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### **Residual Lung Abnormalities Following COVID-19 Hospitalization**

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# Residual lung abnormalities following COVID-19 hospitalization: interim analysis of the UKILD Post-COVID study

(Running head) Lung damage burden after COVID-19 hospitalization

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9.23 Interstitial Lung Disease

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At a Glance Commentary

Current scientific knowledge on the subject: Current studies highlight persistent

breathlessness and radiological patterns suggestive of lung fibrosis, as well as shared

genetic architecture with idiopathic pulmonary fibrosis, in people who are discharged

following severe COVID-19 hospitalisation. Survivors of COVID-19 may develop

parenchymal abnormalities consistent with lung fibrosis.

What this study adds to the field: This study assesses the risk factors for residual lung

abnormalities, provides evidence of persistent abnormalities within a year of discharge

from over 200 CT scans, and estimates the prevalence of lung abnormalities after

discharge to be up to 11% in a broad range of COVID-19 severity. The findings emphasise

the importance for health services to undertake active radiological and physiological

monitoring to assess progression or resolution over time.

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Some of the results of these studies have been previously reported in the form of a

preprint (medRxiv, 16 March 2022

https://www.medrxiv.org/content/10.1101/2022.03.10.22272081v2).

This article has an online data supplement, which is accessible from this issue's table of

content online at www.atsjournals.org.

**Abstract** 

Rationale. Shared symptoms and genetic architecture between COVID-19 and lung

fibrosis suggests SARS-CoV-2 infection may lead to progressive lung damage.

**Objectives.** The UKILD Post-COVID study interim analysis was planned to estimate the

prevalence of residual lung abnormalities in people hospitalized with COVID-19 based on

risk strata.

Methods. The Post-HOSPitalisation COVID Study (PHOSP-COVID) was used for capture

of routine and research follow-up within 240 days from discharge. Thoracic CTs linked by

PHOSP-COVID identifiers were scored for percentage of residual lung abnormalities

(ground glass opacities and reticulations). Risk factors in linked CT were estimated with

Bayesian binomial regression and risk strata were generated. Numbers within strata were

used to estimate post-hospitalization prevalence using Bayesian binomial distributions.

Sensitivity analysis was restricted to participants with protocol driven research follow-up.

Measurements and Main Results. The interim cohort comprised 3700 people. Of 209

subjects with linked CTs (median 119 days, interquartile range 83-155), 166 people

(79.4%) had >10% involvement of residual lung abnormalities. Risk factors included

abnormal chest X-ray (RR 1·21 95%CrI 1·05; 1·40), percent predicted DLco<80% (RR

1.25 95%CrI 1.00; 1.56) and severe admission requiring ventilation support (RR 1.27

95%CrI 1·07; 1·55). In the remaining 3491 people, moderate to very-high risk of residual

lung abnormalities was classified in 7.8%, post-hospitalization prevalence was estimated

at 8.5% (95%CrI 7.6%; 9.5%) rising to 11.7% (95%CrI 10.3%; 13.1%) in sensitivity

analysis.

Conclusions. Residual lung abnormalities were estimated in up to 11% of people

discharged following COVID-19 related hospitalization. Health services should monitor at-

risk individuals to elucidate long-term functional implications.

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1.0 Introduction

Long term symptoms of COVID-19 have been widely reported and can have a severe

impact on quality of life, frequently characterized by chronic breathlessness.[1-3] Post-

mortem studies on COVID-19 patients have highlighted diffuse parenchymal alterations,

including alveolar damage, exudation, and development of pulmonary fibrosis, which may

explain chronic respiratory symptoms in survivors.[4-6]

A number of studies have identified similarities between severe COVID-19 and idiopathic

pulmonary fibrosis (IPF), an archetypal interstitial lung disease (ILD). These include shared

genetic etiology, [7, 8] circulating biomarkers, [9, 10] similarities in pulmonary function

and radiological features.[11] Viral injury may promote lung fibrosis, and chronic viral

infection has been shown to be associated with developing IPF.[12] Consequently,

survivors of COVID-19 may develop parenchymal abnormalities consistent with ILD,

including radiological patterns of ground glass opacities and reticulations.

