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Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study

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Abstract

Background: The coronavirus infectious disease (COVID-19) pandemic is an ongoing global health care challenge. Up to one third of hospitalised patients develop severe pulmonary complications and ARDS. Pulmonary outcomes following COVID-19 are unknown.

Methods: The Swiss COVID-19 lung study is a multicentre prospective cohort investigating pulmonary sequela of COVID-19. We report on initial follow-up four months after mild/moderate or severe/critical COVID-19 according to the WHO severity classification.

Results: 113 COVID-19 survivors were included (mild/moderate 47, severe/critical 66). We confirmed several comorbidities as risk factors for severe/critical disease. Severe/critical disease was associated with impaired pulmonary function, i.e. diffusing capacity (DLCO) %-predicted, reduced 6-MWD, and exercise-induced oxygen desaturation. After adjustment for potential confounding by age, sex, and BMI, patients after severe/critical COVID-19 had a 20.9 (95% CI 12.4-29.4, p=0.01) lower DLCO %-predicted at follow up. DLCO %-predicted was the strongest independent factor associated with previous severe/critical disease when age, sex, BMI, 6MWD, and minimal SpO_2 at exercise, were included in the multivariable model (adjusted odds ratio [OR] per 10%-predicted 0.59 [95% CI 0. 37-0.87], p=0.01). Mosaic hypoattenuation on chest computed tomography at follow-up was significantly associated with previous severe/critical COVID-19 including adjustment for age and sex (adjusted OR 11.7 [95%CI 1.7-239), p=0.03).

Conclusions: Four months after SARS CoV-2 infection, severe/critical COVID-19 was associated with significant functional and radiological abnormalities, potentially due to small airway and lung parenchymal disease. A systematic follow-up for survivors needs to be evaluated to optimize care for patients recovering from COVID-19.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is the coronavirus that leads to coronavirus disease 2019 (COVID-19) and the current pandemic is the most critical ongoing global health care problem. To date, more than 1.4 million people succumbed to COVID-19.[1, 2] In Switzerland, as of November 25th 2020, in total 309 469 patients were diagnosed with COVID-19 and 4 030 patients died.[3]

COVID-19 is a heterogeneous disease with most patients experiencing mild illness and spontaneous recoveries, but a relevant subgroup of individuals requires hospitalization for pneumonia and other complications. In the initial reports from Wuhan, China, up to one third of patients developed severe pneumonia with acute respiratory distress syndrome (ARDS).[4] While we have already discovered much about the pathogenesis and treatment of the acute SARS CoV-2 disease, intermediate and long-term outcomes are still unknown, particularly in survivors of severe disease courses.

Previous coronavirus infections include severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS). Similar to COVID-19, SARS and MERS typically begin with an acute illness from which most patients recover after two weeks. However, up to one third of SARS patients developed severe pulmonary complications and ARDS.[5] A subgroup of SARS survivors developed persistent lung parenchymal abnormalities, including pulmonary fibrosis.[6, 7] The appearance of pulmonary fibrosis correlated with severity and duration of the acute illness,[8, 9] and radiological features of fibrosis persisted in approximately 30% of patients after three and six months.[10, 11] Older age, and male sex were identified as risk factors for poor outcomes and development of lung fibrosis.[10, 12]

With the anticipation of potential long-term sequelae after COVID-19, follow-up strategies have been proposed by several groups from the US, Great Britain, China, and India.[13-16]

Switzerland has been one of the first European countries affected by COVID-19 with increasing number of confirmed cases from February 25th onwards.[3] A nationwide lockdown was installed on March 16th to prevent further spreading. Six months later, we are facing not only challenges in acute COVID-19 patient care, but also in the follow-up and management of COVID-19 survivors presenting with sequelae of the disease.

We initiated the multicentre Swiss national COVID-19 lung study group to assess pulmonary post sequela of COVID-19. In this first analysis of our prospective cohort we report on chronic pulmonary sequelae of patients who had experienced mild to moderate (mild/moderate) and severe to critical (severe/critical) COVID-19, with the goal to improve the current understanding of the heterogeneous COVID-19 trajectories.

METHODS

Study setting, patients, and clinical measurements

This national, multicentre, prospective observational cohort study includes adults who survived acute COVID-19 and presented for clinical follow-up after either mild to moderate or severe to critical COVID-19.

Contributing centres for the Swiss COVID-19 lung study are the University Hospital Bern (Inselspital), Lausanne University Hospital (CHUV), University Hospital Geneva (HUG), University Hospital Zurich (USZ), Kantonspital St. Gallen, Kantonspital Freiburg, Hospital of Sion, Hospital of Basel (Claraspital), and Hospital of Tessin (Clinica Luganese Moncucco). All patients provided written informed consent before inclusion. Ethics approval was obtained prior to start of the study on May 1, 2020 (KEK 2020-00799). Baseline information e.g. symptoms at initial presentation was retrieved from medical record. Pulmonary functional tests, measurement of carbon monoxide diffusing capacity (DLCO), and 6-minute walk tests (6-MWT) were

performed using established protocols.[17-20] Respiratory muscle strength was estimated by measurement of maximum static inspiratory pressure (PImax) and maximum static expiratory pressure (PEmax) at the mouth.[21] Chest computed tomography (CT) scans were performed in clinically symptomatic patients.

