



Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19

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3 months after discharge, a quarter of COVID-19 survivors have reduced gas diffusion capacity and persistent parenchymal opacities. ICU treatment is associated with persistent parenchymal opacities, but not with dyspnoea or reduced diffusing capacity. <https://bit.ly/2J3xH4x>

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ABSTRACT The long-term pulmonary outcomes of coronavirus disease 2019 (COVID-19) are unknown. We aimed to describe self-reported dyspnoea, quality of life, pulmonary function and chest computed tomography (CT) findings 3 months following hospital admission for COVID-19. We hypothesised outcomes to be inferior for patients admitted to intensive care units (ICUs), compared with non-ICU patients.

Discharged COVID-19 patients from six Norwegian hospitals were enrolled consecutively in a prospective cohort study. The current report describes the first 103 participants, including 15 ICU patients. The modified Medical Research Council (mMRC) dyspnoea scale, the EuroQol Group's questionnaire, spirometry, diffusing capacity of the lung for carbon monoxide (D_{LCO}), 6-min walk test, pulse oximetry and low-dose CT scan were performed 3 months after discharge.

mMRC score was >0 in 54% and >1 in 19% of the participants. The median (25th–75th percentile) forced vital capacity and forced expiratory volume in 1 s were 94% (76–121%) and 92% (84–106%) of predicted, respectively. D_{LCO} was below the lower limit of normal in 24% of participants. Ground-glass opacities (GGO) with $>10\%$ distribution in at least one of four pulmonary zones were present in 25% of participants, while 19% had parenchymal bands on chest CT. ICU survivors had similar dyspnoea scores and pulmonary function as non-ICU patients, but higher prevalence of GGO (adjusted OR 4.2, 95% CI 1.1–15.6) and lower performance in usual activities.

3 months after admission for COVID-19, one-fourth of the participants had chest CT opacities and reduced diffusing capacity. Admission to ICU was associated with pathological CT findings. This was not reflected in increased dyspnoea or impaired lung function.

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The full protocol has been published on www.clinicaltrials.gov (NCT04535154). An anonymised data file will be shared through the website of the journal upon publication.

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Introduction

The lower airways and lungs are the primary targets for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The majority of patients requiring hospital admission for coronavirus disease 2019 (COVID-19) have respiratory symptoms such as cough and dyspnoea, in addition to signs of impaired lung function with varying degrees of hypoxaemia [1]. These symptoms are associated with widespread ground-glass opacities (GGO) on chest computed tomography (CT) scans and chest radiography [2, 3]. ~15–30% of hospital-admitted COVID-19 patients develop severe respiratory failure and acute respiratory distress syndrome (ARDS), which necessitate admission to intensive care units (ICUs) and possibly mechanical ventilation [1, 4, 5]. According to the World Health Organization (WHO), the fatality rate from COVID-19 is 1–10%, depending on age and underlying comorbidities [6].

As the COVID-19 pandemic represents a new disease, the long-term pulmonary outcomes in survivors of COVID-19 are unknown. Evidence from other coronavirus pneumonias, such as SARS and Middle East Respiratory Syndrome (MERS), suggests that impaired lung function and parenchymal opacities persist only in a minority of patients not having required mechanical ventilation [7]. However, in patients developing ARDS, as many as 11–45% have impaired lung function and persistent infiltrates on radiography after 10–12 months [8]. In order to identify and manage potential long-term sequelae of COVID-19, more research on the natural course of the disease is warranted [9]. Early reports of survivors following hospital admission for COVID-19 show reduced diffusing capacity, total lung capacity, exercise capacity or abnormal chest CT scan in almost 50% after 1 month [10].

In the current study, we assessed patient-reported dyspnoea, lung function, quality of life (QoL) and parenchymal opacities in chest CT scans 3 months after hospital admission for COVID-19 in a prospective, consecutive Norwegian cohort of patients with or without ICU treatment.