To understand the potential risk of COVID-19 leading to the development of longer term

ILD and fibrosis, the UKILD-Post COVID study aims to investigate the risk factors and

nature of long term lung damage from COVID-19 in a longitudinal observational study. To

support clinical and research management, this planned interim analysis of the UKILD-

Post COVID study addresses the extent of residual lung abnormalities post hospitalization

following completion of an early follow-up visit of the prospective Post-HOSPitalisation

COVID-19 Study (PHOSP-COVID). [13]

2.0 Methods

2.1 Participants

This interim analysis was restricted to participants of the PHOSP-COVID study, a

prospective longitudinal cohort study of adults discharged from National Health Service

hospitals across the United Kingdom following admission for confirmed or clinical-

diagnosed COVID-19, previously described in detail.[14]

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Individuals withdrawing consent from PHOSP-COVID were excluded. Individuals being managed for an *a priori* diagnosed interstitial lung disease or pulmonary fibrosis as recorded by site teams using hospital notes were identified by hand searches of comorbidities and subsequently excluded.

#### 2.2 Interim Study Design

Interim participants were discharged by end of March 2021 representing wave 1 of the pandemic, interim data were collected up to October 2021 and were restricted to within 240 days of discharge. Analyses were performed with data recorded through routine follow-up (PHOSP-COVID Tier 1) and those with completed early research follow-up visits (PHOSP-COVID Tier 2). Clinically indicated thoracic CT scans were identified through the PHOSP-COVID study via linkage to a radiological database, linked CT scans were requested at clinical discretion. The presence of residual lung abnormalities on volumetric CTs was scored on a lobar basis; percentage involvement of ground glass opacities, reticulations, or the sum of involvement were averaged across lobes to quantify residual abnormality. [15] The primary outcome was visually scored residual abnormalities >10% lung involvement on CT.[15]

Risk factors implicated in worse outcomes following COVID-19 hospitalization of individuals with ILD were described.[16] These included sex, age, ethnicity, Body Mass Index (BMI), and Index of Multiple Deprivation (IMD). A modified WHO clinical progression scale was used to define the severity of admission (i. no supplemental oxygen ii. supplemental oxygen only; iii. continuous positive airway pressure (CPAP); iv. invasive mechanical ventilation (IMV), extra-corporeal membrane oxygenation (ECMO)). Abnormal chest X-ray reports were classified at follow-up, defined as "suggestive of lung fibrosis", "extensive persistent changes greater than 1/3 lung involvement" and "indeterminate", compared with "other" or "normal". Breathless and cough symptoms were recorded at follow-up with the Patient Symptom Questionnaire developed for the PHOSP-COVID Study.[14] Percent predicted values for Forced Vital Capacity (ppFVC) and Diffusion capacity across the Lung

for carbon monoxide (ppDLco) were obtained at follow-up visits and calculated using GLI

reference equations.

2.3 Statistical analysis

Risk factor data were presented descriptively overall, according PHOSP-COVID Tier, and

within the sample of linked and scored CTs. Chi-square tests were performed on non-

missing categories. Residual abnormalities on paired CT scans were tested with paired t-

test; changes in scored residual lung abnormalities over time were estimated using linear

mixed effect models, with random effects of timing at the level of the individual, adjusted

for sex and IMD. A random sample of 70 CT scans were tested for inter-rater agreement

by Cohen's kappa  $(\kappa)$  with a second radiologist blinded to scores.

Univariate relative risk ratios of threshold >10% residual abnormalities, and difference in

involvement on CT, were modelled with dichotomized exposure variables. Bayesian

binomial and linear associations were estimated using 12,500 Markov Chain Monte Carlo

iterations including a burn-in of 2,500 and 10,000 subsequent simulations using random-

walk Metropolis Hastings sampling. Non-informative, flat priors were selected and

estimates were reported with 95% credible interval (95%CrI). Linear associations were

additionally adjusted for demographics of sex and IMD.

