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Respiratory function and CT abnormalities among survivors of COVID-19 pneumonia: a nationwide follow-up study

Gisli Thor Axelsson ,[1,2] Arnljotur Bjorn Halldorsson,[3] Helgi Mar Jonsson,[3] Elias Eythorsson,[2] Sigridur Erla Sigurdardottir,[4] Hronn Hardardottir,[1,4] Gunnar Gudmundsson,[1,4] Sif Hansdottir[4]

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[1]Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[2]Department of Internal Medicine, Landspitali, Reykjavik, Iceland
[3]Department of Medical Imaging, Landspitali, Reykjavik, Iceland
[4]Department of Respiratory Medicine and Sleep, Landspitali, Reykjavik, Iceland

Correspondence to
Dr Sif Hansdottir;
sifhan@landspitali.is

ABSTRACT

Introduction Considering the pulmonary burden caused by acute COVID-19, questions remain of respiratory consequences after recovery. The aim of the study was to describe respiratory function of COVID-19 pneumonia survivors at mid-term follow-up (median 68 days) and assess whether impairments were predicted by acute illness severity or residual CT abnormalities.

Methods Residents of Iceland that had COVID-19 and oxygen saturation ≤94% from 28 February 2020 to 30 April 2021 were offered a clinical follow-up visit with an interview, a 6 min walk test (6MWT), spirometry with gas exchange measurement and chest CT. The results of these examinations were described, grouped by the level of care during acute illness. The associations of disease severity and CT abnormalities at follow-up with subjective dyspnoea, 6MWT results and lung function test results were estimated with regression analyses.

Results Of 190 eligible patients, 164 (86%) participated in the study. Of those, 32 had never been admitted to hospital, 103 were admitted to hospital without intensive care and 29 had required intensive care. At a follow-up, need for intensive care during acute illness was associated with shorter walking distance on 6MWT, lower oxygen saturation and lower DL_{CO}. Imaging abnormalities at follow-up were observed for most participants (74%) and the magnitude of these changes was associated with decrements in 6MWT distance, oxygen saturation, forced vital capacity and DL_{CO}.

Conclusions The findings show that impaired exercise capacity and lung physiology at follow-up were primarily observed for patients with COVID-19 pneumonia that required intensive care treatment and/or had persistent imaging abnormalities.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Severe illness due to COVID-19 has been associated with respiratory impairment. However, much of these data are derived from selected populations of patients who experienced severe illness.

WHAT THIS STUDY ADDS

⇒ This comprehensive nationwide follow-up study includes survivors of moderate to severe COVID-19 pneumonia that were treated either as outpatients, inpatients or in intensive care. Impairments at follow-up were mainly associated with need for intensive care during the acute phase and presence of radiologic sequelae of COVID-19.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Respiratory-focused follow-up for survivors COVID-19 pneumonia should be aimed at survivors of the most severe illness and those with extensive long-term radiologic changes.

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2 infection, has burdened healthcare systems worldwide with drastic consequences for public health and the global economy.[1] A viral pneumonia is the main feature of severe COVID-19 disease, often presenting with widespread consolidations on pulmonary imaging. The resulting respiratory failure is the main cause of mortality and need for intensive care among patients with COVID-19.[2]

The large respiratory burden associated with the illness has prompted research of patients' respiratory symptoms and lung function after recovery. While results of such studies have somewhat varied, COVID-19 severity in the acute phase has consistently been associated with radiological abnormalities and impairments of lung function and gas exchange at follow-up. In these studies, patients with more severe illness have had fibrosis-like radiologic changes and decrements in forced vital capacity (FVC) and DL_{CO}.[3–9] Still, most of these studies are limited to patients admitted to hospital with severe or critical disease and some were limited by low