Patients were stratified into the following two groups according to four severity grades described by WHO: 1. Mild disease, or moderate disease with clinical signs of pneumonia and SpO2 ≥90% (mild/moderate), 2. Severe disease with pneumonia and SpO2 <90%, respiratory rate >30/min, or critical disease i.e. ARDS, sepsis, septic shock, and multi organ failure (severe/critical).[1]

Chest CT acquisition

Standard chest CT scans were acquired according to the local protocols in participating centres. 52 follow-up chest CT scans from the 113 included patients were available. All chest CT scans were reconstructed with about 1mm slice thickness. Application of iodine contrast agents was only performed if pulmonary embolism was suspected and/or in case of clinical deterioration. Multiplane reconstructions were performed in axial, coronal and sagittal planes as required. All images were reconstructed with lung- and soft tissue kernels and stored in the local picture archiving and communication system (PACS).

Image analysis

All available CT scans were collected from Bern and Lausanne and de-identified in the local image archive system (PACS Carestream Health, Rochester, United States for Lausanne; Sectra PACS, IDS7, Linköping, Sweden for Bern). Two subspecialized chest radiologists from two tertiary care centres performed a consensus read-out, blinded to the clinical status of the patients. For the reading process, the radiologists reviewed the cases online via screen sharing (Cisco Webex), as the current pandemic regulations restrict physical meetings. The readers

assessed the presence of the following chest CT patterns: consolidation; ground glass opacities (focal, multifocal, diffuse); mosaic attenuation pattern (hypo-, hyperattenuating areas); perilobular consolidation (organizing pneumonia-like pattern); reticulations; architectural distortion; honey combing; traction bronchiectasis; pneumatoceles; curvilinear lines; nodules; pleural thickening or pleural effusion; mucus plugging; vascular abnormalities and additional findings were annotated separately. Pattern distribution was also recorded (upper lobe, middle lobe/ lingula and lower lobe). A semi-quantitative estimation of the disease extent was performed, based on the system proposed by Francone et al..[22] The CT-score is derived from extent of lobar involvement based on a 5 point scale (0:0%; 1, < 5%; 2:5–25%; 3:26–50%; 4:51–75%; 5, > 75%; range 0–5; global score 0–25).

Statistical analysis

Descriptive statistics are reported as mean (standard deviation [SD]) or median (interquartile range [IQR]). Differences between mild/moderate and severe/critical COVID-19 groups were analysed for statistical significance by chi-square or Fisher's exact test for categorical variables and by two-sample t-test or Wilcoxon rank sum test for continuous variables as applicable. The associations of demographic factors, pulmonary and physical function tests, and radiological signs with the COVID-19 severity groups were estimated using linear or logistic regression models where applicable. Models were adjusted for potential confounders with either conceptual importance (age, sex) or a statistically significant relationship to COVID-19 severity ($p<0.1$). Model fit was examined using the area under the receiver operating curve (AUC). 95% confidence intervals (95% CI) for AUC were calculated from bootstrap resampling with 2000 repetitions. The final models were selected based on overall AUC. A two-sided $p<0.05$ was considered for all comparisons. Data were analysed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics and symptoms

Collaborating centres included 113 patients (66 after severe/critical and 47 after mild/moderate COVID-19) from May 1st, 2020 until September 15th, 2020 **(Figure 1)**. Median (interquartile range, IQR) time from initial symptoms to the follow up visit was 128 (108-144) days.

Patients who survived severe and critical COVID-19 were older than patients with follow-up after mild to moderate disease (mean [SD] age 60.3 [12] versus 52.9 [11] years, with equal sex distribution) **(Table 1)**. Smoking history in mild/moderate and severe/critical COVID-19 patients was not significantly different. However, mean (SD) body mass index (BMI) was significantly higher in patients with severe/critical than in patients with mild/moderate disease (29.8 [5.7] versus 25.5 [4.7], p=0.02). Initial comorbidities in both groups are listed in **Table 1**. At follow up patients in both COVID-19 severity groups did not indicate relevant cough (median [IQR] cough visual analogue scale 0 [0-2]). However, patients reported persistent exertional dyspnea in both groups (median [IQR] mMRC 1 [0-1]) at follow-up.

A sensitivity analysis excluding patients with previously diagnosed chronic lung diseases was performed to estimate if the observed differenced in follow-up pulmonary function were mainly driven by pre-existing lung diseases. **Table S1** demonstrates the mainly unchanged findings in this subgroup.

Pulmonary function, physical performance, and oxygenation

Overall, average pulmonary function was normal in patients after mild/moderate COVID-19. Patients after severe/critical COVID-19 had generally lower lung volumes that were still within the normal range, whereas average measures of diffusion capacity (DLCO), physical performance and oxygenation were reduced. Specifically, total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and DLCO were significantly lower in patients after severe/critical COVID-19 compared to patients after mild/moderate

disease. Furthermore, COVID-19 patients with mild/moderate disease course had a higher ratio of FEV1/FVC than those with severe/critical illness **(Table 1)**. Patients with severe/critical disease had impaired and significantly lower DLCO compared to patients with mild/moderate disease (mean [SD] DLCO 73.2 [18.4] versus 95.3 [20.3] %-predicted, p= 0.003). 6-minute walk distance (6MWD) was 120m lower in the severe/critical disease group, with an average S_pO_2 decrease of 5.6 (SD 3.8) % in the severe to critical group compared to 2.5 (3.1) % in the mild to moderate disease group (p= 0.02). Similarly, four months after COVID-19, former severe/critical patients had lower p_aO2 compared to former mild/moderate patients (p_aO_2 79 [12.2] versus 87.5 [9] mmHg, p= 0.0002) **(Table 1)**. Respiratory muscle strength did not differ in both groups.