Clinical risk factors with consistent significant effects were selected to develop risk strata

of suspected residual lung abnormalities Post-COVID hospitalization. For the indexing of

risk strata, missing data on clinical indicators were imputed to the reference (lowest risk)

category. The percentage of participants within moderate to very-high risk strata and no

CT scored were defined as at-risk. Hospital admissions were compared between at-risk

groups using chi-square, 15 index admission variables were selected from 61 by least

absolute shrinkage and selection operator.

Bayesian inference with binomial distribution of at-risk cases and non-cases,[17] was used

to estimate the prevalence of suspected residual lung abnormalities Post-COVID

hospitalization within 240 days of discharge, reported with the 95%CrI. MCMC simulations

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were run as described above. Non-informative, uniform, beta priors were used and compared in sensitivity analyses with uniform Jeffrey's priors, as well as skeptical and power priors informed by published population studies of ILD.[18, 19] Sensitivity analyses were performed in PHOSP-COVID Tier 2 research follow-up participants where data completeness was greater. Analyses were performed in Stata SE16.0 within the Scottish National Safe Haven Trusted Research Environment.

#### 3.0 Results

#### 3.1 Cohort demographics and patterns of lung damage

A total of 3700 PHOSP-COVID participants reached criteria for inclusion in the interim UKILD cohort. This included 1304 patients with data available through routine clinical care (Tier 1) and 2396 who had completed an early follow-up research visit within 240 days of discharge (Tier 2; Figure 1). We observed that 255/3700 people of the interim cohort (6.9%) had a linkable thoracic CT scan performed, 220 were performed in Tier 2 participants (9.2% of 2396) and 35 were performed in Tier 1 participants (2.7% of 1304, p<0.001). Of 255 participants with linked CT scans within 240 days of discharge (median 113 days; IQR 69 to 166, Supplementary Figure 1), a total of 209 (82.0%) were visually scored with inter-rater agreement on 70% of scans (Cohen's κ 0.33). Participants with a CT scored were majority male (68.4%), white (68.9%), had a median age of 58 (52 to 67) and had a median time to early follow-up visit of 140 days (IQR 106 to 170) (Table 1).

Residual lung abnormalities >10% were observed in 166/209 participants (79.4%). Visual scoring of involvement indicated ground glass opacities affected a mean 25.5%  $\pm 15.9$  of the lung, reticulation a mean 15.1%  $\pm 11.0$ , with residual abnormalities involving in a mean a 40.6%  $\pm 20.8$  of the lung (Figure 2A). 33 people had a repeat CT visually scored after a minimum of 90 days (median 161 days; IQR 109 to 187), 28/33 (84.8%) of whom were classified with residual abnormalities >10% on the initial scan, with 26/28 (92.9%) observed to have >10% involvement in subsequent scans. In paired analysis the overall

change in residual lung abnormalities was -3.62% (95%CI -6.10; -1.13, p=0.006; Figure 2B). The involvement of lung reticulations and ground glass opacities did not significantly change with a mean difference of -2.08% (95%CI -4.66; 0.51, p=0.112) and -1.54% (95%CCI -4.74; 1.39, p=0.293), respectively (Figure 2C-2D). Using all scored CT scans, the mean weekly change in lung involvement was estimated at -0.13% per week (95%CI -0.20; -0.05) for reticulations and -0.13% per week (95%CI -0.22; -0.04) for ground glass opacities (Figure 2E). The weekly change in residual lung abnormalities was -0.20% per week (95%CI -0.28; -0.11, Figure 2F). Representative CT images of residual lung abnormality demonstrated persistent involvement >100 days post discharge (Figure 3).

