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Radiological abnormalities persist following COVID-19 and correlate with impaired health-related quality of life: a prospective cohort study of hospitalised patients

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ABSTRACT

Background The radiological trajectory of post-COVID-19 is uncertain. We present a prospective, observational, multicentre cohort study using multimodality imaging to describe the pulmonary sequelae of patients hospitalised with COVID-19, predictors of persistent abnormal radiology and implications on health status.

Methods In survivors of COVID-19, we performed convalescent CT pulmonary angiogram and high-resolution CT imaging as part of the CISCO-19 study (ClinicalTrials.gov ID NCT04403607). This included serial blood biomarkers and patient-reported outcomes 28–60 days following discharge from hospital.

Results Of the COVID-19 cohort, 88 (56%) patients of the COVID-19 cohort (n = 159; mean age, 55 years; 43% female) had persisting radiological abnormalities at 28–60 days postdischarge. This included ground-glass opacification (45%), reticulation/architectural distortion (30%) or mixed pattern (19%). These features were very infrequent among a group of age-matched, sex-matched and cardiovascular risk factor-matched controls (n=29). The majority of COVID-19 cohort (68%) had less than 20% persisting radiological abnormalities, with 67% demonstrating overall improvement compared with admission imaging. Older age, premorbid performance status, typical acute COVID-19 radiological features, markers of severe acute COVID-19, convalescent ICAM-1 and P-selectin were associated with persisting lung abnormalities (all $p<0.05$). Patients with persisting abnormalities were shown to have lower levels of physical activity and predicted maximal oxygen utilisation (derived VO_2) (both $p<0.05$). Higher percentage of abnormal lung parenchyma was associated with lower patient-assessed quality of life (EQ-5D-5L) score ($p=0.03$).

Conclusions Persistent radiological abnormalities post-COVID-19 were common at 28–60 days postdischarge from hospital, although most improved. Patients with persisting radiological abnormalities 28–60 days postdischarge are at risk of persisting health impairment in the longer term and represent a population for targeted intervention.

Trial registration number NCT04403607.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Respiratory symptoms are frequently reported in survivors of COVID-19 but the relationship between persistent abnormal radiological findings and burden of COVID-19 symptoms requires characterisation.

WHAT THIS STUDY ADDS

⇒ Dual lung imaging (high-resolution CT and CT pulmonary angiogram) in survivors of COVID-19 demonstrates improving radiological features, but that persisting radiological changes are associated with impaired qualitative health measures.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the large number of COVID-19 survivors and the risk of future pandemics, the finding of common and important persisting lung abnormalities post-COVID-19 highlights the need for both healthcare services and research to be aware of long-term complications and how to best serve these patients.

INTRODUCTION

COVID-19 is caused by a novel coronavirus, known as SARS-CoV2. From December 2019, it spread rapidly throughout the world, with 700 million confirmed cases including 6.7 million deaths reported globally as of February 2023. Lung injury represents the most common clinical manifestation of COVID-19, ranging from mild asymptomatic cases to acute respiratory failure requiring ventilatory support. There remains limited knowledge regarding the pulmonary sequelae of COVID-19.

Since 2020 the global effort in vaccination has brought the pandemic caused by SARS-CoV2 under control. However,

the virus persists at an endemic level, with seasonal epidemic peaks likely. Although severe COVID-19 illness is currently less frequent, waning immunity and viral adaptation may influence the recurrence of severe illness seen in the future. Therefore, understanding the impact of respiratory sequelae post-COVID-19 remains important for future healthcare and research efforts. The main pathological features of severe acute respiratory syndrome caused by COVID-19 are exudative and proliferative diffuse alveolar damage, similar to severe acute respiratory syndrome coronavirus 1 (SARS) and the Middle East respiratory syndrome (MERS).[1] Long-term respiratory sequelae have been documented in those surviving viral pneumonia from other coronavirus strains including SARS or MERS.[2 3] The concern, therefore, exists as to whether similar sequelae occur after COVID-19.

Studies to date have predominantly characterised early radiological abnormalities due to acute COVID-19 and assessed early in disease recovery.[4] Data on the morphological characteristics and potential medium- to longer-term lung abnormalities are lacking. The requirement for, as well as the duration and timing of, radiological assessment is unknown. Current consensus guidelines for follow-up (published by the British Thoracic Society) are based on expert opinion and have resource implications.[5]

Ongoing respiratory symptoms are frequently reported in the convalescent phase,[6–8] and predicting patients at increased risk of long-term COVID-19 complications is of significant clinical importance. Two definitions are provided for postacute COVID-19 by the National Institute for Clinical Excellence: (1) ongoing symptomatic COVID-19, which includes patients with persistent symptoms up to 12 weeks from symptom onset; and (2) post-COVID-19 syndrome, which includes patients with persistent symptoms beyond 12 weeks.[9] The risk factors of post-COVID-19 syndrome respiratory symptoms include prolonged hospital admission, deconditioning, postintensive care syndrome, the development of pulmonary fibrosis, and impaired lung function post-COVID-19.[10–12] Residual CT lung abnormalities after the acute illness of COVID-19 have been reported, but the relationship between pulmonary changes and persistent symptoms in keeping with post-COVID-19 syndromes is unclear.

Thus, understanding the prevalence of persisting radiological abnormalities, the factors predictive of non-resolution, and implications for patients would aid management of the large post-COVID patient population and healthcare resource allocation. Stratifying patients at greater need for follow-up will potentially allow streamlining of follow-up pathways and utilisation of resources. In addition, identifying phenotypes for patients at higher risk of longer-term sequelae may allow development and targeting of disease-modifying therapies before the onset of complications.

We present a prospective, observational, multicentre, longitudinal, cohort study using multimodality imaging to assess the pulmonary sequelae of COVID-19.