Materials and methods

Design and participants

Patient-Reported Outcomes and Lung Function After Hospital Admission for COVID-19 (PROLUN) is a multicentre prospective cohort study performed in six major hospitals in Norway. The study was approved by the regional ethics committee for South-Eastern Norway (no. 125384), by data protection officers at each participating centre, and registered to ClinicalTrials.gov (NCT04535154).

Patients aged >18 years who had been admitted for >8 h with a discharge diagnosis (International Statistical Classification of Diseases and Related Health Problems 10) of U07.1 (COVID-19, virus identified), U07.2 (COVID-19, virus unidentified) or J12.x (viral pneumonia, in combination with positive SARS-CoV-2 identification in nasopharyngeal swab) were considered for eligibility. Exclusion criteria included living outside the hospitals' catchment areas, inability to provide informed consent or participation in the WHO Solidarity Trial.

Eligible patients were invited by mail ~6 weeks after hospital discharge. Informed consent was obtained by return of a written signed consent form or through a secure digital consent form (Services for Sensitive Data (TSD), University of Oslo, Oslo, Norway). One telephone reminder was performed for nonrespondents.

In accordance with the study protocol, an interim report of the first 100 participants was planned. This number was achieved on June 24, 2020. The current study thus comprises all participants who had attended the 3-month follow-up visit by June 24, 2020 (n=103).

Data collection

Participants returned to the respective hospitals' outpatient clinics for a 3-month follow-up visit. The median (25th–75th percentile) time between the hospital admission and the 3-month visit was 83 (73–90) days;

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82 (73–90) days in the non-ICU group and 85 (81–90) days in the ICU group ($p=0.090$). The criteria for admission to ICU were similar across centres: inability to maintain a satisfactory pulse oximetric saturation (S_{pO_2}) through oxygen supplementation by nasal cannula or non-rebreather mask. In addition, the participants were assessed by an anaesthesiologist before transfer to the ICU.

Self-reported dyspnoea

The modified Medical Research Council (mMRC) dyspnoea scale, range 0–4, was used [11, 12]. This measure was not administered for the first 18 participants, or at St Olavs Hospital (Trondheim, Norway). However, for these participants, we performed additional analyses with the last value carried forward from self-reported mMRC 4–6 weeks prior to the visit.

QoL

The EuroQol Group's EQ-5D-5L questionnaire [13] was used to measure health-related QoL. It contains five items scored on an ordinal scale from 1 (no problems) to 5 (unable/extreme problems). This questionnaire was administered by mail or weblink 4–6 weeks prior to the visit. Scores were available for 88 (89%) of the participants. EQ-5D index values were prepared using the crosswalk method with UK weights [14].

Pulmonary function tests

Spirometry was conducted to measure the forced vital capacity (FVC) and the forced expiratory volume in 1 s (FEV_1) (Jaeger MS-PFT Analyzer Unit, Höechberg, Germany and CareFusion type MasterScreen PFT, Yorba Linda, CA, USA; software SentrySuite V03.0.5; Vyair Medical, Höechberg). The ratio of FEV_1/FVC was calculated. Diffusing capacity of the lungs for carbon monoxide (D_{LCO}) and alveolar ventilation (V_A) were measured, and D_{LCO}/V_A (transfer coefficient of the lung for carbon monoxide) was calculated. All procedures were executed according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines [15, 16]. The Global Lung Function Initiative (GLI) network reference values were used to calculate the percentage of predicted values, the lower limit of normal (LLN) and z-scores [17, 18]. A 6-min walk test (6MWT) was performed according to ATS/ERS guidelines, with baseline S_{pO_2} measured by pulse oximetry on index fingers [19].