Overall, the median time to follow-up in the UKILD interim cohort (N=3700) was 127 days (IQR 91 to 173), the median age was 59 (IQR 50 to 68) and the cohort was majority male (60.7%). Tier 1 participants (n=1304) had a median time to follow-up of 101 days (IQR 82 to 138), a median age of 60 (IQR 51 to 70) and the majority were male (58.9%); demographics were similar in Tier 2 participants (n=2396) with a median time to research visit of 141 days (IQR 100 to 180), a median age of 59 (IQR 50 to 67) and a majority male (61.7%) (Table 1). There was minimal evidence of systematic bias in the characteristics between Tier 2 and Tier 1 participants in non-missing data (Table 1), although the representation of people aged below 60 was greater in Tier 2 participants (52.5% vs 48.8%; p=0.027), similarly there were small differences in representation of ethnicity (p<0.001), greater representation of the lowest deprivation quintile (19.1% vs 16.1%; p=0.031), as well as lower representation of normal CXR (32.5% vs 39.2%; p=0.004).

Tier 2 participants had a median ppFVC at research follow-up of 90.2% (IQR 78.6 to 101.6) with missing records at 55.5%, whilst median ppDLCO was 87.5% (IQR 74.0 to 101.3) with missing records at 78.8%; lung function was largely missing in routine follow-up of Tier 1 participants. We observed 34.6% of people reported worsening cough or dyspnea since discharge in Tier 2. ILD diagnostic criteria of lung function (ppFVC and ppDLCO), CXR and symptoms was frequently missing, particularly in Tier 1 of clinical follow-up

(Supplementary Figure 2). In Tier 1, 578/1304 (44.3%) were missing data on all four characteristics at interim analysis, whilst in Tier 2, 362/2396 people (15.1%) were missing data on all four characteristics. In contrast, a total of 202 Tier 2 participants had complete data on all (8.4%), no Tier 1 participants had complete lung function, CXR or symptom data. In the subsample of participants with scored CTs, data was missing at a rate similar to Tier 2 for lung function (ppDLco 70.3%; ppFVC 60.8%), CXR (47.4%), and Patient Symptom Questionnaire (43.1%) (Table 1).

3.2 Risk of residual lung abnormalities and persistence over time.

Univariate risk ratios were calculated to assess the risk of residual lung abnormalities >10% on CT. A greater risk was observed in males (RR 1.42 95%CrI 1.17; 1.77) and in those over 60 years of age (RR 1.22 95%CrI 1.06; 1.40). Clinical indicators, including severe illness on admission requiring CPAP, IMV or ECMO (RR 1.40 95%CrI 1.23; 1.63), abnormal CXR findings (RR 1.40 95%CrI 1.22; 1.61), and ppDLco <80% (RR 1.26 95%CrI 1.02; 1.58) were also associated with greater risk, with consistent effects for the relative mean difference of percent involvement after adjustment for sex and deprivation quintile (Table 2).

Three significant clinical indicators were selected to index the risk of residual lung abnormalities Post-COVID in the remaining cohort (n=3491) based on combined thresholds: ppDLco <80%; abnormal CXR; and severe illness on admission. Individuals were considered to be at very-high risk when reaching the defined thresholds in all three indicators (risk index 4), high risk when two thresholds were reached (risk index 3), or moderate risk if reaching ppDLco or CXR thresholds alone (risk index 2). Individuals reaching the threshold of severity of illness on admission alone were considered low-risk in the absence of other indicators (risk index 1). Those who did not reach any threshold were considered very low risk (risk index 0). A total 14/3419 participants (0.4%) were considered very-high risk, 143/3419 at high risk (4.1%), and 116/3419 at moderate risk (3.3%), 1256/3419 at low risk (36.0%) and 1962/3419 at very-low risk (56.2%) (Table 3). Combined, 273/3419 (7.8%) people in strata of moderate to very-high risk were

defined as at-risk, 8/46 (17.4%) people with an unscored clinically indicated CT were at-risk. In sensitivity analyses applying risk stratification to Tier 2 alone, 231/2219 (10.4%) people were at moderate to very-high risk including 20% of those with an unscored clinically indicated CT (Table 3).