METHODS

Study design and setting

We performed convalescent CT pulmonary angiography (CTPA) and high-resolution thoracic (HRCT) imaging in survivors of COVID-19, 28–60 days following discharge from hospital. The study was undertaken in the West of Scotland across three sites, the Queen Elizabeth University Hospital, Glasgow Royal Infirmary and the Royal Alexandra Hospital in Paisley. The methods have been published in detail previously.[13]

Inclusion and exclusion criteria

The criteria for eligibility included the following: (1) adults aged ≥18 years old; (2) history of unscheduled hospital attendance as a result of acute COVID-19 infection confirmed by PCR-positive nasopharyngeal swab (Roche Cobas 6800 or Seegene SARS-CoV-2 PCR); (3) able to comply with the study procedures; and (4) able to provide written informed consent. Accredited radiologists reported the imaging results according to contemporary national guidelines.[14]

The exclusion criteria for the CISCO-19 study were the following: (1) contraindication to MRI as the primary outcome pertained to myocarditis and (2) inability to provide informed consent.

Control participants

29 COVID-19-negative, age-matched, sex-matched and cardiovascular-matched control volunteers were recruited following informed written consent to undergo identical study assessments to participants with COVID-19. Negative COVID-19 status was confirmed based on absence of clinical history and a negative IgG antibody result (SARS-CoV-2 IgG II Quant assay).

Research schedule and assessments

The research schedule included two assessments: (1) a baseline visit, performed at enrolment either during the index hospitalisation episode or as soon as possible following discharge, and (2) the imaging visit (28–60 days postdischarge) consisting of cardiovascular MRI and high-resolution CT of the thorax followed by CT pulmonary and coronary angiography. At each visit, patients underwent a 12-lead electrocardiogram (Beneheart R3, Mindray, Huntingdon, UK); provided blood samples for biomarkers of cardiovascular injury, inflammation, thrombosis and renal status; provided a urine sample for albumin to creatinine ratio; and completed health status questionnaires.

Imaging protocol

A 320-detector CT scanner (Aquillon ONE, Canon Medical Systems Corporation) was used for the combined protocol of initial unenhanced helical scan of the thorax and subsequent coronary and pulmonary angiography. A contrast bolus timing acquisition was performed to assess

Table 1 Clinical characteristics of the study population

	COVID-19 n=159	Controls n=29	P value
Demographics			
Age (years), mean (SD)	54.5 (11.9)	57.3 (9.6)	0.374
Male sex, n (%)	90 (56.6%)	18 (62.1%)	0.685
Female sex, n (%)	69 (43.4%)	11 (37.9%)	
SIMD quintile (most deprived), n (%)	61 (40.4%)	5 (17.9%)	0.032
Body mass index (kg/m^2), mean (SD)	30.5 (7.1)	30.7 (5.0)	0.555
Pre-COVID-19 performance status, n (%)			
Grade 0	130 (88.4%)	*	
Grade 1	14 (9.5%)	*	
Grade 2	2 (1.4%)	*	
Grade 3	1 (0.7%)	*	
Grade 4	0 (0.0%)	*	
Grade 5	0 (0.0%)	*	
Occupation, n (%)			
Healthcare worker	32 (20.6%)	*	
Non-healthcare key worker	33 (21.3%)	*	
Non-person facing	26 (16.8%)	*	
Not working/retired	28 (18.1%)	*	
Ethnicity, n (%)			
Arab	4 (2.5%)	0 (0.0%)	0.788
Black	2 (1.3%)	0 (0.0%)	
East Asian	4 (2.5%)	0 (0.0%)	
South Asian	8 (5.0%)	2 (6.9%)	
West Asian	2 (1.3%)	1 (3.4%)	
Latin American	0 (0.0%)	0 (0.0%)	
White	139 (87.4%)	26 (89.7%)	
Smoking status, n (%)			
Never smoker	106 (66.7%)	18 (62.1%)	0.737
Former smoker	44 (27.7%)	9 (31.0%)	
Current smoker	9 (5.7%)	2 (6.9%)	
Cardiovascular history, n (%)			
Hypercholesterolaemia	76 (47.8%)	13 (44.8%)	0.841
Hypertension	56 (35.2%)	10 (34.5%)	1.000
Diabetes mellitus	35 (22.0%)	2 (6.9%)	0.075
Chronic kidney disease	7 (4.4%)	0 (0.0%)	0.598
Myocardial infarction	17 (10.7%)	0 (0.0%)	0.079
Heart failure	2 (1.3%)	1 (3.4%)	0.397
Stroke or TIA	5 (3.1%)	3 (10.3%)	0.108
Peripheral vascular disease	1 (0.6%)	0 (0.0%)	1.000
Cardiovascular disease or treatment	74 (46.5%)	14 (48.3%)	1.000
Respiratory history, n (%)			
No chronic lung disease	126 (81.3%)	28 (96.6%)	0.169
Chronic obstructive pulmonary disease	8 (5.2%)	0 (0.0%)	

Continued

Table 1 Continued

	COVID-19 n=159	Controls n=29	P value
Asthma	17 (11.0%)	0 (0.0%)	
Bronchitis	2 (1.3%)	1 (3.4%)	
Pulmonary vascular disease	1 (0.6%)	0 (0.0%)	
Interstitial lung disease/pulmonary fibrosis	1 (0.6%)	0 (0.0%)	
Pre-existing maintenance medication, n (%)			
Oral anticoagulant	8 (5.0%)	1 (3.4%)	1.000
Antiplatelet	15 (9.4%)	2 (6.9%)	1.000
Immunosuppression	4 (2.5%)	0 (0.0%)	1.000

*Data not available on occupation for control comparison.

cardiopulmonary transit times. Contrast-enhanced angiographic breath-hold ECG-gated volumes were acquired with adjustment for optimum pulmonary and systemic arterial tree opacification. The remaining CT coronary angiography and MRI protocol have been published previously.[13] Patients with severe renal dysfunction or history of contrast reaction underwent non-contrast acquisitions. Features of pulmonary involvement following COVID-19 were classified as atelectasis, reticulation and/or architectural distortion, and ground-glass opacity. This was categorised based on expert radiology opinion.

