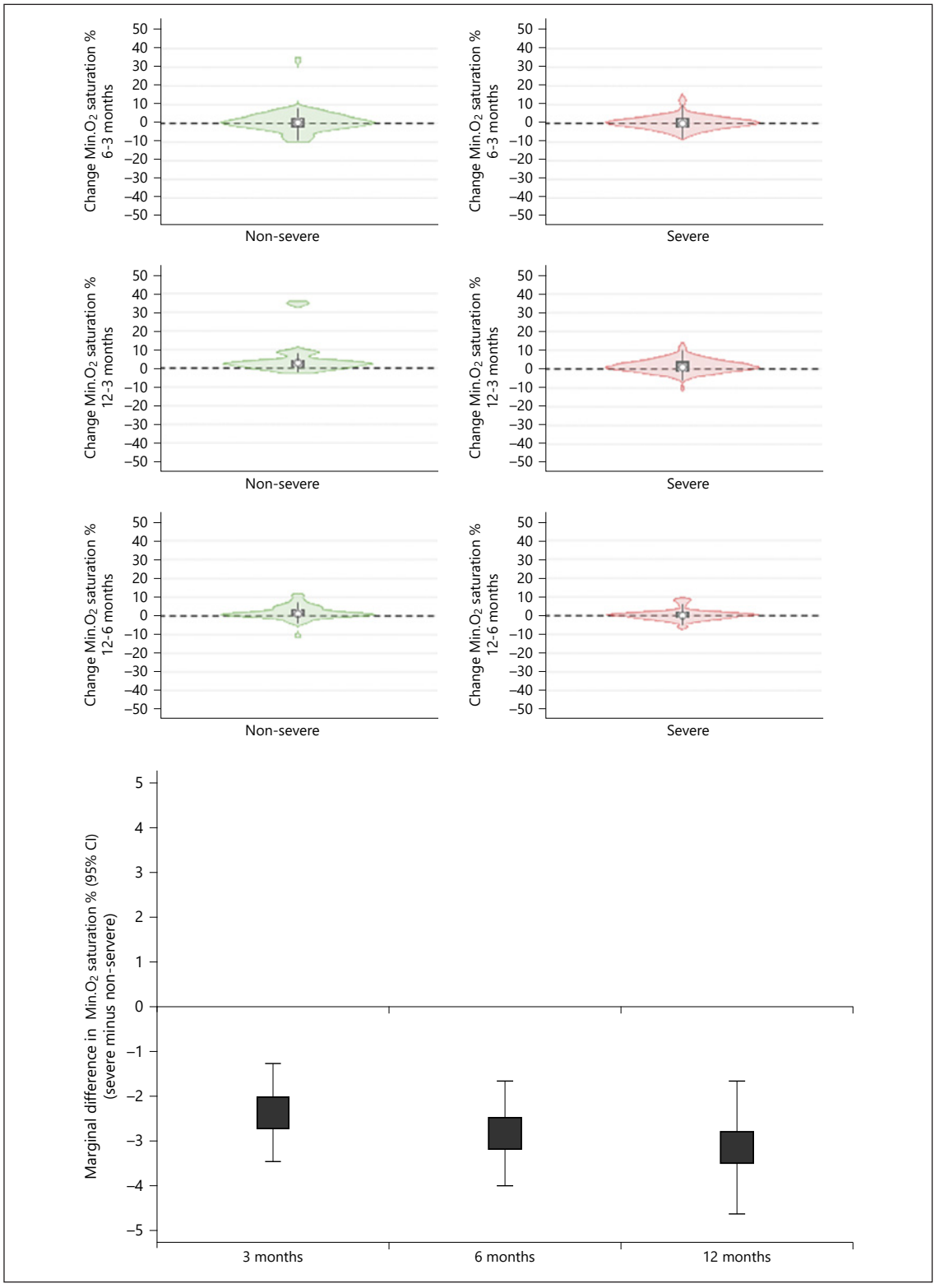

Fig. 4. Differences in SpO_2 (min) at 6MWT between patients with non-severe and severe COVID-19 at 3, 6, and 12 months. Post-COVID-19 change and marginal differences with 95% CI from simple full-factorial general linear mixed models in SpO_2 min(%) comparing severe versus non-severe COVID-19 patients. SpO_2 min, minimal oxygen saturation on 6MWT.