No differences were observed between at-risk participants (n=273) and participants with >10% residual abnormalities on CT (n=166) according to representation of males, older age, ethnicity, deprivation, BMI, severity of admission, ppFVC <80% or Patient Symptom Questionnaire (Supplementary Table 1). There was lower representation of normal CXR in the at-risk group (14.7% vs 30.1%, p<0.001) and more representation of ppDLco <80% (55.3% vs 14.5%, p<0.001). The percentage of people who did not have a severe admission requiring CPAP, ECMO or IMV was similar in both groups (44.3% vs 45.2%), whilst CXR was missing in 26.0% of the at-risk group and 48.2% of people with residual abnormalities scored.

Comparing at-risk participants to low-risk participants, there were more records of immunosuppressant (18.3% vs 9.9%, p=0.001) and corticosteroid treatments (35.3% vs 26.5%, p=0.019) pre-admission, intensive care unit stays (50.0% vs 33.4%, p<0.001), and complications of acute respiratory distress syndrome (ARDS; 25.0% vs 13.7%, p<0.001) (Supplementary Table 2). Additionally, there were more recorded unscheduled emergency visits post discharge (34.8% vs 25.2%, p=0.001), with a greater representation of visits where patients presented with symptoms of shortness of breath (33.7% vs 24.3%, p=0.046). Findings were similar in comparisons of CT scored residual lung abnormalities >10% compared to those not reaching this threshold, although statistical significance was not always met (Supplementary Table 2).

Based on the distribution of at-risk cases, the prevalence of residual lung abnormalities post-COVID hospitalization was estimated at 8.51% (95%CrI 7.56; 9.51%) using non-informative priors, or 6.49% (95%CrI 5.75; 7.27) with skeptical priors based on ILD population prevalence estimated at 1 in 1,000 (Table 4, Supplementary Figure 3).[18, 19] In sensitivity analyses based on Tier 2 distribution, the prevalence of residual lung

abnormalities post-COVID hospitalization was estimated at 11.67% (95%CrI 10.28; 13.14) using non-informative priors, or 7.74% (95%CrI 6.79; 8.72) using skeptical priors.

#### 4.0 Discussion

These data demonstrate that residual lung abnormalities were visually identifiable on clinically indicated thoracic follow-up CT imaging in a substantial proportion of patients within 8 months of discharge following COVID-19 hospitalization. The involvement of scored residual lung abnormalities minimally declined per week following discharge, whilst minimal resolution was observed in paired subsequent scans at least 90 days apart. Key clinical risk factors associated with residual abnormalities in the early follow-up period included abnormal CXR, ppDLco <80% and severe admissions requiring invasive support (IMV, CPAP, ECMO). In those without a scored CT, 0.4% were in very-high risk strata (all three indicators present), 4.1% in high risk strata (any two indicators present), and 3.3% in moderate risk strata (presence of either ppDLco<80% or abnormal CXR, alone). Combining these risk strata, 7.8% of the interim cohort had suspected residual lung abnormalities Post-COVID hospitalization, which increased to 10.4% in sensitivity analysis on those with planned research follow-up. Based on Bayesian modelling, we estimate the prevalence of suspected residual lung abnormalities with >10% lung involvement to be up to 11.7% in people hospitalized with acute COVID-19 infections before March 2021.

This UKILD Post-COVID interim analysis of residual abnormalities in patients hospitalized for COVID-19 offers the largest assessment of prevalence in hospitalized individuals to date, and is consistent with findings from a number of smaller studies that demonstrate persistent radiological patterns and impaired gas transfer during extended follow-up of patients with COVID-19.[20-23] At the time of this interim analysis it is not possible to determine whether the observed residual lung abnormalities represent early interstitial lung disease (ILD) with potential for progression, or whether they reflect residual pneumonitis that may be stable or resolve over time.[24] The 10% threshold used was determined to support distinction of interstitial lung damage from interstitial lung

abnormalities.[15] Longer term follow-up and mechanistic studies will be required to determine the clinical trajectory of these observations.