Radiological assessment and blinding

Reports were provided by two independent radiologists (GR and DBS) without any knowledge of the additional study visits. Clinical reports were generated and incidental findings followed up as per local policies. Visual estimate of percentage total lung volume abnormal was assessed using a modification of the technique described by Charpentier *et al* with the percentage score for each lung recorded in decile ranges.[15] Imaging at diagnosis (CT or chest X-ray) was compared with research imaging CT in order to assess trajectory of radiological changes.

Health status questionnaires and patient-reported outcome measures

Participants completed written questionnaires at enrolment and at the imaging visit (28–60 days following discharge from hospital). Standardised questionnaires with relevant permissions included the EuroQoL EQ-5D-5L, Brief Illness Perception Questionnaire, The Patient Health Questionnaire-4, the Duke Activity Status Index questionnaire and The International Physical Activity Questionnaire–Short Form.

Clinical outcomes and follow-up

Participants provided written consent for longitudinal follow-up using digital health records. The occurrence of serious adverse events and NHS resource utilisation including referrals to secondary care were assessed in concordance with a predefined charter as per protocol.

Statistics

Statistical analysis was performed according to a predefined analysis plan. Missing data are reported. 95% CIs accompany two-sided p values for estimated effect sizes and measures of association. The widths of the CIs have not been adjusted for multiplicity. The p values for subgroup differences were calculated using the Fisher exact test and the Kruskal-Wallis test for categorical and continuous data. Stepwise multivariable logistic regression was undertaken to assess for the relationship between clinical characteristics, blood and imaging biomarkers, patient-reported outcomes and persisting pulmonary abnormalities. Analysis was performed using the statistical programming language R V.4.0.3.

Patient and public involvement (PPI)

Patient and public input into the study design and conduct was obtained by regular discussion at our healthboard COVID-19 PPI group.

RESULTS

In total, 1306 patients were screened between 22 May 2020 and 16 March 2021, and 267 patients provided written informed consent. 159 patients were evaluated at 28–60 days after the last episode of hospital care with COVID-19 (table 1). Their average age was 55 years, 139 (87%) were White, 90 (57%) were male, 74 (46%) had a history of cardiovascular disease or treatment and 61 (40%) were in the highest quintile of social deprivation. The majority (81%) had no history of prior respiratory disease and 106 (67%) were never smokers. The majority of patients had a WHO performance status of zero (able to carry out all normal activity without restriction) prior to the COVID-19 and 32 (21%) were healthcare workers. Acute COVID-19 characteristics are described in online supplemental table 1. Regarding

Table 2 Description of radiological features within study population

	COVID-19 n=159	Controls n=29	P value
CT of chest 28–60 days postdischarge, mean (SD)			
Ground-glass opacity, n (%)	70 (44.6%)	1 (4.2%)	<0.001
Reticulation/architectural distortion, n (%)	47 (29.9%)	1 (4.2%)	0.006
Ground-glass opacity and reticulation, n (%)	29 (18.5%)	0 (0.0%)	0.016
Ground-glass opacity and/or reticulation, n (%)	88 (56.1%)	2 (8.3%)	<0.001
Atelectasis, n (%)	13 (8.3%)	0 (0.0%)	0.222
New pulmonary arterial thrombus, n (%)	5 (3.3%)	0 (0.0%)	1.000
Visual estimate of % of total lung area abnormal, mean (SD)			
Less than 20%, n (%)	107 (68.2%)	23 (95.8%)	0.006
Between 20% and 49%, n (%)	38 (24.2%)	0 (0.0%)	
Greater than 50%, n (%)	12 (7.6%)	1 (4.2%)	
Visual estimate of % of total lung area abnormal, mean (SD)	14.3 (19.0)	2.2 (10.2)	<0.001
Pulmonary vascular diameter, mean (SD)			
Pulmonary trunk (millimetres)	25.1 (3.4)	23.9 (3.6)	0.062
Right pulmonary artery (millimetres)	21.2 (2.8)	20.4 (3.4)	0.201
Left pulmonary artery (millimetres)	21.2 (2.5)	19.4 (2.7)	<0.001
Pulmonary artery to aorta ratio	0.8 (0.1)	0.8 (0.1)	0.111
Trajectory of radiographic changes*†, n (%)			
Normal/improving	23 (15.3%)	2 (40.0%)	0.174
Normal/static	27 (18.0%)	2 (40.0%)	
Abnormal/improving	78 (52.0%)	1 (20.0%)	
Abnormal/static	20 (13.3%)	0 (0.0%)	
Abnormal/worsening	2 (1.3%)	0 (0.0%)	
Timelines (days), mean (SD)			
Days from diagnosis to admission CT/chest X-ray	15.5 (22.5)	10.0 (14.1)	0.813
Days from admission CT/chest X-ray to imaging visit CT	46.1 (17.9)		
Diagnosis to imaging visit CT (days)	61.4 (20.2)		

*Trajectory of radiological change is comparison of the 28–60 days postdischarge CT with the COVID-19 acute admission imaging. The postdisharge CT being either normal or abnormal, and either static, improving or worsening compared with admission imaging.
†Initialy imaging undertaken in five controls for non-COVID-19 clinical indications, allowing comparison to research CT.

acute COVID-19 therapies, 50 (31%) patients did not receive oxygen therapy, 20 (13%) patients required non-invasive ventilation, mechanical invasive ventilation was used in 5 (3%) patients and an additional 10 (6.3%) patients received organ support. 89 (56%) patients were treated with steroids.