Chest CT

Low-dose, thin-section CT images were obtained in supine and prone positions, during breath-holding and deep inspiration. The same CT protocol, adjusted for the different CT scanners employed, was used for all examinations. The tube current settings were adjusted to each patient's weight, with low-dose references at 120 kVp, high pitch and shortest possible rotation time. For evaluation of lung parenchyma, we applied thin reconstructed slice thickness (0.9–1.25 mm), with a high spatial frequency kernel, and a softer kernel with thicker (2–3 mm) slices for mediastinal evaluation. Two experienced thoracic radiologists independently reviewed all images, blinded to the participants' clinical history. The degree of consensus was high. The presence, extent and distribution of interstitial findings were registered using nomenclature recommended by the Fleischner Society [20]. For the purpose of the current analysis, GGO and parenchymal bands were assessed. Findings were registered in four separate apicobasal zones of the lungs using anatomical landmarks in the mediastinum [21].

Other clinical variables

Baseline demographic characteristics (sex, age, height, weight, history of smoking), body mass index (BMI), comorbidities (diabetes or hypertension) and data from the COVID-19 hospital admissions were obtained from the electronic patient records. Clinical variables indicating the severity of COVID-19 were use of oxygen, admission to ICU, use of mechanical ventilation, the maximal levels of C-reactive protein (CRP) and D-dimer.

All collected data was stored in TSD, designed for storing and post-processing sensitive data in compliance with the Norwegian Personal Data Act and Health Research Act.

Statistical analyses

For continuous data, median and 25th–75th percentiles were reported in descriptive statistics. Group comparison was performed with Mann–Whitney U-tests or Chi-squared tests, as appropriate. For lung function variables the predicted value was calculated, reporting LLN and z-score.

Descriptive analyses of the cohort were considered important for this interim report. We also tested the hypothesis that participants admitted to the ICU would have more dyspnoea, lower lung function, lower QoL and more pathological CT findings than participants not admitted to the ICU.

The main outcome measures were 1) mMRC ≥ 1 ; 2) D_{LCO} below LLN; 3) $>10\%$ GGO in at least one lung zone; and 4) the presence of parenchymal bands. Secondary outcomes were 6MWT distance, S_{pO_2} , EQ-5D-5L scores and EQ-5D index. The association between COVID-19 severity indices and main outcomes were assessed by univariate logistic regression analyses. The association between ICU admission, pre-defined as the major indicator of COVID-19 severity, and the main outcomes were adjusted by multivariable analysis. Due to a limited number of participants, only a few independent variables were allowed: age and sex, except for D_{LCO} below LLN, in which current/previous smoking *versus* never smoking was adjusted for. All statistical analyses were performed using Stata (version 16.1; StataCorp, College Station, TX, USA). A p-level <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics from the hospital admission are shown in table 1. Several indices of COVID-19 severity were higher in participants admitted to ICU than in the non-ICU participants: length of stay, oxygen therapy, the maximum levels of CRP and D-dimer and the prevalence of bilateral lung densities. However, the demographic variables (sex, age, BMI and smoking status) were comparable between the groups. Hypertension was less commonly observed in those admitted to ICU than in non-ICU participants. The median (25th–75th percentile) time from symptom onset to admission was 7 (5–9) days and 9 (6–11) days in ICU and non-ICU participants, respectively (p=0.125).

Table 2 presents self-reported dyspnoea, pulmonary function tests and results of chest CT scans in the whole group, as well as according to ICU admission subgroup during the hospital stay. Dyspnoea (mMRC score >0) was reported by 37 (54%) of the respondents, while 13 (19%) reported mMRC score >1 (n=69). The prevalence of dyspnoea 3 months after discharge was similar between ICU and non-ICU participants (table 2). In sensitivity analyses including additional 23 participants with mMRC scores reported a few weeks earlier, the prevalence of mMRC score >0 and mMRC score >1 were 52 (56%) and 22 (24%), respectively (n=93). For all pulmonary function tests, the majority of participants had values within the limits of normal. $\sim 10\%$ had FVC or FEV₁ below LLN, while 24% had significantly reduced D_{LCO} . Furthermore, patients admitted to ICU during hospital admission did not have reduced lung function, 6-min walk distance or oxygen saturation compared to those not admitted to ICU (table 2).