Within the subgroup of patients who needed mechanical ventilation (39 patients with severe/critical disease) several measures of pulmonary function at follow-up were negatively correlated with the duration of mechanical ventilation during acute COVID-19 (**Table S2**). Specifically, DLCO and TLC showed a moderately strong negative correlation with duration of ventilation (r=-0.43/p=0.008 and r=-0.42/p=0.01, respectively).

Clinical associations with a severe/critical disease course

Unadjusted analysis showed patients after severe/critical COVID-19 being 7.4 (95% CI 3-11.7, p=0.002) years older and having a 4.4 (95% CI 2.3-6.4, p<0.001) higher BMI than patients after mild/moderate disease. FVC %-predicted was 9 percent lower (95% CI 1.5 to 16.4) and TLC %-predicted was 15.9 percent lower (95% CI 8.3 to 23.6) lower after severe/critical than after mild/moderate COVID-19. After adjustment for age, sex, and BMI, TLC %-predicted remained significantly lower in the severe/critical disease group (14.6 [95% CI 6.3 to 22.8], p<0.001), whereas FVC %-predicted lost statistical significance (5.6 [95% CI -2.6 to 13.8], p=0.18). DLCO %-predicted was significantly higher after mild/moderate COVID-19 on unadjusted analysis

(22.1 [95% CI 14.4-29.8], p=0.001), and after adjustment for above confounders (20.9 [95% CI 12.4-29.4], p=0.01).

Similarly, survivors of severe/critical COVID-19 had a markedly lower 6MWD on unadjusted (120 [95% CI 80-160] meters, p=0.001) and adjusted analyses (86 [95% CI 45-127] meters, p=0.001). After adjustment for age, sex, and BMI, minimal SpO_2 on 6MWD was 2.2 (95% CI 0.4-4.0, p=0.01) % and p_aO2 was 5 (95% CI 0.3-10.2, p=0.06) mmHg lower after severe/critical disease.

Figure 2 shows the association of follow-up clinical variables with initial severe/critical and mild/moderate COVID-19. **Table 2** illustrates the final multivariable model including clinical and functional variables statistically and conceptually associated with a severe/critical course of COVID-19 in our cohort. High DLCO %-predicted at follow-up was the factor with the strongest independent association with a more favourable previous course of disease (p=0.01). A good model fit was demonstrated by the overall AUC of 0.95 (95% CI 0.88-1.00).

Radiological features

In our cohort, typical radiological follow-up sequelae of COVID-19 included uni- or multi-lobular hypoattenuated areas without or with bulging of the lobular margins, ground-glass opacities with a mosaic attenuation pattern, linear/curvilinear densities, reticulations, honeycombing, traction bronchiectasis with architectural distortion in various locations as well as pneumatoceles **(Figure 3)**. Extensive pulmonary fibrosis was rarely observed **(Figure S3)**.

Radiological features that were significantly more prevalent after severe/critical than after mild/moderate COVID-19 included mosaic attenuation pattern with hypoattenuated areas (66% versus 13%, p=0.007), and reticulations (59% versus 13%, p=0.02), architectural distortion (52% versus 13%, p=0.055) was marginally more frequent in severe/critical disease **(Table S2)**.

Our patients with a mosaic attenuation pattern with hypoattenuation areas on chest CT scan were more than 13-times more likely to have suffered a severe/critical disease course in our study **(Table 3)**. This association remained statistically significant with accounting for potential confounding by age and sex (OR 13 [95% CI 1.7-239], p=0.03). Similarly, reticulations increased the odds of past severe/critical COVID-19 by 10-fold (95% CI 1.6-198, p=0.04). (**Table 3**).

DISCUSSION

To our knowledge, this is the first European study reporting on respiratory follow-up outcomes after SARS CoV-2 infection. After an average observation time of four months, our cohort reveals impairments in pulmonary function and physical performance that were more pronounced in patients with previously severe and critical COVID-19 courses, compared to those with mild and moderate illness. Specifically, DLCO %-predicted at four months was the most important, independent correlate of a more severe initial disease. Furthermore, in the subcohort of patients with available chest CT scan, we identified a mosaic attenuation pattern with hypoattenuated areas of various size limited by geographic margins with bulging of secondary pulmonary lobules, as well as reticulations as distinct radiological features after severe/critical COVID-19.

Information on risk factors for the development of COVID-19 pneumonia and a severe disease course is increasing, and our study supports many of the findings from previous reports.[23-25] **In our cohort, we can confirm that age and age-associated comorbidities significantly contribute to the inter-individual heterogeneity in the severity of acute COVID-19.[24]** For example, with obesity emerging as a risk factor for severe COVID-19 and mortality,[27-29] findings from the Swiss COVID-19 lung cohort confirm the importance of this modifiable risk factor.

COVID-19 primarily affects the lung and airways and may lead to respiratory failure.[25] Five-year survivors of ARDS were found to be functionally impaired with a median 6MWD of 76% predicted.[30] Similarly, a meta-analysis on long-term outcomes after SARS and MERS, identified a reduced 6MWD and DLCO compared to healthy individuals.[31] A 3-month follow-up study of a Wuhan cohort (mostly mild pneumonia) demonstrated reduced pulmonary function in 14 out of 55 cases, including 9 out of 55 cases with reduced DLCO.[32] In our study, reduced DLCO, decreased distance of 6MWT and desaturation during 6MWT were associated with the a severely impaired COVID-19 phenotype, and importantly this relationship was not confounded by age, sex, or BMI.