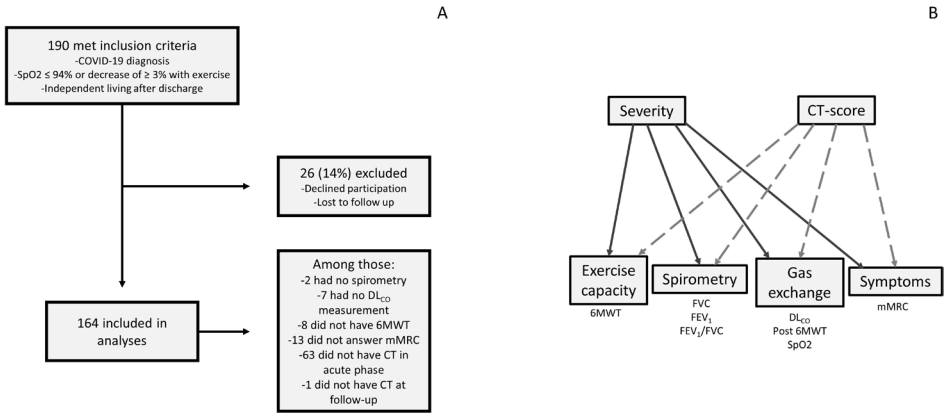

Figure 1 Overview of study design. (A) A flow chart of participants' inclusion. (B) A graphic overview of the study research questions. 6MWT, 6 min walk test; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council.

rates of participation and lack of simultaneous acquisition of radiologic and functional outcomes.[3–9]

In Iceland, all patients with COVID-19 have been registered and monitored in a single centre in a standardised fashion.[10] This creates an opportunity for population-level follow-up studies. With this background, this study aimed to determine whether the severity of COVID-19 and radiologic changes were related to physiological and functional impairments in a nationwide follow-up of patients that had COVID-19 pneumonia prior to the emergence of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants.

The primary objective of the study was to assess the relationship of COVID-19 illness severity with dyspnoea, exercise capacity, spirometry results and measures of gas exchange after recovery. Secondarily, we sought to assess whether radiologic sequelae of COVID-19, detected by chest CT, were associated with the same parameters.

METHODS

Patient selection for follow-up

The study period was from 28 February 2020 (the date of the first COVID-19 diagnosis in Iceland) to 30 April 2021. All adult patients in Iceland that tested positive for SARS-CoV-2 in this period were followed by a specialised ambulatory clinic at the Landspitali-The National University Hospital of Iceland (LUH). LUH is the country's only tertiary care hospital where patients were monitored by way of telemedicine and those with worsening symptoms presented for ambulatory visits and/or hospitalisations. This has been previously described in detail.[10]

A clinical follow-up visit, focused on respiratory care, was offered to all COVID-19 survivors that had an oxygen saturation of ≤94% on room air or a decline in in oxygen saturation by ≥3% during a 2 min walking test during acute illness and were discharged to independent living. These criteria are comparable with oxygen saturation criteria for moderately severe or severe COVID-19 from the NIH.[11]

Follow-up visit

At follow-up, patients went through a standardised interview of their medical history and symptoms at time of follow-up with an experienced nurse, followed by a clinically focused interview with a pulmonologist. They underwent a 6 min walk test (6MWT) overseen by a physiotherapist, spirometry and DL_{CO} measurement with an experienced technician according to standardised protocols and a CT scan of the chest without an intravenous contrast agent. Three multidetector CT scanners from Toshiba and Canon (an 80-slice, 160-slice and a 320-slice scanners) were used for all examinations. The imaging technique used was non-contrast-enhanced standard helical CT with 120 kilovoltage peak (kVp) with traditional patient-regulated radiation dose. The images were reconstructed with 1 mm slice thickness in axial, coronal and sagittal planes and evaluated with a window level of 30 Hounsfield units (HU) and a window width of 400 HU for soft tissues and window level of –500 HU and window width of 1500 HU for the lungs.