Table 3. Prevalence and extent of CT scan abnormalities at 3 and 12 months after acute COVID-19

CT patterns	Prevalence (n = 25 patients)		Mean extent per affected patient (% total lung volume)		Prevalence and spread over time, p value[c]
	initial CT[a]	follow-up[b]	initial	follow-up	
Consolidation	3 (2)	3 (2)	13.9%	5.6%	1
Reticulation	10 (1)	11 (2)	18.3%	14.4%	1
Cysts	1 (0)	2 (1)	4.2%	8.3%	1
Bronchiectasis	5 (2)	8 (5)	18.3%	11.5%	1
GGO focal	9 (8)	2 (1)	14.4%	6.3%	<0.001
GGO diffuse	1 (1)	0 (0)	58.3%	0.0%	0.001
GGO mosaic	24 (1)	24 (1)	32.1%	46.9%	<0.001
Arcades	21 (2)	19 (0)	18.8%	20.2%	1
Curvilinear	10 (0)	18 (8)	9.6%	10.6%	0.060
Plugging	0 (0)	1 (1)	0.0%	4.2%	1
Total volume affected			63.2%	67.8%	NA

Results are expressed per patient. Follow-up analysis on CT scans was available for 25 patients. COVID-19, coronavirus disease 2019; GGO, ground glass opacities. [a]No longer present on follow-up CT. [b]New on follow-up CT. [c]Fisher's exact test for change in prevalence and in spread over time.

Similarly, the difference for FVC (%predicted) decreased over time (online suppl. Table S2). In contrast, the difference in SpO_2 (min) in the 6MWT between the two groups remained stable over time and was consistently lower for patients following severe COVID-19 (at all 3 visits approximately 2.4% lower SpO_2 [min] in severe compared to non-severe COVID-19 patients) (online suppl. Table S3). Adjusted differences comparing severe versus non-severe COVID-19 patients were similar to the unadjusted differences (online suppl. Table S1, S2, and S3).

Chest CT Imaging Findings

Follow-up CT scan was not performed if the patient recovered, therefore chest CT scans were only available for a subgroup of the cohort (online suppl. Fig. S4). For 25 patients, follow-up chest CT imaging was available at both 3 and at 12 months. Mosaic attenuation with areas of GGO was the most prevalent CT pattern in initial and follow-up imaging, followed by perilobular densities (termed "arcades"); these two patterns were also the most extensive parenchymal findings at 12 months as shown in Table 3. In general, the upper and the lower lobes were more involved by mosaic attenuation pattern compared to the middle lobe and the lingua. A representative example of hypoattenuation is shown in Figure 5. Considering the prevalence and the spread, focal or extensive GGO decreased over time, whereas GGO mosaic pattern with hypoattenuated areas increased significantly per patient after 12 months as shown in Table 3.

There was a significant negative correlation between total affected lung volume (any pattern) and $DLCO_{corr}$ (r = −0.551, p = 0.026) as well as a positive correlation between total affected lung area and ΔSpO_2 in the 6MWT (r = 0.622, p = 0.005) at the initial CT examination. In Table 4, findings for initial and follow-up CT are presented separately. FEV_1 and FVC showed a nonsignificant negative correlation with the extent of total abnormal lung volume on CT.

In terms of specific patterns, the extent of traction bronchiectasis and consolidations showed the strongest positive correlation with ΔSpO_2 in the 6MWT (r = 0.662, p < 0.001 and r = 0.434, p = 0.041, respectively). The extent of bronchiectasis also showed the strongest negative correlation with impaired $DLCO_{corr}$ (r = −0.558, p = 0.001), followed by the extent of consolidations (r = −0.409, p = 0.071). FVC % predicted and FEV_1% predicted were significantly associated with the extent of GGO (r = −0.498, p = 0.009 and r = −0.448, 0.030, respectively) as shown in online supplementary Table S5.

Discussion

The purpose of this multicentre cohort study was to prospectively assess the lung functional and radiological evolution in patients 12 months, following a SARS-CoV-2 infection. We found that 1 year after acute COVID-19, patients who had been admitted with a severe disease