Comparison with controls

29 control patients with similar age, sex, ethnicity and history of cardiovascular and respiratory disease underwent the same research procedures. Their characteristics are described in table 1 and online supplemental tables 1 and 2. Compared with controls, COVID-19 patients had multisystem differences in keeping with acute illness at enrolment (online supplemental table 1). Compared with controls, at enrolment and 28–60 days postdischarge, COVID-19 patients had lower health-related quality of life, enhanced illness perception, higher levels of anxiety and depression, lower levels of physical activity and lower predicted maximal oxygen utilisation (mL/kg/min) (online supplemental table 2).

Imaging

Chest CT was undertaken 28–60 days postdischarge in COVID-19 patients and compared with admission imaging undertaken during the acute illness (CT n=92, or CXR n=58). The mean interval between admission imaging and research CT was 46 days (SD 18) and between diagnosis of COVID-19 and research CT 61 days (SD 20) (table 2).

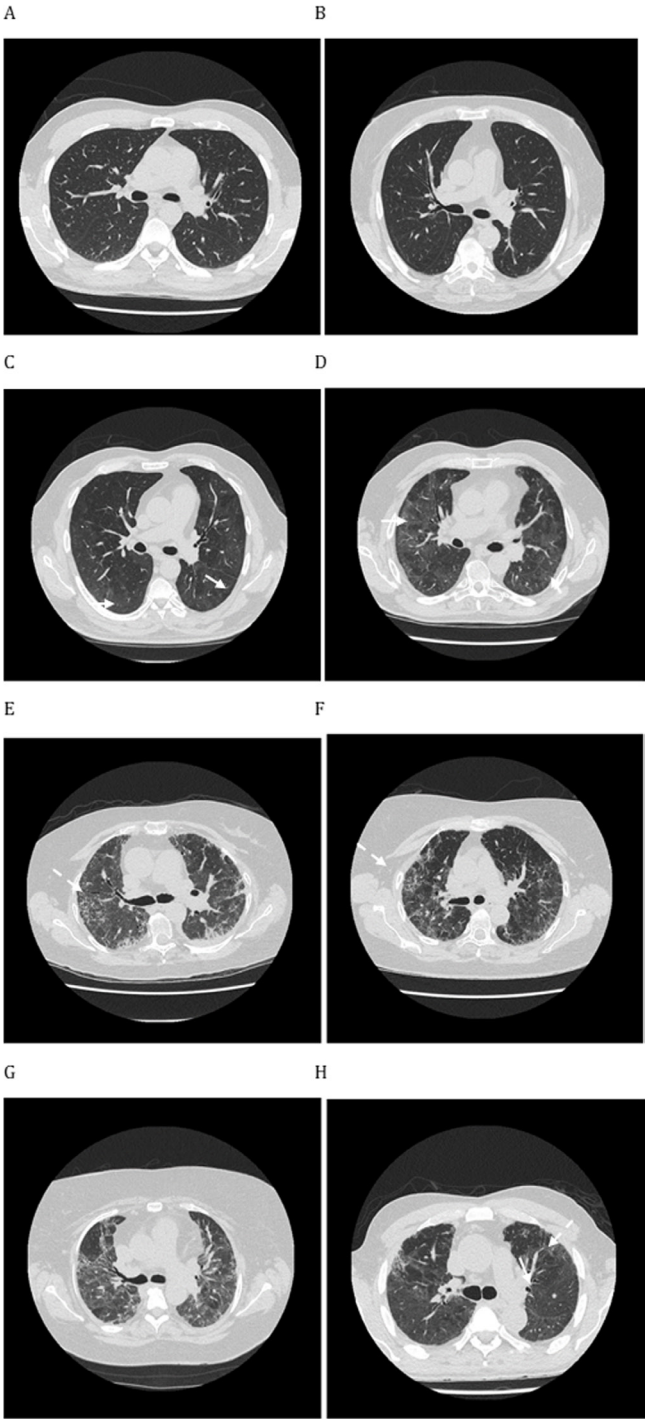

Figure 1 Radiological features on CT at 28–60 days postdischarge from hospital for COVID-19 infection. (A, B) Normal lung parenchyma. (C, D) Persistent ground-glass opacities (GGOs; examples indicated by solid arrows) scattered throughout the lung parenchyma. Ranging from faint peripheral GGO (C) compared with more florid persisting changes (D). (E, F) Reticular changes (examples indicated by dashed arrows). (G, F) Mixed persisting GGO and reticular changes.

Radiological features post-COVID-19

In patients hospitalised with COVID-19, compared with controls, the lung imaging revealed persisting abnormalities at days 28–60 postdischarge (table 2 and figure 1). The most common persisting radiological feature was ground-glass opacity (table 2, figure 1C,D), seen in 45% of patients, followed by reticulation/architectural distortion, seen in 30% of patients (table 2, figure 1E,F), and a mixed pattern in 19% (table 2, figure 1G,H). The majority of patients (68%) had less than 20% persisting abnormal lung tissue on imaging. Pulmonary arterial thrombus was observed in six patients, other than one case with a single lobar pulmonary artery involved, all were segmental/subsegmental and five (3.3%) were new diagnosis since COVID-19 discharge. Although the left pulmonary artery was statistically larger in COVID-19 patients compared with controls, the absolute difference was negligible. There was overall no statistical or clinically significant difference in any other pulmonary vascular measurements (table 2).

Compared with admission imaging, the majority of patients demonstrated improvement in radiological changes, either improving to normal (15%) or improved but with persisting abnormalities (52%) (table 2). COVID-19 patients with persistent CT abnormalities were compared with those COVID-19 patients with no persisting radiological abnormalities (table 3 and online supplemental table 3). Those with persisting ground-glass opacification and/or reticular changes were older (p<0.001), had slightly worse pre-COVID-19 performance status (p=0.018), had higher rates of hypercholesterolaemia (p<0.001) and were more likely to be former or current smokers (p=0.022). There was, however, no difference between groups in the rates of pre-existing chronic respiratory disease. Patients with persistent abnormal radiology were more likely to have markers of more severe acute illness (online supplemental table 3), including lower admission saturations, higher rates of oxygen therapy, longer admissions, higher risk scores (ISARIC-4C and Charlson comorbidity index) and more frequent laboratory features of severe acute COVID-19 (lymphocyte counts, peak ferritin, peak D-dimer, peak C-reactive protein).