GGO were common; 24% of the participants had one or more lung zones with $\geq 10\%$ presence of GGO. The presence of GGO was associated with age and CRP in univariable logistic regression analysis (p=0.009 and p=0.001, respectively) (supplementary table S1). The crude prevalence of GGO was not significantly different between ICU and non-ICU participants; however, after adjustment for age and sex, the odds of

TABLE 1 Clinical characteristics during admission for coronavirus disease 2019 (COVID-19)

	Total	ICU admission	No ICU admission	p-value
Subjects	103	15	88	
Demographic data				
Male	54 [52]	11 [73]	43 [49]	0.098
Age years	59 [49–72]	52 [50–59]	61 [49–74]	0.116
Body mass index kg·m ⁻²	25.8 [23.8–29.6]	24.9 [23.7–29.3]	25.9 [23.8–29.1]	0.885
Current smoker	3 [3.4]	0 [0]	3 [4]	0.216
Previous smoker	34 [39]	3 [21]	31 [42]	
Medical comorbidity				
History of hypertension	35 [35]	1 [7]	34 [40]	0.017
History of diabetes	8 [8]	0 [0]	8 [9]	0.599
COVID-19 hospital admission				
Length of stay days	6 [3–11]	17 [12–25]	5 [3–9]	<0.001
Oxygen treatment	67 [66]	15 [100]	52 [59]	0.003
ICU admission	15 [15]	N/A	N/A	N/A
Invasive ventilation	9 [9]	9 [60]	N/A	N/A
Bilateral densities on chest radiography	48 [49]	14 [93]	34 [41]	<0.001
Maximum level of CRP mg·L ⁻¹	120 [48–217]	246 [189–290]	107 [34–175]	<0.001
Maximum level of D-dimer mg·L ⁻¹	1.0 [0.4–1.9]	3.5 [1.9–4.5]	0.8 [0.4–1.4]	<0.001
Lowest level of lymphocytes $\times 10^9$ cells·L ⁻¹	0.9 [0.6–1.4]	0.8 [0.6–1.0]	1.0 [0.6–1.5]	0.129

Data are presented as n, n (%) or median [25th–75th percentile] unless otherwise stated. ICU: intensive care unit; CRP: C-reactive protein; N/A: not applicable.

TABLE 2 Pulmonary outcomes 3 months after hospitalisation

	Subjects	All	ICU admission	No ICU admission	p-value
Subjects			15	88	
Spirometry	103				
FVC L		3.6 [2.1–6.0]	3.8 [3.2–5.1]	3.6 [3.0–4.4]	0.392
FVC % predicted		94 [76–121]	92 [81–110]	95 [87–108]	0.730
FVC z-score		-0.39 [-0.81–0.37]	-0.58 [-1.34–0.19]	-0.33 [-0.80–0.42]	0.457
FVC <LLN		7 (7)	2 (13)	5 (6)	0.269
FEV ₁ L		2.8 [2.2–3.3]	2.9 [2.5–3.9]	2.7 [2.2–3.2]	0.119
FEV ₁ % predicted		92 [84–106]	93 [82–112]	92 [84–106]	0.706
FEV ₁ z-score		-0.51 [-1.11–0.32]	-0.54 [-1.2–0.67]	-0.50 [-1.11–0.22]	0.973
FEV ₁ <LLN		11 (11)	2 (13)	9 (10)	0.661
FEV ₁ /FVC %		0.77 [0.73–0.81]	0.79 [0.76–0.85]	0.76 [0.72–0.81]	0.049
Gas diffusion	102				
D _{LCO} mmol.kPa ⁻¹ .min ⁻¹		6.8 [5.7–8.8]	7.9 [5.2–9.4]	6.7 [5.7–8.3]	0.794
D _{LCO} % predicted		83 [72–92]	83 [66–86]	83 [72–94]	0.278
D _{LCO} z-score		-0.86 [-1.52–0.06]	-0.74 [-1.04–0.60]	-0.88 [-1.54–0.02]	0.279
D _{LCO} <LLN		24 (24)	4 (29)	20 (23)	0.735
D _{LCO} /V _A mmol.kPa ⁻¹ .min ⁻¹ .L ⁻¹		1.39 [1.16–1.54]	1.34 [1.18–1.55]	1.39 [1.16–1.53]	0.876
D _{LCO} /V _A % predicted		95 [83–105]	95 [94–97]	96 [95–98]	0.899
D _{LCO} /V _A z-score		-0.28 [-1.13–0.39]	-0.46 [-0.90–0.09]	-0.17 [-1.17–0.41]	0.915
Dyspnoea oxygen saturation and exercise capacity					
Dyspnoea mMRC >0	69	37 (54)	5 (42)	32 (56)	0.526
Peripheral oxygen saturation at rest %	74	96 [95–97]	95 [94–97]	96 [95–98]	0.283
6-min walk distance m	73	580 [500–640]	615 [441–705]	588 [500–640]	0.540
Chest CT	100				
GGO >10% in at least one zone		25 (25)	6 (43)	19 (22)	0.108
Parenchymal bands		19 (19)	5 (36)	14 (16)	0.134