The prevalence and extent of pulmonary function and physical impairment after different clinical courses of COVID-19 are still uncertain. In our cohort we demonstrate lower lung volumes (TLC, FVC, and FEV1) in patients after severe/critical COVID-19, the higher FEV1/FVC ratio in the severe/critical subgroup suggests a tendency toward a restrictive physiology, and the lack of difference in respiratory muscle strength suggest a lung parenchymal rather than a respiratory muscle issue. Furthermore, we demonstrate a negative correlation between the duration of mechanical ventilation during the acute disease and pulmonary function at 4-month follow-up. This might be due to a prolonged impairment after very severe COVID-19 or related to more severe disease course in susceptible patients. Alternatively, ventilator induced lung-injury is a well-described challenge post-ARDS, which can impact on pulmonary function after recovery from the acute illness.[30]

On chest CT scans, acute COVID-19 typically presents with progressive ground glass opacities, alveolar consolidations, with a common subpleural and basal location, rounded lesions, crazy paving pattern, linear densities, parenchymal bands and architectural distortion perhaps representing organizing pneumonia and/or fibrotic changes. [33] This presents as an overall radiological picture that is distinct from other viral infections, such as influenza.[34, 35] Similar to

the clinical evolution, the trajectory of radiological patterns is reported as heterogeneous. After a mean observation time of 10 days, lung parenchymal abnormalities seem to have improved in most cases, while some patients persistently show mild signs of pulmonary fibrosis.[36] At short-term follow up, the most frequent radiological abnormalities included ground glass opacities, consolidation, and parenchymal bands.[37] Reports on medium or long-term development of radiological abnormalities are currently very limited.

Four months after the initial diagnosis the predominant finding in our severe/critical subcohort was a mosaic attenuation pattern, characterized by abnormally hypodense areas corresponding to one or several contiguous secondary pulmonary lobules alternating with normal or abnormally hyperdense areas (i.e. ground glass attenuation), as well as more frequent reticulations. In most cases, there was a sharp demarcation and delineation of the margins of the involved secondary pulmonary lobules, with sometimes hyperdense bands silhouetting the abnormal lobules. The combination of mosaic attenuation pattern and impaired DLCO can either be attributed to abnormalities in the distal airways such as constrictive bronchiolitis with air trapping and secondary reflex vasoconstriction or a primary pulmonary vascular disease that may induce secondary airway disease. Both mechanisms can cause ventilation-perfusion mismatch contributing to the reduced physical performance and hypoxemia that we observed in our severe/critical subcohort. Endothelial injury and alveolar capillary microthrombosis have been discussed as underlying mechanisms of pulmonary vascular disease.[38] Airway disease and air trapping were also described after adult ARDS in the setting of influenza, MERS and SARS.[7, 39, 40] Overall, observations from previous studies combined with the high prevalence of the mosaic attenuation pattern specifically in our severe/critical COVID-19 subcohort, suggest that this pattern is an important late feature of severe COVID-19. Signs of fibrosis that we observed in our cohort (reticulations, bronchiectasis and honeycombing) are frequently encountered in survivors of ARDS. While initial observations reported fibrosis after

COVID-19 associated ARDS,[40] mosaic attenuation and air trapping has not been described after COVID-19 before. We recently reported that radiological mosaic attenuation and air trapping might indicate small airway disease.[41] This finding has previously been reported after coronavirus infection and virus-associated ARDS. [7, 39, 40] The radiological and functional abnormalities observed in our study might represent residual damage after ARDS in general, after ventilator-induced lung injury, or specifically after SARS-CoV-2 infection. Potential development of progressive interstitial lung disease after COVID-19 might be attributed to stimulation of autoimmune pathways triggered by SARS-CoV-2 or progression from pre-existing interstitial lung abnormalities to clinically significant ILD.

Prolonged functional impairment with slow recovery over several years after ARDS is not uncommon,[30] however potential long-term consequences specifically after COVID-19 still need to be investigated in future observational studies.

The design of our study does not allow any inference on prevalence of severe/impaired and mild/moderate COVID-19 as patients who deceased were not included, and we did not include asymptomatic patients for follow-up. Initial pulmonary function tests and imaging were not available, consequently patients who experienced severe/critical disease might have had a predisposing undiagnosed lung disease and consequently poorer pulmonary function at follow-up. Patients were questioned thoroughly for symptoms and a medical history that might have indicated previous lung disease. However, asymptomatic underlying chronic lung disease cannot be completely excluded. In addition, initial interstitial lung abnormalities or involvement of the airways in COVID-19 infection cannot be assessed due to the lack of previous chest CT scan in most cases. However, our findings combined with previous studies support the hypothesis that severe COVID-19 causes a medium-term decrease in DLCO, limitations in gas exchange and a spectrum of radiological features not previously reported pointing towards a considerable small airway component.