Factors associated with persistent radiological abnormalities post-COVID-19

Univariate and multivariable associations between selected demographic and clinical measures and persistent post-COVID-19 radiological abnormalities at days 28–60 postdischarge were assessed with logistic regression models (table 4). Older age (OR (95% CI): 2.48 (1.21, 5.55); p=0.018), pre-COVID-19 performance status (24.44 (2.45, 467.71); p=0.016) and typical COVID-19 changes on admission imaging were multivariable associates of persistent radiological abnormalities. Anticoagulation regimens were also associated with persistent abnormalities but with wide CIs observed (table 4). The levels of ICAM-1 (6.23 (2.57, 16.47); p<0.001 on univariate analysis) and P-selectin (6.17 (1.35, 34.87); p=0.026 on multivariable analysis) measured at 28–60 days postdischarge

Table 3 Clinical characteristics in patients with presence of ground-glass opacity (GGO) and/or reticular changes compared with COVID-19 patients with normal high-resolution thorax CT (HRCT)

	GGO and/or reticular changes at 28–60 days postdischarge	Normal HRCT at 28–60 days postdischarge	P value
	n=88	n=55	
Demographics			
Age (years), mean (SD)	57.5 (10.4)	49.4 (13.5)	<0.001
Male sex, n (%)	54 (61.4%)	28 (50.9%)	0.229
Female sex, n (%)	34 (38.6%)	27 (49.1%)	0.229
SIMD quintile (most deprived), n (%)	34 (41.5%)	19 (35.8%)	0.590
Body mass index (kg/m^2), mean (SD)	31.4 (7.8)	29.6 (6.0)	0.247
Performance status, n (%)			
Grade 0	70 (83.3%)	49 (98.0%)	0.018
Grade 1	12 (14.3%)	1 (2.0%)	
Grade 2	2 (2.4%)	0 (0.0%)	
Grade 3	0 (0.0%)	0 (0.0%)	
Grade 4	0 (0.0%)	0 (0.0%)	
Grade 5	0 (0.0%)	0 (0.0%)	
Occupation, n (%)			
Healthcare worker	11 (12.5%)	15 (28.3%)	0.021
Non-healthcare key worker	23 (26.1%)	8 (15.1%)	
Non-person facing	13 (14.8%)	12 (22.6%)	
Not working/retired	19 (21.6%)	4 (7.5%)	
Ethnicity, n (%)			
Arab	1 (1.1%)	2 (3.6%)	0.834
Black	1 (1.1%)	1 (1.8%)	
East Asian	2 (2.3%)	1 (1.8%)	
South Asian	4 (4.5%)	4 (7.3%)	
West Asian	1 (1.1%)	1 (1.8%)	
White	79 (89.8%)	46 (83.6%)	
Smoking status, n (%)			
Never smoker	52 (59.1%)	44 (80.0%)	0.022
Former smoker	30 (34.1%)	8 (14.5%)	
Current smoker	6 (6.8%)	3 (5.5%)	
Cardiovascular history, n (%)			
Hypercholesterolaemia	51 (58.0%)	15 (27.3%)	<0.001
Hypertension	37 (42.0%)	14 (25.5%)	0.050
Diabetes mellitus	25 (28.4%)	9 (16.4%)	0.111
Chronic kidney disease	2 (2.3%)	2 (3.6%)	0.639
Myocardial infarction	10 (11.4%)	6 (10.9%)	1.000
Heart failure	0 (0.0%)	1 (1.8%)	0.385
Stroke or TIA	4 (4.5%)	1 (1.8%)	0.649
Peripheral vascular disease	1 (1.1%)	0 (0.0%)	1.000
Cardiovascular disease or treatment	47 (53.4%)	22 (40.0%)	0.126
Respiratory history, n (%)			
No chronic lung disease	71 (81.6%)	46 (85.2%)	0.455
Chronic obstructive pulmonary disease	6 (6.9%)	1 (1.9%)	

Continued

Table 3 Continued

	GGO and/or reticular changes at 28–60 days postdischarge	Normal HRCT at 28–60 days postdischarge	P value
	n=88	n=55	
Asthma	9 (10.3%)	6 (11.1%)	
Pulmonary vascular disease	0 (0.0%)	1 (1.9%)	
Interstitial lung disease/pulmonary fibrosis	1 (1.1%)	0 (0.0%)	
Pre-existing maintenance medication, n (%)			
Oral Anticoagulant	4 (4.5%)	4 (7.3%)	0.484
Antiplatelet	11 (12.5%)	2 (3.6%)	0.082
Immunosuppression	3 (3.4%)	1 (1.8%)	1.000

were the only convalescent biomarkers associated with persistent radiological abnormalities (table 5).

Association of persistent radiological abnormalities post-COVID-19 with health status

COVID-19 patients with persistent ground-glass opacities and/or reticular changes, compared with those with normal radiology, at 28–60 days postdischarge had lower levels of physical activity and lower predicted maximal oxygen utilisation (online supplemental table 4). The relationship between percentage abnormal lung at 28–60 days postdischarge and measures of health status was assessed by linear regression (table 6). On multivariable analysis, percentage abnormal lung was associated with lower patient-assessed quality of life (EQ-5D-5L) score (coefficient (95% CI): −0.23 (−0.38, −0.08); p=0.03), but not other health status scores.