Data are presented as n, median [25th–75th percentile] or n (%), unless otherwise stated. ICU: intensive care unit; FVC: forced vital capacity; LLN: lower limit of normal; FEV₁: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; mMRC: modified Medical Research Council dyspnoea scale; CT: computed tomography; GGO: ground-glass opacities.

having these pathological CT findings were significantly higher in participants admitted to ICU, compared to those not admitted to ICU (table 3). Parenchymal bands, indicating early progression to fibrosis, were found in one out of five participants. With regard to parenchymal bands, an association with CRP and

TABLE 3 Association of dyspnoea, gas diffusing capacity, ground-glass opacities (GGO) or parenchymal bands with admission to the intensive care unit (ICU)

	Subjects n	OR (95% CI)	p-value
Dyspnoea[#] (mMRC >0 versus mMRC=0)	69		
Male sex		0.39 [0.14–1.08]	0.069
Age per 10 years		0.81 [0.57–1.14]	0.231
ICU admission		0.67 [0.18–2.50]	0.553
Gas diffusing capacity[#] (D_{LCO} <LLN versus D_{LCO} ≥LLN)	102		
History of smoking		1.56 [0.61–4.03]	0.356
ICU admission		1.54 [0.42–5.61]	0.517
GGO in chest CT[#] (>10% GGO in ≥1 zone versus none)	101		
Male sex		1.25 [0.45–3.46]	0.662
Age per 10 years		1.81 [1.21–2.72]	0.004
ICU admission		4.22 [1.14–15.6]	0.031
Parenchymal bands in chest CT[#] (yes versus no)	101		
Male sex		1.35 [0.47–3.89]	0.584
Age per year		1.19 [0.81–1.74]	0.376
ICU admission		2.99 [0.83–10.8]	0.093

Multivariate logistic regression analysis. mMRC: modified Medical Research Council dyspnoea scale; D_{LCO}: diffusing capacity of the lung for carbon monoxide; LLN: lower limit of normal; CT: computed tomography. [#]: dependent variable.