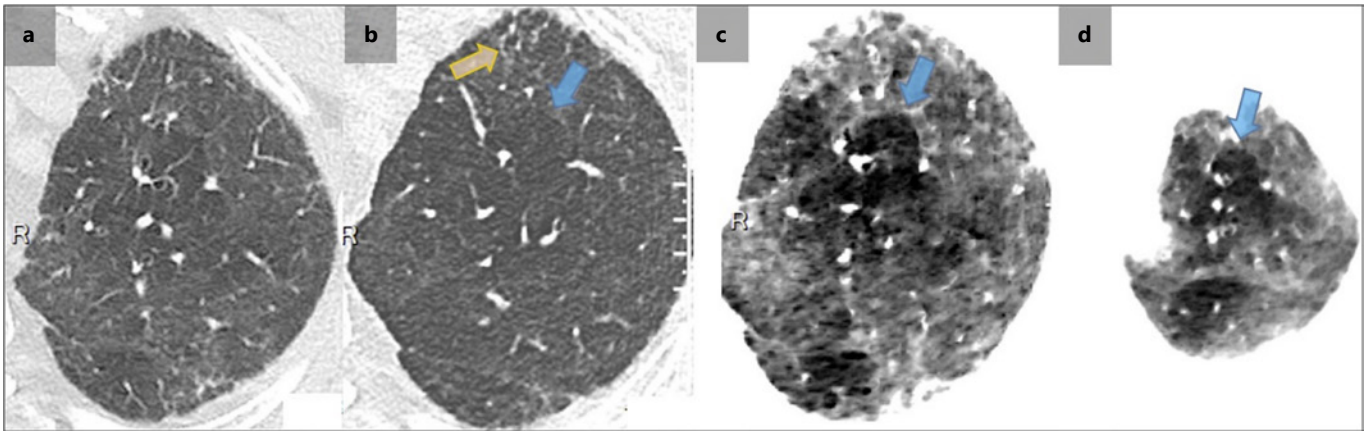

Fig. 5. Radiological imaging 12 months after COVID-19 in comparison with imaging at 3 months. 1-mm-thick slices at the level of the apex of the left upper lobe at 3 months (**a**) and at 12 months (**b**, **c**, **d**). At 12 months, almost complete disappearance of multifocal areas of subtle ground glass opacities (GGO) observed at 3 months. In (**b**), tiny GGO with intralobular reticulations (orange arrow) alternate with subtle hypoattenuated areas almost non-visible on regular lung windowing (blue arrow). By using soft kernel and minIP reformat 4 mm thick in (**c**), mosaic attenuation is perfectly assessed (blue arrow). Air trapping on expiration in the same areas (blue arrow) reinforces the hypothesis of at least a component of small airway disease. minIP, minimum-intensity projection.

course had persistently lower TLC and $DLCO_{corr}$ % predicted as well as lower minimal saturation on exertion (6MWT), compared to patients that had mild or moderate COVID-19. The longitudinal analysis between 6 and 12 months after acute SARS-CoV-2 disease showed that patients who had been admitted to ICU exhibited a greater recovery in $DLCO_{corr}$, and the difference between the two groups diminished over time, with the exception of minimal oxygen saturation on exertion. While the overall extent of radiological disease decreased over time, the mosaic attenuation pattern and the frequency of "arcades" and curvilinear lines increased relative compared to other radiological abnormalities, reflecting the discordance between lung functional measurement and radiological image patterns. Patients with pulmonary function impairment also showed more overall and specific radiological abnormalities.

Our results are in line with the first meta-analysis comparing lung function and radiological patterns over time after infection with SARS-CoV-2, severe acute respiratory syndrome virus, and Middle East respiratory syndrome virus [17]. Other studies showed that at 3 months, 42% of patients that had not required mechanical ventilation [18] and 82% of those that had COVID-19-related ARDS [19] displayed decreased DLCO. Wu and colleagues showed that approximately one-third of COVID-19 patients had persistently impaired DLCO at 12 months after COVID-19 [10]. However, patients who required mechanical ventilation were not included, and no associations between DLCO, length of hospital stay, and CT pneumonia scores were observed. Huang et al. [1] found that 87% of severe COVID survivors had radiological abnormalities at 12 months, predominantly GGO that were associated with abnormal DLCO. Our data confirm that low DLCO at follow-up is associated with initial disease severity. Although no lung function differences were observed in a Norwegian study 3 months after admission for COVID-19 in patients requiring ICU compared to those who did not, ICU survivors had a higher prevalence of GGO on chest CT acquired during acute disease [20]. Overall, our study adds to the growing data underlining the importance of follow-up after severe COVID-19, with pulmonary function tests including measurement of DLCO, starting about 3 months after acute disease [12].