DISCUSSION

Persisting radiological abnormalities were common findings in post-COVID-19 patients 28–60 days after hospital discharge. Common persistent pulmonary parenchymal features include ground-glass opacities and reticulation/architectural distortion, with infrequently observed pulmonary artery thrombus. COVID-19 patients had 14% of total lung volume remaining abnormal up to 60 days, compared with 2% in control patients without pre-existing lung disease. At this time, 32% of COVID-19 patients still had at least 20% of total lung parenchyma abnormal on CT. Most (67%) COVID-19 patients exhibited improving pulmonary radiological changes over time, but persistent abnormalities were linked to health status impairments.

To our knowledge, this is the largest study in the UK using both HRCT and CTPA to define lasting radiological abnormalities.[16–18] While our study revealed improving radiology, persistent abnormalities were frequent up to 60 days after discharge. Ground-glass opacities (45%) and reticular changes/architectural distortion (30%) were the most common radiological sequelae. Few long-term studies post-COVID-19 have been reported, but CT follow-up at up to a year showed persistent abnormalities in 32–34%.[17 18] Improving diagnostics, like hyperpolarized xenon MRI, can help identify pulmonary disorders in post-COVID-19 patients with reduced gas transfer despite normal CT pulmonary imaging.[19]

Acute COVID-19 is linked to a hypercoagulable state and increased risk of thrombosis and thromboembolic events, which contribute to higher morbidity and mortality.[20] Limited data exist on postdischarge thrombotic events and the risk of lasting pulmonary vascular abnormalities, including pulmonary hypertension. Using convalescent CTPA, we found a low prevalence of pulmonary thrombosis (3%) up to day 60 and no significant difference in CT pulmonary vascular measures. The UK-wide multicentre Helping to Alleviate the Longer-term consequences of COVID-19 (HEAL-COVID) trial recently reported that the oral anticoagulant apixaban did not reduce the risk of re-admissions or death post-COVID-19.[21]

Factors influencing susceptibility to persistent symptoms in COVID-19 patients remain unclear. Modifying factors include sex, age, epigenetics, lifestyle, comorbidity burden, vaccine status, SARS-CoV-2 strain, severity of illness, treatment regimen, complications, hospital stay duration and rehabilitation.[22–26] The factors causing lasting post-COVID-19 pulmonary radiological abnormalities are also uncertain. Our study is novel in incorporating dual modality imaging with a large panel of relevant biomarkers and patient characteristics. Age, pre-COVID-19 performance status and typical acute radiological changes are non-modifiable factors linked to persisting abnormal radiology in our cohort. The increased ICAM-1 and P-selectin levels observed in COVID-19-recovered patients indicate endothelial dysfunction, which may cause blood clotting, impaired blood flow and chronic inflammation, leading to persistent pulmonary abnormalities.[27] Moreover, endotheliitis may explain multi-organ involvement in long COVID, as endothelial cells are present throughout the body, and their inflammation and dysfunction may contribute to symptoms. Hence, targeting acute endothelial damage and dysfunction in

Table 4 Stepwise multivariable logistic regression of clinical characteristic predictors of persistent abnormal C19-related radiology: ground-glass opacity (GGO) and/or reticular changes at 28–60 days postdischarge

	Univariate		Multivariable	
Variable	**OR (95% CI)**	**P Value**	**OR (95% CI)**	**P value**
Demographics				
Age (decades)	1.64 (1.23, 2.23)	0.001	2.48 (1.21, 5.55)	0.018
Female sex (vs male sex)	0.69 (0.36, 1.30)	0.249	0.64 (0.17, 2.37)	0.506
Performance status				
Grade 1 (vs grade 0)	5.14 (1.33, 33.89)	0.037	24.44 (2.45, 467.71)	0.016
Occupation				
Non-healthcare key worker (vs healthcare worker)	4.39 (1.59, 12.92)	0.005		
Non-person facing (vs healthcare worker)	1.91 (0.67, 5.62)	0.232		
Not working/retired (vs healthcare worker)	4.03 (1.41, 12.33)	0.011		
Presenting characteristics, mean (SD)				
Body mass index (kg/m^2)	4.35 (0.97, 21.48)	0.061		
Heart rate (beats per minute)	1.01 (1.00, 1.03)	0.158		
Systolic blood pressure (mm Hg)	0.99 (0.98, 1.01)	0.308		
Diastolic blood pressure (mm Hg)	0.97 (0.95, 1.00)	0.046		
Peripheral oxygen saturation (%)	0.85 (0.77, 0.92)	<0.001		
Fraction of inspired oxygen at presentation (%)	1.17 (1.04, 1.38)	0.032		
Respiratory rate (breaths per minute)	1.97 (0.74, 5.86)	0.194		
WHO clinical severity score				
Oxygen by mask or nasal prongs (vs hospitalised, no oxygen therapy)	5.36 (2.43, 12.58)	<0.001		
Non-invasive ventilation (vs hospitalised, no oxygen therapy)	31.09 (7.50, 216.05)	<0.001		
Radiology, chest radiograph or CT scan				
Atypical features of COVID-19 (vs typical)	0.51 (0.14, 1.87)	0.287	0.23 (0.02, 2.32)	0.212
Unlikely (vs typical)	0.14 (0.01, 1.14)	0.094	0.01 (0.00, 0.25)	0.009
Normal (vs typical)	0.04 (0.01, 0.16)	<0.001	0.08 (0.01, 0.54)	0.018
Acute COVID-19 therapy				
Oxygen	8.58 (4.01, 19.65)	<0.001		
Steroid	3.71 (1.92, 7.31)	<0.001		
Antiviral	3.37 (1.56, 7.82)	0.003		
Non-invasive respiratory support	15.63 (4.44, 99.40)	<0.001		
Acute COVID-19 anticoagulation strategy				
Prophylactic anticoagulation (vs no anticoagulation)	7.26 (2.28, 32.50)	0.003	12.05 (1.67, 148.13)	0.026
High-dose prophylaxis (vs no anticoagulation)	130.33 (24.92, 1152.12)	<0.001	150.76 (11.44, 4258.91)	<0.001
Therapeutic anticoagulation during admission only (vs no anticoagulation)	7.67 (0.26, 234.43)	0.186	8.59 (0.07, 1463.28)	0.411
Prior or newly commenced therapeutic anticoagulation continuing postdischarge (vs no anticoagulation)	21.47 (4.98, 124.10)	<0.001	43.43 (2.97, 1206.38)	0.012
Cardiovascular history				
History of smoking (vs never smoker)	2.14 (1.04, 4.60)	0.044		
Hypercholesterolaemia	2.43 (1.28, 4.69)	0.007		
Diabetes mellitus	2.34 (1.06, 5.50)	0.041		
Duration of admission, mean (SD), days (log)	3.25 (2.12, 5.37)	<0.001		