Data collection, CT analysis and definition of outcomes

Data on demographic covariates were obtained from standardised interviews and as needed from electronic medical records. Smoking history was classified as never smokers, ever smokers with less than 20 pack years and ever smokers with over 20 pack-years. Data on symptoms of dyspnoea, that is, the modified Medical Research Council (mMRC) and medical history was obtained from interviews. For the CT analysis, a semiquantative CT severity score was used based on the extent of anatomic involvement in each pulmonary lobe. Zero points were given if there was no involvement, 1 point for <5% involvement, 2 points for 5%–25% involvement, 3 for 25%–50% involvement, 4 for 50%–75% involvement and 5 points for >75% involvement. Points from each pulmonary lobe were added up and the resulting total CT score therefore ranged from 0 to 25 points. This method has been used in other studies of COVID-19

Table 1 Baseline characteristics of study participants by treatment level

	Total	Treatment level			P value
		Ambulatory	Inpatient	ICU	
No	164	32	103	29	
Gender—male (%)	90 (55)	11 (34)	57 (55)	22 (76)	0.005
Age—mean (SD)	60 (14)	51 (12)	63 (14)	60 (11)	0.0001
BMI—mean (SD)	32 (6.5)	31 (7.2)	31 (6.2)	33 (6.9)	0.63
Smoking history					0.20
Never (%)	74 (45)	14 (44)	46 (45)	14 (48)	
Under 20 pack-years (%)	29 (18)	10 (31)	14 (14)	5 (17)	
Over 20 pack-years (%)	61 (37)	8 (25)	43 (42)	10 (35)	
History of type 2 diabetes	21 (13)	2 (6)	13 (13)	6 (21)	0.29
History of any lung disease	43 (26)	9 (28)	28 (27)	6 (21)	0.79
History of hypertension	67 (41)	6 (19)	46 (45)	15 (52)	0.01
Chest CT changes					
CT-score during acute illness (mean (SD))	14 (6.0)	8.5 (12)	13 (5.5)	18 (4.9)	<0.0001
CT score at follow-up (mean (SD))	6.5 (6.3)	1.3 (2.3)	6.5 (5.0)	12 (8.0)	<0.0001
Reticular changes at follow-up (%)	39 (24)	1 (3)	28 (27)	10 (36)	0.002
Subpleural banding at follow-up (%)	56 (34)	2 (6)	37 (36)	17 (61)	<0.0001
mMRC score (%)					0.55
0	56 (37)	15 (52)	32 (33)	9 (35)	
1	58 (38)	11 (38)	35 (37)	12 (46)	
2	29 (19)	2 (6.9)	23 (23)	4 (15)	
3	7 (4.6)	1 (3.4)	5 (5.2)	1 (3.8)	
4	2 (1.3)	0 (0.0)	2 (2.1)	0 (0.0)	
Pulmonary function testing					
FVC <80% N (%)	19 (11.7)	2 (6.5)	10 (9.8)	7 (24)	0.09
FEV_1<80% N (%)	16 (9.9)	2 (6.5)	10 (9.8)	4 (14)	0.60
FEV_1/FVC <70% N (%)	24 (15)	5 (16)	18 (18)	1 (3.4)	0.16
DL_{CO}<70% N (%)	36 (23)	0 (0)	24 (24)	12 (43)	<0.0001
SpO2 <92% N (%)	10 (6.4)	2 (6.2)	5 (5.2)	3 (11)	0.52
FVC <80% and FEV_1/FVC >70% N (%)	14 (8.6)	1 (3.2)	6 (5.9)	7 (24)	0.01
FVC <80%, FEV_1/FVC >70% and DL_{CO}<70% N (%)	7 (4.3)	0 (0)	1 (1.0)	6 (21)	0.0002

BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICU, intensive care unit; mMRC, modified Medical Research Council.

patients in which the CT score is associated with the severity of the disease.[12–14] The presence of reticular changes and subpleural bands in the lung parenchyma was also noted. Reticular changes are defined as several small interlacing shadows forming a web-like pattern. Chronic reticular changes can be a manifestation of pulmonary fibrosis.[15] Subpleural bands are band-like changes in the periphery of the lungs which can appear in the later stages of the disease.[16] These changes are a sign of fibrosis in the lungs as part of the healing process of the tissue and can be seen late in the disease.[17] The image analysis was done by two independent readers, a radiologist and a resident in radiology with 3 years of experience. Mutual consensus was reached for cases with discordant scores. For the 101 participants (62%) that underwent a chest CT during the acute phase, images were evaluated in an identical manner. The continuous outcomes of interest were registered during the clinic visit and are presented as absolute values and some as ratios of predicted values. The predicted values for FVC and forced expiratory volume in 1 s (FEV_1) were based on age, sex, height and race,[18] predicted values for DL_{CO} were additionally adjusted for haemoglobin, while predicted values for 6MWT were based on the Gibbons formula.[19] The number of participants meeting commonly used clinically relevant cut-offs for FVC (<80% of predicted), FEV_1 (<80% of predicted), FEV_1/FVC (<70% of predicted), DL_{CO} (<70% of predicted) and O_2 saturation (<92%) were calculated.