In conclusion, with the analysis of pulmonary function, physical performance, oxygenation and radiological findings four months after COVID-19 our study adds to the growing body of evidence on post COVID-19 trajectories. We identified DLCO %-predicted at four months as the single most important factor associated with severe/critical respiratory COVID-19 which translates to reduced walking distance and oxygen desaturation on exercise. The peculiar radiological presentation should be further investigated to provide an overall assessment of the disease in conjunction with other functional parameters. These results emphasize the importance of a systematic follow up after severe and critical COVID-19, with appropriate management of pulmonary sequelae.

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FIGURE LEGENDS

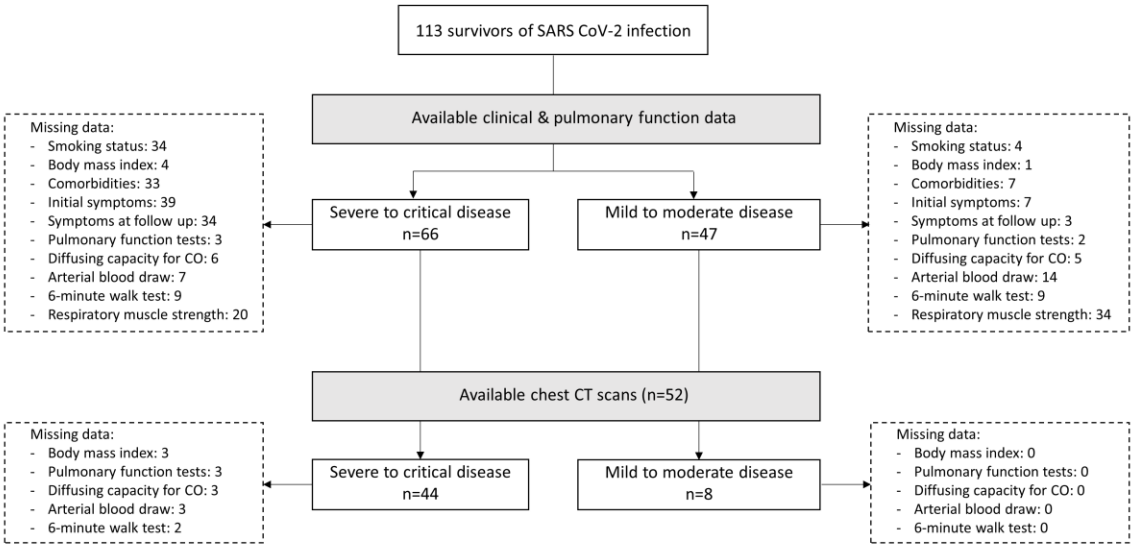
Figure 1: PRISMA flow diagram of the study.

Figure 2. Variables associated with past COVID-19 disease severity.

Association of demographic and functional parameters with mild/moderate and severe/critical COVID-19 disease. OR and corresponding 95%CI from unadjusted analysis (orange) and individual multivariable models for each parameter adjusting for confounding by age and sex (green).

Figure 3. Characteristic radiological changes of a patient with severe sequelae 3 months after COVID-19 pneumonia.

Extensive involvement of both lungs is present in a patient 3 months after a severe COVID-19 pneumonia. Diffuse mosaic attenuation pattern in all lung lobes seen on axial 1 mm-thick CT (A) and 10 mm-thick minimum intensity projection (mIP) slices, 1 mm-thick CT (C) and 10 mm-thick minimum intensity projection (mIP) sagittal reformats (D) in lung windowing. This combines classical features of lung fibrosis with architectural distortion, reticulations, honeycombing (arrowhead in A) and traction bronchiectasis (orange arrows in A-D), as well as sharply demarcated areas of low attenuation in both lungs (orange circles in A-D). Clusters of contiguous hypoattenuating lobules and traction bronchiectasis are better visualized on mIP images with narrow window settings (B and D). Note the bulging of the interlobular septae (B and D, blue curved arrows) as well as the subpleural pneumatocele in C and D.