ORs, 95% CIs and p values derived from logistic regression models. Univariate models include one predictor only. Multivariable model was adjusted for age and sex, and included any other factors found to have p<0.05 in univariate analysis (ie, healthcare worker status and acute kidney injury). For each predictor, the OR relates to the specified between-group difference (categorical predictors), or increase (continuous predictors).

Table 5 Stepwise multivariable logistic regression of laboratory/biomarker predictors of persistent abnormal C19-related radiology: ground-glass opacity (GGO) and/or reticular changes at 28–60 days postdischarge

	Univariate		Multivariable	
Variable	OR (95% CI)	P value	OR (95% CI)	P value
Laboratory results, index admission				
Initial lymphocyte count (×10^9/L), mean (SD), (log)	0.38 (0.19, 0.70)	0.004		
Peak D-dimer (ng/mL), mean (SD), (log)	6.82 (2.90, 20.48)	<0.001		
Peak creatinine (µmol/L), mean (SD), (log)	2.51 (1.21, 5.95)	0.022		
Minimum eGFR (mL/min/1.73 m^2), mean (SD)	0.98 (0.97, 0.99)	0.006		
Acute kidney injury, n (%)	8.56 (2.33, 55.35)	0.005		
Peak ferritin (mg/L), mean (SD), (log)	2.11 (1.52, 3.05)	<0.001		
Peak C-reactive protein (mg/L), median (IQR), (log)	2.50 (1.78, 3.71)	<0.001		
Initial albumin (g/L), mean (SD)	0.81 (0.75, 0.88)	<0.001		
Biomarkers at enrolment, central laboratory				
Ferritin (µg/L), median (IQR), (log)	1.54 (1.09, 2.22)	0.016	2.04 (0.92, 4.92)	0.093
Triglycerides (mmol/L), mean (SD), (log)	2.24 (1.16, 4.52)	0.019		
HDL cholesterol (mmol/L), mean (SD), (log)	0.23 (0.07, 0.67)	0.009		
D-Dimer (ng/mL), mean (SD), (log)	2.57 (1.59, 4.32)	<0.001		
Fibrinogen (g/L), mean (SD), (log)	2.42 (1.06, 5.77)	0.040		
Factor VIII (IU/dL), mean (SD), (log)	3.15 (1.62, 6.43)	0.001		
VWF:GP1bR (IU/dL), mean (SD), (log)	3.81 (2.01, 7.64)	<0.001		
VWF:Ag (IU/dL), mean (SD), (log)	5.46 (2.60, 12.70)	<0.001		
ICAM-1 (ng/mL), mean (SD), (log)	4.58 (1.89, 12.47)	0.002		
VCAM-1 (ng/mL), mean (SD), (log)	2.43 (1.22, 5.21)	0.016		
Endothelin-1 (pg/mL), mean (SD), (log)	2.25 (1.11, 4.82)	0.029		
Interleukin-6 (pg/mL), mean (SD), (log)	1.47 (1.10, 2.03)	0.013		
ST-2 (ng/mL), mean (SD), (log)	1.57 (1.06, 2.44)	0.032		
P-selectin (ng/mL), mean (SD), (log)	2.73 (1.36, 5.81)	0.006		
Biomarkers at 28–60 days postdischarge, central laboratory				
eGFR (mL/min/1.73 m^2), median (IQR), (log)	1.00 (0.98, 1.02)	0.794	1.06 (1.02, 1.12)	0.011
VWF:Ag (IU/dL), mean (SD), (log)	2.37 (1.10, 5.47)	0.033		
ICAM-1 (ng/mL), mean (SD), (log)	6.23 (2.57, 16.47)	<0.001	64.72 (4.86, 1349.12)	0.003
VCAM-1 (ng/mL), mean (SD), (log)	2.59 (1.08, 6.52)	0.037	0.06 (0.00, 1.00)	0.059
Endothelin-1 (pg/mL), mean (SD), (log)	3.32 (1.24, 9.50)	0.02		
P-selectin (ng/mL), mean (SD), (log)	3.34 (1.56, 7.67)	0.003	6.17 (1.35, 34.87)	0.026
LDH (U/L), mean (SD), (log)	3.28 (1.59, 7.22)	0.002		

ORs, 95% confidence intervals and p values derived from logistic regression models. Univariate models include one predictor only. Multivariable model was adjusted for age and sex, and included any other factors found to have p<0.05 in univariate analysis (ie, healthcare worker status and acute kidney injury). For each predictor, the OR relates to the specified between-group difference (categorical predictors), or increase (continuous predictors).

COVID-19 could be a potential strategy for the prevention of post-COVID-19 syndromes.