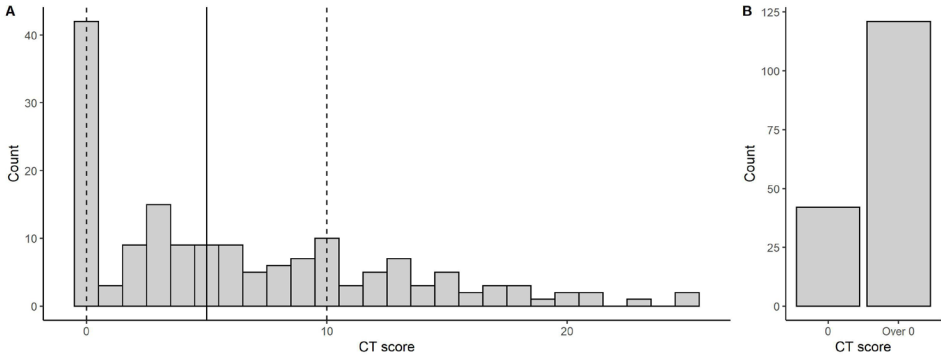

Figure 2 Numerical distribution of CT score at follow-up histogram of CT score at follow-up. Line denotes median value; dashed lines denote quartile marks. (A) Distribution across the range of observed values. (B) Distribution grouped by a score of 0 (NO abnormalities) or a score >0 (any abnormalities).

Data handling and statistical analyses

Summary statistics for outcomes, covariates and CT score during acute illness and at follow-up were computed for participants, in total and grouped by treatment level. Fisher's exact tests and analysis of variance (ANOVA) were used to compare differences between treatment levels as appropriate. Data for continuous outcomes, as proportions of predicted values, were graphically depicted per treatment level. The means of these values were compared between treatment levels using ANOVA and comparisons between treatment level pairs were done using t-tests.

Associations of treatment level and CT score at follow-up with outcomes were tested with regression analyses (figure 1B). Prior to these, multiple imputation of missing data (1.9%) (figure 1B), based on all predictors, outcomes and covariates was performed with use of the R function *aregImpute* from the *Hmisc* package.[20] This method uses flexible additive modelling with predictive mean matching in a bootstrap dataset. This resulted in five imputed versions of the data. Continuous outcomes were assessed with linear regression using both absolute outcome values and ratios of predicted values where appropriate. Associations of treatment level and CT score at follow-up with mMRC were modelled with ordinal regression. All regression models were adjusted for age, sex, body mass index (BMI), and history of smoking, type 2 diabetes, hypertension and any self-reported lung disease with age modelled with four-knot restricted cubic splines. All regressions were performed in all five imputations, with the mean values then calculated and presented as final results. For comparison, the analyses were repeated using complete-case analyses of the original data.

A priori, the significance level for the study was decided to be 0.05. Statistical analyses were conducted using R.

Patient and public involvement

Patients or public were not involved in the design of the study.