113 survivors of SARS CoV-2 infection
Available clinical & pulmonary function data
Missing data:
- Smoking status: 34
- Body mass index: 4
- Comorbidities: 33
- Initial symptoms: 39
- Symptoms at follow up: 34
- Pulmonary function tests: 3
- Diffusing capacity for CO: 6
- Arterial blood draw: 7
- 6-minute walk test: 9
- Respiratory muscle strength: 20
Severe to critical disease n=66
Mild to moderate disease n=47
Missing data:
- Smoking status: 4
- Body mass index: 1
- Comorbidities: 7
- Initial symptoms: 7
- Symptoms at follow up: 3
- Pulmonary function tests: 2
- Diffusing capacity for CO: 5
- Arterial blood draw: 14
- 6-minute walk test: 9
- Respiratory muscle strength: 34
Available chest CT scans (n=52)
Missing data:
- Body mass index: 3
- Pulmonary function tests: 3
- Diffusing capacity for CO: 3
- Arterial blood draw: 3
- 6-minute walk test: 2
Severe to critical disease n=44
Mild to moderate disease n=8
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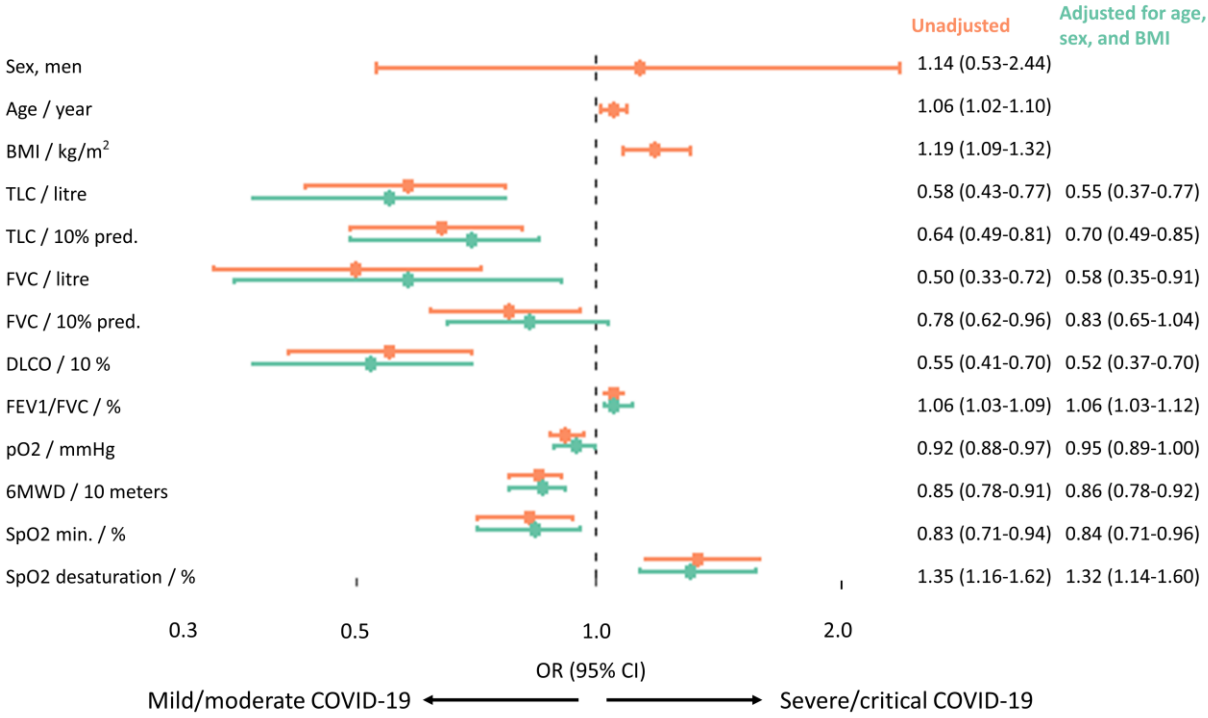
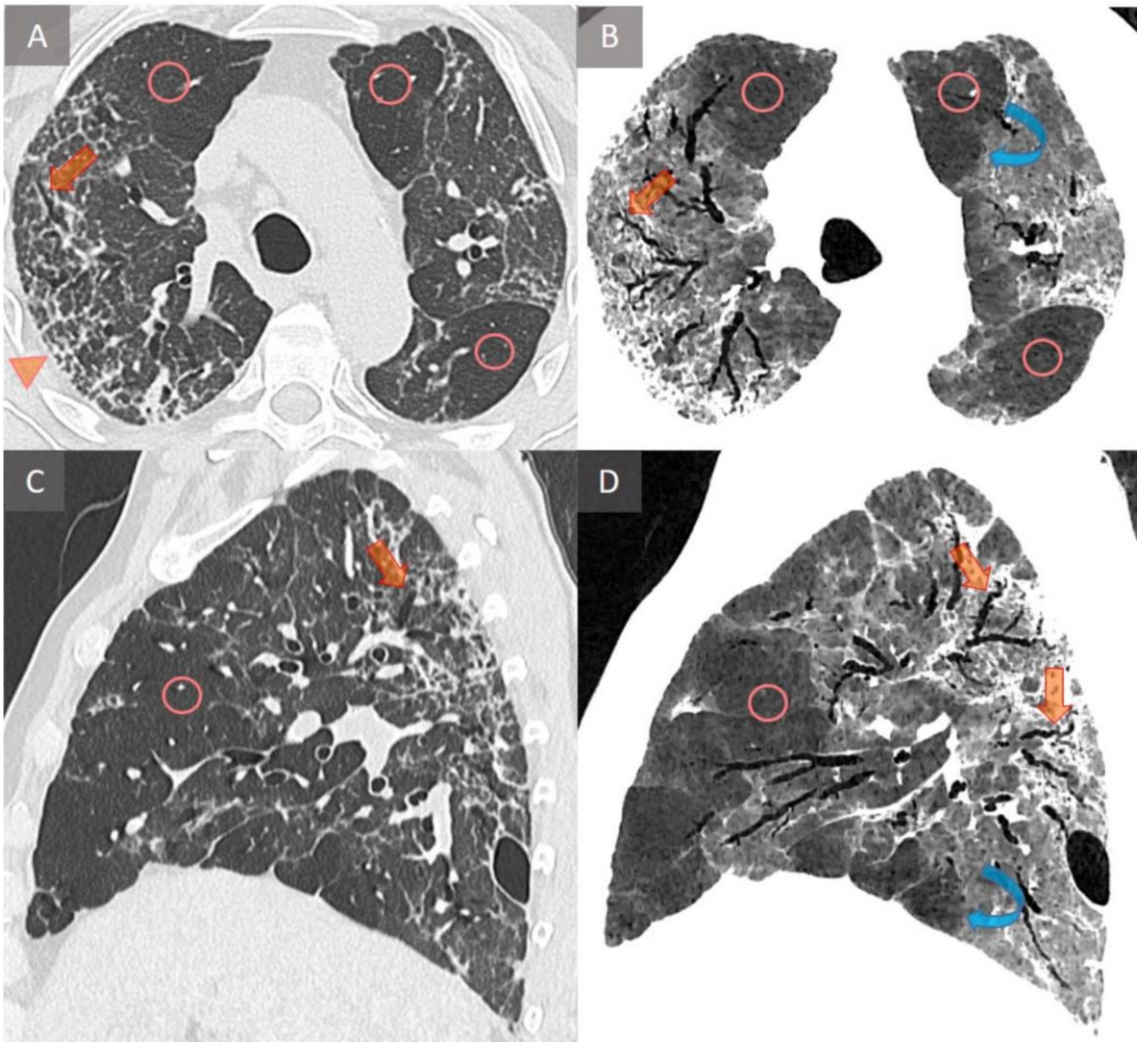
- 6-minute walk test: 0