As COVID-19 vaccination and increased immunity from infection have become widespread, acute COVID-19 illness-related morbidity and mortality have decreased.[28] However, persistent illness in COVID-19 survivors, estimated to affect 145 million patients, which is more prevalent in patients hospitalised with COVID-19 than in non-hospitalised patients (52% vs 38%), remains a concern.[29 30] The aetiology of postacute COVID-19 syndromes or 'long COVID' is uncertain, and treatments are lacking. With the scale of the COVID-19 pandemic, even a small proportion of patients with lasting symptoms will significantly impact individual patients and the global economy.[31–33] Importantly, we found that persistent radiological abnormalities post-COVID-19 were associated with health status impairments, resulting in poorer patient-assessed quality of life. Lower levels of

Table 6 Health status, illness perception, anxiety and depression, and physical function assessed by linear regression of percentage abnormal lung at 28–60 days postdischarge from hospital for COVID-19 infection

	Univariate		Multivariable	
Variable	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Health status				
Health-related quality of life EQ-5D-5L score at enrolment	−15.32 (−29.44, 1.19)	0.034		
Health-related quality of life EQ-5D-5L score 28–60 days postdischarge	−14.97 (−27.40, 2.53)	0.019		
Change in health-related quality of life EQ-5D-5L score	−1.87 (−16.48, 12.74)	0.8		
Patient-assessed EQ-5D-5L score at enrolment, EQ-5D-5L score	−0.12 (−0.26, 0.02)	0.09		
Patient-assessed EQ-5D-5L score at 28–60 days postdischarge	−0.23 (−0.38, 0.08)	0.003	−0.23 (−0.38, 0.08)	0.003
Change in patient-assessed EQ-5D-5L score	−0.06 (−0.21, 0.09)	0.424		
Illness perception				
Brief Illness Perception Questionnaire score at enrolment	0.17 (−0.07, 0.44)	0.147		
Brief Illness Perception Questionnaire score 28–60 days postdischarge	0.12 (−0.09, 0.32)	0.266		
Change in Brief Illness Perception Questionnaire score	−0.02 (−0.26, 0.22)	0.869		
Anxiety and depression				
PHQ-4 anxiety score at enrolment	−0.15 (−1.65, 1.35)	0.847		
PHQ-4 anxiety score at 28–60 days postdischarge	−0.32 (−1.85, 1.20)	0.675		
PHQ-4 depression score at enrolment	0.11 (−1.51, 1.73)	0.894		
PHQ-4 depression score at 28–60 days	−0.37 (−1.98, 1.23)	0.645		
PHQ-4 total score at enrolment	−0.02 (−0.85, 0.81)	0.969		
PHQ-4 total score at 28–60 days postdischarge	−0.19 (−1.01, 0.63)	0.644		
IPAQ category at enrolment				
Moderate (vs high)	−10.79 (−20.94, 0.64)	0.037		
Low (vs high)	−2.01 (−14.01, 9.98)	0.741		
IPAQ category at 28–60 days postdischarge				
Moderate (vs high)	−4.53 (−12.13, 3.06)	0.24		
Low (vs high)	−0.90 (−11.09, 9.29)	0.861		
Physical function				
Duke Activity Status Index at enrolment	−0.19 (−0.37, 0.01)	0.037		
Duke Activity Status Index at 28–60 days postdischarge	−0.20 (−0.37, 0.03)	0.022		
Change in Duke Activity Status Index	0.01 (−0.18, 0.20)	0.914		
Predicted maximal O_2 utilisation (mL/kg/min) at enrolment	−0.44 (−0.85, 0.03)	0.037		
Predicted maximal O_2 utilisation (mL/kg/min) at 28–60 days postdischarge	−0.46 (−0.86, 0.07)	0.022		
Change in predicted maximal O_2 utilisation (mL/kg/min)	0.02 (−0.41, 0.46)	0.914		

IPAQ, The International Physical Activity Questionnaire; PHQ-4, The Patient Health Questionnaire-4.

physical activity and predicted maximal oxygen utilisation (derived VO_2) in those with persisting ground glass or reticular changes/architectural distortion suggest an important physiological implication of these abnormalities for patients. In addition, the greater amount of lung remaining abnormal resulted in poorer patient-assessed quality of life. Therefore, our findings suggest important future implications for both patients surviving COVID-19 and healthcare resources.

Limitations

Our study is limited to a 60-day follow-up postdischarge, so long-term radiological sequelae are undefined. Previous studies have shown conflicting results regarding the resolution of radiological abnormalities 6 months to 1 year post-COVID-19.[16–18] However, early detection of persistent radiological and physiological impairment, in the months posthospital discharge, is likely to be an important window of opportunity to direct rehabilitation

and research efforts to prevent longer-term sequelae in pandemics. Although we reported health status measures correlated with radiology, we did not include measures of physiological impairment such as lung function testing and 6 min walk testing. Post-COVID-19 studies have reported impairments in lung function, particularly diffusing capacity of the lung for carbon monoxide (lung transfer factor). Larger long-term prospective follow-up cohort studies, such as the UK-based PHOSP-COVID (ISRCTN10980107), will provide insights into the convalescent course of COVID-19 and further define radiological, physiological and symptom burden in survivors.[34]

Our study includes hospitalised patients with a range of illness severity; however, 31% were in the milder severity group requiring no supplementary oxygen therapy (online supplemental table 1). Typical COVID-19 radiological changes are more likely to be seen in those with severe disease and thus case mix is likely to influence prevalence of radiological findings. However, it is also important to include the low illness severity patient group as the majority of COVID-19 did not cause severe illness and most previous studies have focused on resolution in those with more severe acute illness.

Systemic steroids were only used in 56% of our patient cohort which reflects both our enrolment beginning prior to the RECOVERY dexamethasone results in June 2020 and the number of patients not being eligible for steroid treatment due to no oxygen requirement. The long-term effect, if any, of acute dexamethasone in patients surviving COVID-19 is unknown.

CONCLUSION

In conclusion, while most COVID-19 patients show improving radiological abnormalities, persistent abnormalities are common and associated with health status impairments. These results present healthcare implications concerning the development of chronic lung disease and the health system resources required to serve the large number of COVID-19 survivors.

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