RESULTS

Patient characteristics

A total of 190 patients met the inclusion criteria during the study period, of which 164 (86%) came for follow-up and were included in the study (figure 1A). The mean age of study participants was 60 years and 45% were female. The median time from diagnosis to follow-up was 68 days (IQR=61–84 days, range=28–176 days). An overview of study participants stratified by treatment level is shown in table 1. Most patients were admitted to a general hospital ward (103 patients, 63%) while 29 (18%) were admitted to an intensive care unit. One-fifth of patients only required ambulatory follow-up. Participants that needed higher levels of care were older, more often male and had a higher CT score during the acute illness and at follow-up as well as reticular changes and subpleural banding. They were also more likely to have a history of hypertension, evidence of restriction on spirometry (defined as normal FEV_1/FVC but low FVC) and reduced DL_{CO} at follow-up (table 1). The distribution of participants' CT score at follow-up, as well as the numbers of participants with and without any changes on CT, are graphically depicted in figure 2. The majority of participants (74%) had some imaging abnormality at follow-up (CT score of over zero), with a median score of 5 (IQR 0–10). The distributions of participants' CT score, stratified by the existence of reticulations and subpleural banding is shown in online supplemental figure S1.

Figure 3 shows the distribution of variables representing pulmonary function at follow-up, grouped by treatment levels. A significant difference between any treatment levels was noted for the percentage of predicted distance on 6MWT (p=0.0003), the FVC percentage (p=0.016), FEV_1/FVC ratio (p=0.01), the DL_{CO} percentage of predicted ($p=5\times10^{-6}$) and oxygen saturation after the 6MWT (p=0.003) but not for the percentage of predicted FEV_1 (p=0.53). Significant differences were found between all pairs of treatment levels excluding the ambulatory and inpatient groups for percentage of predicted FVC value and oxygen saturation after 6MWT.

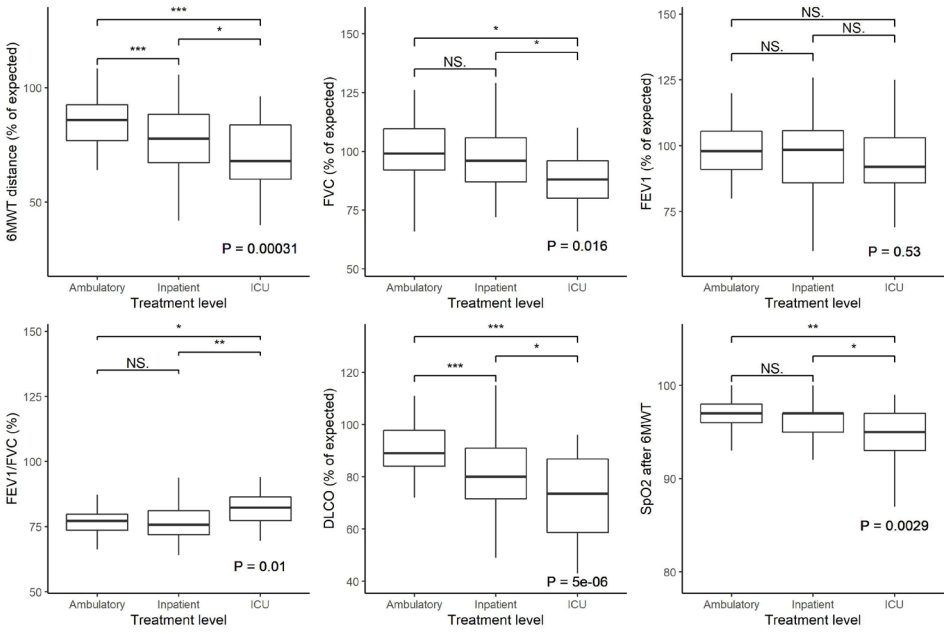

Figure 3 Pulmonary outcome variables at follow-up stratified by treatment levels box plots of the distributions of 6 min walking test (6MWT) performance, forced vital capacity (FVC), forced expiratory capacity in 1 s (FEV_1) and diffusion capacity of carbon monoxide (DL_{CO}), all as percentages of predicted values as well as the FEV_1/FVC ratio in absolute values. P values are from one-sided analyses of variance testing differences among any group. Dashes indicate differences between indicated groups, tested with t-tests. *p<0.05, **p<0.01, ***p<0.001 NS refers to p>0.05. ICU, intensive care unit; NS, not significant.