Severity of lung function abnormalities after acute COVID-19 correlated with radiological abnormalities after 3 months [19, 21], but subsequent trajectories remain unclear. Our data suggest a distinct CT pattern in patients after COVID-19. We identified a pattern of mosaic lung attenuation with perilobular GGO (termed "arcades"), curvilinear lines, and bronchiectasis in 47% of patients with available CT imaging at one-year follow-up. Additional findings included reticulations and cysts. These imaging patterns were identified already 3 months after the infection, with most of the chest CT manifestations

Table 4. Correlation between percent (%) of total lung volume affected on chest CT (any pattern) and functional parameters

	Initial CT	Follow-up CT	Women	Men
FVC %				
R	−0.513	−0.366	−0.4648	−0.160
p value	0.059	0.495	0.438	1.000
95% CI	−0.768 to −0.116	−0.703 to 0.106	−0.809 to 0.116	−0.509 to 0.234
FEV_1%				
R	−0.509	−0.160	−0.375	−0.020
p value	0.052	1.000	0.746	1.000
95% CI	−0.762 to −0.123	−0.573 to 0.3173	−0.755 to 0.194	−0.397 to 0.363
$DLCO_{corr}$%				
R	−0.551	−0.409	−0.243	−0.566
p value	0.026	0.327	1.00	0.007
95% CI	−0.785 to −0.180	−0.728 to 0.055	−0.700 to 0.355	−0.775 to −0.2444
ΔSpO_2				
R	0.622	0.607	0.4376	0.687
p value	0.005	0.030	0.619	<0.001
95% CI	0.292 to 0.820	0.195 to 0.837	−0.182 to 0.809	0.428 to 0.842

r, correlation coefficient; *p*, significance level; 95% CI, 95% confidence interval for *r*; ΔSpO_2, O_2 desaturation at 6MWT; DLCO%, diffusion capacity for carbon monoxide in %predicted; FEV1, forced expiratory volume in the first second; in %predicted; FVC, forced vital capacity, in %predicted.

persisting at long-term follow-up. In fact, a modified mosaic attenuation pattern with hypoattenuated areas, arcade-like opacities, and curvilinear lines even increased over time. A possible explanation may be that underlying abnormalities become more detectable after improvement of initial predominant radiological patterns, especially consolidations or areas of GGO. Other recent studies have shown that patients with more severe disease, i.e. ICU patients, have more pronounced radiological and lung functional impairment compared to less severe disease courses [22]. The impairment improves over time in all patients, but some display persistent sequelae [22]. After 2 years, no difference between disease severity and persistent impairment was detectable [23], which is in line with our finding that differences of diffusion capacity diminished over time.

Pathophysiological and immunological mechanisms leading to persistent lung function impairment and radiological abnormalities after COVID-19 are largely unknown. Regarding radiological involvement, mosaic attenuation pattern, appearing as a patchwork of regions of different attenuation, may represent patchy interstitial disease, obliterative small airways disease, or occlusive vascular disease [24]. On the other hand, pathophysiological and immunological hypotheses include cytokine overexpression, small airway impairment, vascular, and microcirculatory inflammation [25, 26]. Increased inflammatory markers were shown to predict persistent pulmonary impairment [22]. However, data from autopsy series and the increased dead space observed in COVID-19 ARDS patients favor the hypothesis of vascular impairment [27]. In addition, given the lack of evidence for small airways disease when examining lung function in post-COVID patients, mosaic attenuation may be caused by residual clots and small vessel injury as suggested by some case series [28]. Microvessel occlusion by immune related processes during the acute disease may contribute to persistent vascular abnormalities [29]. Presumably, a combination of microvascular and small airways disease ultimately leads to the mosaic pattern that is encountered in the post-COVID patients. Of note, similar patterns are found in patients post-ARDS and have also been described in Middle East respiratory syndrome virus and severe acute respiratory syndrome virus infections [30–33].

An arcades-like pattern has been described in some aspects of organizing pneumonia (OP) named perilobular OP [34, 35]. Although not specific, OP can be induced by a variety of factors, including infections. Certain components of OP might contribute to the post-COVID-19 impairment and long-COVID symptoms. Given the sensitivity of OP to steroid administration, this might explain

the benefit of corticosteroid treatment observed in a proportion of long-COVID patients [36]. The use of steroids should be individually evaluated awaiting randomized controlled clinical trials [12].

Bronchiectasis in combination with reticulations, curvilinear lines, and architectural distortion features are considered signs of fibrotic lung disease. Although a decrease was observed in the 12-month follow-up, the persistence of interstitial markings indicates chronic residual pulmonary disease that is likely attributable to the severity of the initial course of disease with numerous patients in this cohort having suffered from ARDS. Fibrotic residues are a common CT finding in patients that suffered from ARDS, independently of the initial cause.