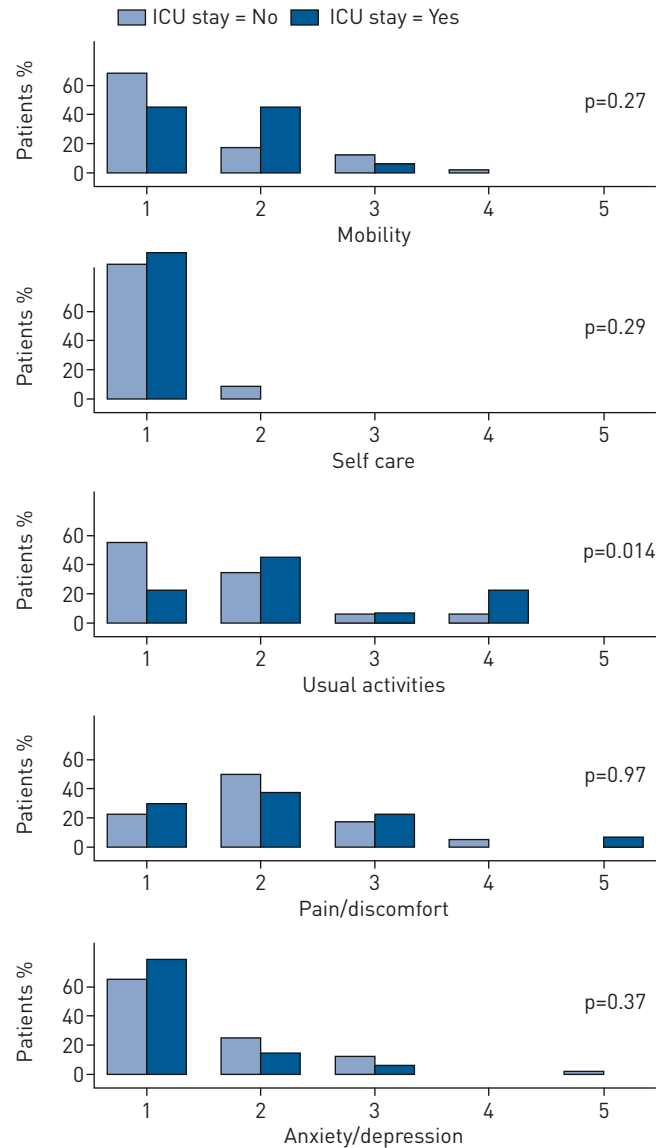


FIGURE 1 Distribution of EQ-5D-5L dimension scores for intensive care unit (ICU) (n=13) and non-ICU patients (n=75). 1: no problems, 2: slight problems, 3: moderate problems, 4: severe problems, 5: unable/extreme problems.

ventilator treatment was observed (p=0.018 and p=0.038, respectively) (supplementary table S1). There was no difference between participants admitted to ICU and participants not admitted to ICU (table 3).

The scores on the five EQ-5D-5L items are shown in figure 1. Participants admitted to ICU had a higher median score on usual activities than participants admitted to regular wards only: 4 (25th–75th percentile 2–4) versus 2 (1–2), respectively (p=0.014). The median±SD EQ-5D index scores were 0.61±0.23 and 0.72±0.19 for ICU and non-ICU patients, respectively (p=0.087).

Discussion

In this 3-month follow-up of a prospective cohort study of patients surviving hospital admission for COVID-19, approximately half of all participants had persistent dyspnoea on exertion, and one in four had reduced D_{LCO} . Persistent GGO on CT scans were present in one-fourth of the participants, while one in five had parenchymal bands. Participants admitted to ICU during hospital admission had higher prevalence of persistent CT abnormalities and reported more problems in usual activities, but similar lung function and self-reported dyspnoea to those not admitted to ICU.

The favourable spirometry outcomes observed in this cohort were accompanied by a low prevalence of reduced peripheral oxygen levels and reduced exercise capacity, as indicated by the 6MWT. In total, our results indicate that development of chronic respiratory failure after 3 months is not common in survivors of COVID-19 hospital admission, including survivors of ICU admission. The degree of self-reported dyspnoea 3 months after hospital admission was not associated with prior ICU stay, which we used as a

marker of COVID-19 severity. Dyspnoea is subjective and may be influenced by a number of other variables. The proportion of participants in our study with reduced diffusing capacity after 3 months was comparable to studies of SARS and MERS, and to other early reports in COVID-19 survivors [7, 10, 22, 23].