The associations of acute-phase treatment level with pulmonary function parameters at follow-up

Results from regression analyses of the association of treatment level with pulmonary outcomes are shown in table 2. Compared with ambulatory care, intensive care treatment was associated with shorter 6MWT distance (β = −14% of predicted, p=0.0001) and lower DL_{CO} (β = −20% of predicted, p<0.0001), both in models using absolute values and proportions of predicted values. In addition, intensive care treatment was associated with decreased saturation after 6MWT (β=−2.1% of predicted, p=0.004). Hospital admission was associated with 6MWT distance reduction when modelled using absolute values (β = −39 m, p=0.043) but not when using proportions of predicted values. Inpatient treatment was associated with a decrease in DL_{CO} as a proportion of a predicted value (β=−7.9% of predicted, p=0.01) and an increase in dyspnoea as measured by the mMRC scale (β=1.0 points, p=0.049).

The associations of CT score at follow-up with pulmonary function parameters at follow-up

Results from regression analyses of the associations of CT score with pulmonary outcomes are shown in table 3. CT score was associated with decreased distance covered on 6MWT (β per point in CT score=−0.82% of predicted, p<0.0001), FVC decrease (β=−0.46% of predicted, p=0.02), an increase in FEV_1/FVC ratio (β=0.26%, p=0.04), a decrease in DL_{CO} (β=−1.1% of predicted, p<0.0001) and decreased oxygen saturation after 6MWT (β=−0.11%, p=0.004) regardless of modelling method. It was associated with a decrease in the absolute FEV_1 value (β=−0.02 L, p=0.011) but not with a change in percentage of predicted FEV_1. CT score at follow-up was not associated with dyspnoea as measured by the mMRC scale. Results of complete-case models were similar to models for which missing data were imputed (online supplemental tables S1–S2).

DISCUSSION

We describe the symptoms, exercise capacity, imaging findings and respiratory function at follow-up from a nationwide cohort of survivors of COVID-19 showing significant lower respiratory affection. The range of participants' illness during the acute phase ranged from ambulatory clinic visits to intensive care management. The findings show that CT changes at follow-up were highly prevalent in this group, with a majority having some changes and half having a CT score over 5. The magnitude of interstitial lung changes at follow-up was associated with impairments in lung function, exercise capacity and pulmonary gas exchange, but not with increased dyspnoea. Gas exchange and exercise capacity were related to need for intensive care during the acute illness phase, but less consistently with care at a general inpatient ward. Radiologic sequelae were related to a higher FEV1/FVC ratio. A substantial share of patients that needed intensive care had functional impairment consistent with restrictive physiology, although that association was not supported by adjusted models.

Table 2 Associations of treatment level with pulmonary outcomes at follow-up

	Models using absolute values		Models using % of predicted	
	Beta (95% CI)	P value	Beta (95% CI)	P value
6MWT (metres)				
Inpatient	−39 (−77 to −1.6)	0.043	−4.8 (−11 to 0.92)	0.10
ICU	−96 (−143 to −50)	<0.0001	−14 (−21 to −7.0)	0.0001
FVC (litres)				
Inpatient	0.09 (−0.23 to 0.41)	0.90	−1.4 (−8.0 to 5.2)	0.69
ICU	−0.34 (−0.73 to 0.05)	0.09	−7.7 (−16 to 0.5)	0.07
FEV_1 (litres)				
Inpatient	0.06 (−0.16 to 0.3)	0.57	−2.0 (−8.8 to 4.7)	0.55
ICU	−0.13 (−0.41 to 0.14)	0.34	−4.5 (−13 to 3.8)	0.29
FEV_1/FVC (%)				
Inpatient	1.6 (−6.2 to 3.0)	0.51	–	–
ICU	2.1 (−3.5 to 7.7)	0.46	–	–
DL_{CO} (mL/min/mm Hg)				
Inpatient	−0.31 (−0.95 to 0.32)	0.33	−7.9 (−14 to −1.8)	0.01
ICU	−1.6 (−2.4 to −0.83)	<0.0001	−20 (−27 to −13)	<0.0001
Saturation after 6MWT (%)				
Inpatient	−0.21 (−1.4 to 0.9)	0.71	–	–
ICU	−2.1 (−3.5 to −0.71)	0.004	–	–
mMRC				
Inpatient	1.0 (0.006 to 2.0)	0.049	–	–
ICU	0.75 (−0.38 to 1.9)	0.19	–	–

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICU, intensive care unit; mMRC, modified Medical Research Council; 6MWT, 6 min walk test.