The radiological patterns changed during the period between 3 and 12 months after acute COVID-19, and we observed a correlation between imaging findings and lung function parameters. Radiographic patterns and lung function parameters significantly correlated with DLCO. The decrease of the extent of GGO paralleled the improvement in lung function.

Our study has several limitations. Selection bias may have occurred if patients with impaired baseline lung function prior to COVID-19 were more frequently admitted with severe disease. Only few patients in our cohort had previously known lung diseases and available lung function measurements. In addition, information on (nosocomial) respiratory infections or thromboembolic complications during acute COVID-19 was not available and the sample size was too limited to analyse differences between ICU patients who were mechanically ventilated and those who were not, or further investigate subgroups with specific comorbidities. Comparison of lung functional improvement might be biased at 12 months as many patients without any impairment or symptoms did not continue follow-up. Furthermore, while differences at 12 months between groups were considerable for DLCO (10%) and TLC (7%), the clinical relevance of the difference in minSpO_2 at 6MWT (2.6%) is more debatable. The relatively small number of patients with available CT imaging at follow-up reflected a pragmatic clinical approach where CT scans were obtained only if clinically indicated, but this limited the completeness of radiological analyses of the cohort.

In conclusion, 1 year after the SARS-CoV-2 infection, patients who had severe COVID-19 exhibited reduced lung function parameters as compared to those that had mild or moderate disease. Lung function findings are paralleled by evolving chest CT imaging patterns with uncharacteristic features, especially "arcades." The correlation between lung function parameters and imaging delineates some aspects of the impact of long-COVID syndrome on the lung. Whether these changes reflect microvascular involvement, small airway disease, fibrotic changes, or another compensatory mechanism necessitates further investigation.

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Statement of Ethics

This study protocol was reviewed and approved by the Ethical Committee directed by Prof. Dr. med. Christian Seiler, president, and Dr. sc. nat. Dorothy Pfiffner, vice president of the Ethical Committee, University of Bern, project ID and approval number KEK 2020-00799. All participants provided written informed consent. The study is registered at clinicaltrial.gov (NCT04581135).

Conflict of Interest Statement

Christian Clarenbach received advisory fees from Roche, Novartis, Boehringer, GSK, AstraZeneca, Sanofi, Vifor, OM Pharma, Grifols, and Mundipharma within the last 36 months. Christophe von Garnier obtained advisory fees from AstraZeneca, Boehringer Ingelheim, GSK, Mundipharma, Novartis, OM Pharma, Pfizer, PneumRx and Pulmonx, and Sanofi and received financial support from the Ligue pulmonaire vaudoise, the Yuchum Foundation, and the Placide Nicod Foundation. Manuela Funke-Chambour has received research funding from Boehringer Ingelheim and Roche and advisory fees from Boehringer Ingelheim, MSD, Daiichi Sankyo, and Novartis unrelated to the presented study. Marco Mancinetti received financial support from the University and Hospital of Fribourg, Switzerland, to cover protected time for clinical research. Lise Piquilloud obtained lecture fees for conferences given in scientific symposium for different ventilator manufacturers (Getinge, Hamilton, General Electrics, Fisher, and Paykel). Sebastian Ott is supported by the Lungenliga beider Basel. Sebastian Ott received consulting fees from GSK and honoraria from Novartis and participated in advisory boards for GSK, Boehringer Ingelheim, and Novartis.

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Author Contributions

Manuela Funke-Chambour designed and coordinated the study as principal investigator. Alexandra Lenoir, Andreas Christe, Lukas Ebner, Catherine Beigelman-Aubry, Pierre-Olivier Bridevaux, Martin Brutsche, Christian Clarenbach, Christian Garzoni, Thomas Geiser, Sabina Anna Guler, Frédéric Lador, Marco Mancinetti, Sebastian Ott, Lise Piquilloud, Maura Prella, Yok-Ai Que, Christophe von Garnier, and Manuela Funke-Chambour collected data. Lukas Ebner and Andreas Christe performed the radiological analysis. Alexandra Lenoir, Christophe von Garnier, Berra Erkosar, Dik Heg, Lukas Ebner, Andreas Christe, and Manuela Funke-Chambour analyzed data. Alexandra Lenoir, Lukas Ebner, Andreas Christe, Christophe von Garnier, and Manuela Funke-Chambour drafted the manuscript. All coauthors revised and approved the manuscript in its final form and take responsibility for its content.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary materials. Further enquiries can be directed to the corresponding author.

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