Unadjusted
Adjusted for age, sex, and BMI
Sex, men
1.14 (0.53-2.44)
Age / year
1.06 (1.02-1.10)
BMI / kg/m2
1.19 (1.09-1.32)
TLC / litre
0.58 (0.43-0.77)
0.55 (0.37-0.77)
TLC / 10% pred.
0.64 (0.49-0.81)
0.70 (0.49-0.85)
FVC / litre
0.50 (0.33-0.72)
0.58 (0.35-0.91)
FVC / 10% pred.
0.78 (0.62-0.96)
0.83 (0.65-1.04)
DLCO / 10 %
0.55 (0.41-0.70)
0.52 (0.37-0.70)
FEV1/FVC / %
1.06 (1.03-1.09)
1.06 (1.03-1.12)
pO2 / mmHg
0.92 (0.88-0.97)
0.95 (0.89-1.00)
6MWD / 10 meters
0.85 (0.78-0.91)
0.86 (0.78-0.92)
SpO2 min. / %
0.83 (0.71-0.94)
0.84 (0.71-0.96)
SpO2 desaturation / %
1.35 (1.16-1.62)
1.32 (1.14-1.60)
0.3
0.5
1.0
2.0
OR (95% CI)
Mild/moderate COVID-19
Severe/critical COVID-19


A
B
C
D

TABLES

Table 1. Baseline characteristics and follow-up findings in patients with severe/critical and mild /moderate COVID-19.

COVID-19 survivors	**Severe/critical disease (n=66)**	**Mild/moderate disease (n=47)**	
	Number (%), mean (SD), median (IQR)		*p-value**
	CHARACTERSTICS AT BASELINE		
Gender, men/women	40/26	27/20	0.89
Age, years	60.3 (12.0)	52.9 (10.9)	<0.001
Ever smokers %[#]	56%	37%	0.16
Body mass index, kg/m^2	29.8 (5.7)	25.5 (4.7)	0.02
D-Dimers, μg/l[†]	1011 (366-1989)	387 (1-658)	0.26
Mechanical ventilation*	71%	-	-
Duration of mechanical ventilation, days*	11.9 (9.5-18)	-	-
	COMORBIDITIES		
Interstitial lung disease	6%	3%	0.58
COPD	12%	3%	0.18
Asthma	9%	19%	0.32
Arterial hypertension	55%	8%	0.003
Diabetes	35%	0%	0.04
GERD	10%	9%	1
Sleep apnea	16%	3%	0.09
Chronic heart failure	10%	9%	1
Chronic renal failure	19%	0%	0.009
Cancer	6%	5%	1
Depression or antiety	12%	7%	0.66
	PULMONARY FUNCTION AT FOLLOW-UP (n=72)		
FEV/FVC, %	94.7 (13.7)	84.2 (14.3)	<0.001
TLC, liters	5.22 (1.5)	6.5 (1.6)	0.050
TLC, % predicted	86.0 (20.0)	102.0 (19.3)	0.047
FVC, liters	3.28 (1.01)	4.12 (1.2)	<0.001
FVC, % predicted	86.6 (20.1)	95.6 (17.9)	0.02
FEV1, liters	2.64 (0.8)	3.34 (1.1)	<0.001
FEV1, % predicted	89.4 (20.7)	94.0 (15.6)	0.19
DLCO, % predicted	73.2 (18.4)	95.3 (20.6)	0.003
PImax, kPa	10.3 (8.8)	8.1 (2.6)	0.14
PEmax, kPa	8.7 (3.3)	10.3 (4.1)	0.20
	OXYGENATION AT FOLLOW-UP (n=72)		
p_aO2, mmHg	79.0 (12.2)	87.5 (9.0)	0.0002
6-MWD, meters	456 (105)	576 (78)	0.001
O2 nadir on 6MWT	90 (4.5)	93 (3.1)	0.001
O2 desaturation 6MWT	5.6 (3.8)	2.6 (3.1)	0.02

*p-values from two-sample t-tests, Wilcoxon Rank Sum test, chi square test, or Fisher's Exact Test.

[#]38 missing, [†]59 missing, *11 missing

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced vital capacity in 1 minute; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; p_aO2, arterial partial pressure of oxygen; PImax, maximal inspiratory pressure; PEmax, maximal expiratory pressure; TLC, total lung capacity; 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test

Table 2. Complete clinical multivariable model for severe/critical disease.