The findings are largely in concordance with prior follow-up studies of COVID-19 pneumonia showing that reduced performances on spirometry and exercise testing are common among survivors of severe COVID-19 pneumonia, as are changes on chest CT scan.[3 5 6] Our study has the added value of demonstrating this in a nationwide follow-up study with excellent participation limiting the risk of selection bias. The evaluation across a spectrum of disease severity shows that the risk of pulmonary sequelae after COVID-19 is largely limited to those with severe disease, that is, patients needing intensive care treatment for respiratory failure. These results, in conjunction with

Table 3 Associations of CT-score at follow-up with pulmonary outcomes

	Models using absolute values		Models using % of predicted	
	Beta (95% CI)	P value	Beta (95% CI)	P value
6MWT (metres)				
CT score	−5.4 (−7.7 to −3.1)	<0.0001	−0.82 (−1.2 to −0.47)	<0.0001
FVC (litres)				
CT score	−0.04 (−0.05 to −0.02)	0.0002	−0.46 (−0.86 to −0.07)	0.02
FEV_1 (litres)				
CT score	−0.02 (−0.03 to −0.004)	0.011	−0.17 (−0.57 to 0.24)	0.41
FEV_1/FVC (%)				
CT score	0.26 (0.01 to 0.51)	0.04	–	–
DL_{CO} (mL/min/mm Hg)				
CT score	−0.11 (−0.15 to −0.08)	<0.0001	−1.1 (−1.5 to −0.77)	<0.0001
Saturation after 6MWT (%)				
CT score	−0.11 (−0.18 to −0.03)	0.004	–	–
mMRC				
CT score	0.02 (−0.03 to 0.08)	0.44	–	–

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council; 6MWT, 6 min walk test.

results of prior studies, imply that long-term follow-up of COVID-19 patients for respiratory concerns could be limited to patients that needed high levels of care during the acute phase. The results also imply that chest CT imaging could play a central role in such surveillance as the magnitude of COVID-19 related imaging changes correlates well with physiologic impairments.

Associations of COVID-19 imaging findings at follow-up with functional impairments consistent with restrictive physiology hint at a possible connection between severe COVID-19 and development of fibrotic lung changes. Still, the main imaging variable used in this study, the CT involvement score, is based on lung lesion size and does not consider their character. Therefore, it does not differentiate between ground glass opacities and other lung changes more associated with fibrosis such as reticular changes and changes that distort the architecture of the lungs.[21] While our data show that patients with reticular changes or subpleural banding (as an example of architectural distortion) on follow-up CT had significantly higher involvement score and higher treatment level, the study was not powered for adjusted analyses of these imaging findings. Further research is needed regarding the possible association between severe COVID-19 and development of fibrosis-like lung changes.

The correlation of CT changes with physiologic impairments makes the large proportion of participants that had any CT abnormalities noteworthy. However, the effect sizes of the associations of CT findings with physiologic measurements were small. For every added point in the CT score at follow-up, participants could, for example, be expected to have a decrease in DL_{CO} by 1.1% of the predicted value or a decrease in FVC by 0.5% of the predicted value. This suggests that CT abnormalities at follow-up must be of considerable extent for the associated functional impairment to have plausible clinical significance. This is supported by the lack of correlation between CT score at follow-up and perceived dyspnoea as measured with the mMRC scale. It can also be mentioned that the strength of some associations was modified when outcomes were analysed as percentages of predicted values. Although all analyses were adjusted for covariates, these differences may be caused by the weights of covariates in calculations of predicted values.[18]