Where linked longitudinal scans were available most patients did not show evidence of substantial improvement, although such clinically requested CTs may be over-represented by those with slower recovery. However, approximately half the people with visually scored residual abnormalities above the 10% threshold did not require CPAP, IMV or ECMO during their admission and less than one quarter had ARDS recorded as a complication, suggesting medium and longer term disability consequent to severe COVID-19 infection, consistent with prior studies. [18]

The risk factors for residual abnormality as scored in the CT subsample (abnormal CXR, ppDLco <80% and severe admissions requiring invasive support) were applied to the remaining hospitalized cohort to generate clinically applicable risk strata. For participants in receipt of a clinically indicated but unscored CT, 17.4% of people were in moderate to very-high risk strata for residual lung abnormalities (sensitivity 20.0%). These rates were similar to meta-analysis estimates of the percentage of clinically indicated CT scans with radiological patterns suggestive of fibrosis (29%; 95%CI 22% to 37%) and people with impaired gas transfer (17%; 95%CI 13% to 23%), neither of which were associated with timing of follow-up within the first year post-COVID.[25] In paired CT scans greater than 90 days apart we demonstrate no significant difference in the mean change for percent involvement of reticulations and ground glass opacities, whilst the scored involvement of reticulations and ground glass opacities based on all CT scans declined by 0.13% per week of study from discharge, suggesting persistence over time in at-risk groups.

Differences between individuals at moderate to very high risk and those at lower risk suggested more immunosuppressant and corticosteroid treatment pre-admission, intensive care unit stays and ARDS complications, as well as further unscheduled emergency visits post discharge both overall and including presentation with breathlessness. Classification of at-risk participants using clinically applicable strata identified those who may have had a more severe viral injury and inflammatory response

during acute infection, as well as subsequent respiratory exacerbations post COVID.

Recent analysis identified a hyper inflammatory phenotype of COVID-19 related ARDS was

associated with worse outcomes, with better survival linked to corticosteroid

treatment.[26] Surviving a hyper inflammatory response to COVID-19 may be consistent

with residual lung abnormalities, including fibrosing non-specific interstitial pneumonia and

alveolar damage.[27]

Residual lung abnormalities Post-COVID were not uncommon in this hospitalized

population and may persist long-term, but indicators that could support diagnosis and

clinical management of lung disease were frequently unavailable. Considering

approximately 280,000 people were discharged following confirmed COVID-19 admission

in the UK National Health Service by end of March 2021,[28] these results emphasize the

importance for health services to undertake active radiological and physiological

monitoring especially in people at moderate, or above, risk.[15]

4.1 Strengths and Limitations

The UKILD long-COVID cohort excluded participants with any evidence of ILD prior to

hospitalization, and we used informative skeptical priors and power priors for more

conservative estimates of prevalence, which continued to suggest a substantial burden of

residual lung abnormalities Post-COVID hospitalization. The approach we report can be

reasonably applied to other cohorts and time points, with current findings used as

informative priors for updating Bayesian inference.

Whilst included CTs were assumed to be representative of clinically indicated radiology,

this is limited by local management protocols, timing of services, and changes to

healthcare service prioritization during the COVID-19 pandemic, which increases chances

of selection and ascertainment bias. Furthermore, individuals with linked CT may have

unrecorded pre-existing disease or present with radiological patterns other than

reticulation and ground glass opacities. Fair inter-rater agreement (kappa 0.33) of CT

scoring was observed, representing agreement in 70% of scans.

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We recognize these interim findings may also be limited by misclassification. Descriptive analyses identified substantial missing data in clinical risk factors, limiting multiple imputation techniques. We used dichotomized thresholds with single data imputation at the reference category to support risk strata classification, maintain denominators, and provide conservative estimates. In contrast, lung involvement of reticulation and ground glass opacities was frequently scored on CTs which were clinically indicated, contributing to selection bias. It is similarly likely that repeat CT scans reflect a sample of individuals that did not experience clinical improvement over time. We report estimates from multilevel models to support interpretation of residual lung abnormalities over time.