	OR (95% CI)	***p-value****
DLCO, 10%-pred.	0.59 (0.37-0.87)	0.01
Age, year	0.98 (0.92-1.05)	0.62
Sex, men	1.98 (0.50-8.56)	0.34
BMI, kg/m^2	1.19 (1.03-1.41)	0.02
6MWD, 10m	0.88 (0.67-0.95)	0.01
Min. SpO2, %	0.80 (0.44-0.95)	0.07

Effect estimates indicate the associations of the variables with severe/critical disease in the context of the complete multivariable model. E.g. for every 10 meters increase in 6MWD the odds for severe/critical disease decreases by 12% adjusting for age, sex, BMI, DLCO, and minimal SpO2. The overall area under the receiver operating curve (AUC) of the multivariable model including DLCO, age, sex, BMI, 6MWD, and minimal SpO2 was 0.95 (95% CI 0.88-1.00).

Abbreviations: AUC, area under the receiver operating curve; BMI, body mass index; CI, confidence interval; DLCO, diffusing capacity of the lung for carbon monoxide; OR, odds ratio; 6MWD, 6-minute walk distance; min. SpO2, minimal oxygen saturation on 6-minute walk test.

Table 3. Unadjusted and adjusted association of radiological features with previous severe/critical COVID-19.

Radiological sign	***Unadjusted***		***Adjusted for age and sex***	
	OR (95% CI)	*p**	*OR (95% CI)*	*p**
Hypoattenuation	13.5 (2.1-265)	0.02	11.7 (1.7-239)	0.03
Reticulations	10.1 (1.6-198)	0.04	8.73 (1.3-174)	0.06

**p-value for the radiological sign*

Odds ratios indicate the associations of the radiological variables at follow-up with severe/critical disease. E.g. the odds of severe/critical disease is 11.7 times higher for a patient with than for a patient without hypoattenuation, adjusting for age and sex.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; DLCO, diffusing capacity of the lung for carbon monoxide, OR, odds ratio.

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Supplement

Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study

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Table S1. Functional and radiological features at follow-up after severe/critical and mild /moderate COVID-19 after exclusion of patients with previously diagnosed chronic lung disease.

	Severe/critical disease (n=60)	**Mild/moderate disease (n=46)**	
	Number (%), mean (SD)		*p-value**
	FUNCTIONAL PARAMETERS AT FOLLOW-UP		
FEV/FVC, %	95.8 (11.8)	85.3 (12.5)	<0.001
TLC, % predicted	85.5 (19.1)	101.0 (18.6)	<0.001
FVC, % predicted	87.6 (20.1)	94.8 (17.3)	0.056
FEV1, % predicted	91.5 (19.6)	93.7 (15.7)	0.51
DLCO, % predicted	75.4 (17.3)	96.3 (19.6)	<0.001
p_aO2, mmHg	80.8 (11.4)	88.2 (8.1)	<0.001
6-MWD, meters	464 (95)	576 (78)	<0.001
O2 nadir on 6MWT	90 (3.9)	92 (3.1)	0.008
O2 desaturation 6MWT	5.3 (3.5)	2.7 (3.1)	<0.001
	RADIOLOGICAL FEATURES AT FOLLOW-UP (n=48)		
Hypoattenuation mosaic pattern	65%	13%	0.01
Reticulations	58%	13%	0.047

From the original cohort (n=113), 2 patients with ILD and 5 patients with COPD (2 of those with relevant emphysema) were excluded.

Abbreviations: COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced vital capacity in 1 minute; FVC, forced vital capacity; p_aO2, arterial partial pressure of oxygen; TLC, total lung capacity; 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test

Table S2. Correlation between duration of mechanical ventilation and functional parameters at follow-up.

Duration of mechanical ventilation, days	**Spearman's correlation, r**	**p-value**
TLC, % predicted	-0.43	0.008
FVC, % predicted	-0.28	0.09
FEV1, % predicted	-0.23	0.16
FEV1/FVC, %	-0.01	0.93
DLCO, % predicted	-0.42	0.01
p_aO2, mmHg	-0.23	0.18
6-MWD, meters	-0.22	0.18
O2 nadir on 6MWT	-0.07	0.68
PImax, kPa	0.06	0.73
PEmax, kPa	0.21	0.26

Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced vital capacity in 1 minute; FVC, forced vital capacity; p_aO2, arterial partial pressure of oxygen; PImax, maximal inspiratory pressure; PEmax, maximal expiratory pressure; TLC, total lung capacity; 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test

Table S3. Radiological features at follow-up after severe/critical and mild /moderate COVID-19.

	Severe/critical disease (n=44)	**Mild/moderate disease (n=8)**	
	Number (%), mean (SD), median (IQR)		*p-value*
Hypoattenuation mosaic pattern	66%	13%	**0.007**
Reticulations	59%	13%	1
Architectural distortion	52%	13%	0.055
Bronchiectasis	43%	13%	0.13
Curveylinear lines	39%	5%	0.69
Consolidation	30%	25%	1
Honeycombing	11%	0	1
Cysts	9%	0	1
Interlobular septal thickening	2%	0	1
Pleural thickening	2%	0	1
Tree in bud pattern	0	0	
Solid nodules	5%	0	1
Multifocal distribution	47%	13%	0.12
Focal distribution	22%	24%	0.64
Diffuse distribution	11%	0	1

Abbreviations: COVID-19, coronavirus disease 2019

Figure S1. Post COVID-19 pulmonary fibrosis 3 months after acute respiratory distress syndrome (ARDS).

Extensive architectural distortion, reticulations and honeycombing representing late effects of post-COVID-19 ARDS.