The study is subject to important limitations. First, the different strengths of the presented associations should be mentioned. Some of the observed associations, such as those of mMRC with treatment levels and FEV_1/FVC with imaging changes, barely met the threshold for statistical significance. As the total number of participants was low, although higher than in some prior studies,[3 6] and the distribution with regards to level of care was imbalanced, the limited statistical power of analyses also raised the possibility of type II error. Second, severe COVID-19 is a multi-system illness, raising the possibility of residual confounding that could affect at least some of the outcomes studied, even though the presented analyses were adjusted for important comorbidities. Different levels of deconditioning could, for example, partly explain the relationship between illness severity and exercise capacity. Third, respiratory symptoms were estimated by the mMRC scale. Its uneven distribution necessitated the grouping of answers for analyses. Fourth, some of the changes could be the result of reverse causation, for example, that those that had worse lung function had worse respiratory complications of COVID-19 and more CT abnormalities at follow-up. Fifth, the presented data are obtained from unvaccinated participants prior to the emergence of viral variants such as the Delta variant and later the Omicron variant that has less propensity for pulmonary involvement than previous variants of SARS-CoV-2.[22] Last, participants received different acute-phase treatments during the study period as key therapeutic interventions were discovered during the period.[23 24] During the first 3 months of the study period, medical treatment consisted of azithromycin and hydroxychloroquine, both of which were subsequently found to be ineffective. In the fourth month of the study period, remdesivir was introduced, followed shortly by dexamethasone. This study is not powered to evaluate the potential effects of different therapies in the acute phase. Vaccination became available, in limited amounts, 10 months into the study period and thus participants were not immunised. For this study and other follow-up studies of COVID-19 patients, it remains to be seen whether results from the first waves of the pandemic can be extrapolated to vaccinated patients with novel viral variants.

The presented findings suggest several needs for further research. It will be necessary to conduct longer-term follow-up studies of COVID-19 survivors with pulmonary CT imaging, as it will be of great interest to see whether the described CT abnormalities and physiological impairments, believed to be sequelae of COVID-19, regress, remain unchanged or progress. Small longitudinal long-term studies suggest that a significant portion of participants has non-resolving abnormalities.[25] If such developments are variable between patients, it would be useful to discover their determinants. It would also be interesting to see if CT changes and pulmonary function abnormalities better correlate with dyspnoea at longer-term follow-up. In addition, future follow-up studies of severely ill patients should investigate whether vaccination status, different pharmacological treatments or viral variants alter the pulmonary sequelae of COVID-19.

In conclusion, a significant share of survivors of COVID-19 pneumonia have impairments of respiratory function and exercise capacity. These impairments are associated with need for intensive care during the acute illness and the degree of disease-related changes on pulmonary imaging.

Results from regression models of treatment level, adjusted for age, sex, BMI and history of smoking, type 2 diabetes, lung disease and hypertension, with the specified outcome (its absolute value on the left and, when applicable, percentage of a predicted value on the right), with participants that never required hospital admission

as the reference level. Results are averages of results over five data imputations. Models are linear models, except for mMRC modelled with proportional odds models. mMRC was modelled using three categories (1,2 and 3 or more). Age is modelled using a restricted cubic spline with four knots.

Results from regression models of CT score, adjusted for age, sex BMI and history of smoking, type 2 diabetes, lung disease and hypertension, with the specified outcome (its absolute value on the left and, when applicable, percentage of a predicted value on the right). Results are averages of results from five imputed data sets. Models are linear models, except for mMRC modelled with proportional odds models. mMRC was modelled using three categories (1, 2 and 3 or more). Age is modelled using a restricted cubic spline with four knots.

Contributors SH and GG accept full responsibility for the work and/or the conduct of the study, had full access to all data in the study and had final responsibility for the decision to submit for publication. Study concept and design: GTA, ABH, HH, GG and SH. Statistical analyses: GTA and EE. Interpretation of the data: GTA, ABH, HMJ, EE, HH, GG and SH. Drafting the manuscript: GTA, ABH, HH, GG and SH. Revision of the manuscript for important intellectual content: GTA, ABH, HMJ, EE, HH, GG and SH.

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ORCID iD

Gisli Thor Axelsson http://orcid.org/0000-0002-7156-9080

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