Persistent opacities in $\geq 10\%$ of one or more lung parenchyma zones, as assessed by CT, were present in approximately one in four participants after 3 months. Compared with reports after 4 weeks of follow-up in another cohort [10], this finding suggests that COVID-19 related GGO may resolve without development of persistent fibrosis. However, some of these CT findings may persist and gradually develop into fibrotic changes, as reflected by the finding of parenchymal bands in one-fifth of our study population [24]. In a retrospective study of COVID-19 patients 8 weeks after hospital discharge, $\sim 25\%$ showed signs of early fibrosis [22]. This is consistent with findings in our cohort. We found that age was associated with persistent GGO in our material, which is consistent with findings regarding community-acquired pneumonia [25]. In addition, explorative analyses find the inflammatory marker CRP to be associated with both persistent GGO and parenchymal bands. Interestingly, parenchymal bands were also associated with ventilator treatment. However, it is still unknown if the persistent pathological CT findings will progress to symptomatic pulmonary fibrosis over time or if various treatments for COVID-19 may influence the long-term outcome of parenchymal opacities.

We found CT abnormalities after 3 months to be more common in participants admitted to ICU. Yet, there were no differences in lung function or diffusing capacity, S_{pO_2} or 6MWT distance between these participants and participants not admitted to ICU, despite ICU patients having more bilateral lung opacities on chest radiography and higher levels of markers of systemic inflammation during hospital admission. In addition, all patient-reported outcomes were similar between groups, except that more participants admitted to ICU reported an impaired ability to perform usual activities. If replicated in additional studies, the association between ICU admission, persistent pathological CT opacities and lower performance of usual activities may indicate that patients admitted to ICU warrant closer clinical follow-up than other patients admitted to hospital for COVID-19.

A strength of the study is the multicentre prospective design, where all survivors from hospitals covering a catchment area of 1.8 million residents were assessed for eligibility. The age and prevalence of ICU admission were similar between our sample and metadata from the Norwegian COVID-19 statistics (<https://www.fhi.no/sv/smittsomme-sykdommer/corona>). Yet, we cannot exclude participation bias. Participation in the WHO Solidarity trial was an exclusion criterion, but the hospitals in the current study started inclusion in Solidarity only towards the end of the inclusion period of the current study. Overall, we believe the study cohort to be representative for survivors of COVID-19 hospital admission in Norway. Finally, due to the limited sample size, the current study was not powered to explore associations between possible pathophysiological mechanisms and persistent dyspnoea, reduced diffusing capacity or parenchymal opacities.

Conclusion

In our Norwegian cohort, approximately half of all participants reported dyspnoea on exertion 3 months after hospital admission for COVID-19. The majority of participants had lung volumes within the reference limits, while one-fourth had reduced diffusing capacity. CT scans showed that one in four had persistent GGO, and one in five had parenchymal bands. ICU admission was associated with persistent CT abnormalities and reduced ability to perform usual activities, but not with dyspnoea, impaired lung function or reduced functional capacity, 3 months after discharge from the hospital.

Author contributions: G. Einvik conceived the study. The protocol was designed by T.M. Aaløkken, E. Brønstad, E. Ikdahl, M.T. Durheim, K. Stavem, O.H. Skjønsberg, H. Ashraf and G. Einvik in collaboration. Patient inclusion and data collection were performed by T.V. Lerum, E. Brønstad, B. Aarli, K.M.A. Lund, K. Tonby, K. Stavem, O.H. Skjønsberg and G. Einvik. T.M. Aaløkken, J.R. Rodriguez, C. Meltzer and H. Ashraf interpreted and analysed the CT findings. Statistical analyses were performed and analysed by T.V. Lerum, K. Stavem and G. Einvik. The first draft of the manuscript was written by T.V. Lerum, O.H. Skjønsberg, K. Stavem and G. Einvik. All authors contributed with considerable critical review of the manuscript and approval of the final version.

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