Whist our findings are based on people hospitalized with mixed severity of COVID-19 infection, we recognize that they may not be generalizable to all populations especially those people not admitted to hospital. Severe admissions requiring CPAP or IMV were over-represented in the PHOSP-COVID dataset relative to hospitalized survivors of COVID-19.[14] Linked clinical admission data suggested 50% of at-risk individuals and those scored with residual abnormalities attended intensive care units during admission, and up to 25% had complications of anemia and ARDS. Furthermore, these data reflect people who were discharged before end of March 2021, and do not represent later SARS-CoV-2 variants in fully vaccinated populations that more frequently led to milder infections.

#### 4.2 Conclusion

Thresholds of ppDLco, CXR and severity of admission can stratify risk of residual abnormalities on CT involving more than 10% of the lung, informing clinical management particularly of individuals meeting moderate to very-high risk strata. Longitudinal analysis of CT scans suggested persistence of abnormalities over study time, although the longer term functional consequence is unknown and may be limited by clinical indication. These findings highlight the importance of radiological and physiological monitoring of patients at both early and later follow-up, and suggest up to 11% of people discharged from an acute COVID-19 admission are at risk of residual lung abnormalities. Further study is

required to elucidate progressive development of radiological patterning, or resolution over time.

#### **Acknowledgements**

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#### **Competing Interests**

JJ reports fees from Boehringer Ingelheim, F. Hoffmann-La Roche, GlaxoSmithKline, NHSX, Takeda and patent: UK patent application number 2113765.8 all unrelated to the submitted work. PMG reports honoraria from Boehringer Ingelheim, Roche, AstraZeneca, Cipla, Brainomix. JCP reports grants from LifeArc, NIHR, Breathing Matters, consulting fees from Carrick Therapeutics, AstraZeneca and honoraria from The Limbic. RAE reports

speaker fees from Boehringer Ingelheim and membership positions on European Respiratory Society and American Thoracic Society committees. PM reports consulting fees from EUSA pharma and SOBI, and honoraria from SOBI, UCB, Lilly, and Abbvie. MGS reports grants from NIHR, MRC, board positions on Pfizer External Data Monitoring Committee and Integrum Scientific LLC Infectious Disease Scientific Advisory Board, member positions of HMG UK SAGE and MHG UK NERVTAG, stocks in Integrum Scientific LLC and MedEx Solutions Ltd, gifts from Chiesi Farmaceutici S.p.A. AART reports grants and travel support from Janssen-Cilag Ltd. CEB reports consultancy fees paid to institution from GSK, AstraZeneca, Sanofi, Boehringer Ingelheim, Chiesi, Novartis, Roche, Genentech, Mologic, 4DPharma, TEVA. LVW reports recent and current research funding from GSK and Orion, and consultancy from Galapagos. RGJ reports honoraria from Chiesi, Roche, PatientMPower, AstraZeneca, GSK, Boehringer Ingelheim, and consulting fees from Bristol Myers Squibb, Daewoong, Veracyte, Resolution Therapeutics, RedX, Pliant, Chiesi. All remaining authors declare no competing interests.

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#### **Figure Legends**

#### Figure 1. CONSORT Flow diagram of UKILD interim cohort definition

White boxes derived from PHOSP-COVID database. Blue boxes represent CT sample linked with PHOSP-COVID identifiers a radiological database.

#### Figure 2. Extent of residual lung abnormalities on linked CT

A) Mean percentage lung involvement of reticulations, ground glass opacities, and residual abnormalities within 240 days of discharge with visually scored involvement >10%, presented with standard deviation (n=166). Percentage lung involvement of B) residual abnormalities, C) reticulations and D) ground glass opacities at initial and repeat CT scans with >90days between (n=33), with p-values from paired t-test. E) Estimated percent lung involvement of ground glass opacities (top, blue) and reticulations (bottom, red) from linear mixed effects by weeks post discharge (n=209, scans=242), F) estimated percent lung involvement of residual abnormalities from linear mixed effects by weeks post discharge, presented with mean weekly effect and 95% confidence intervals (n=209, scans=242).

#### Figure 3. Representative CT images of residual lung abnormalities

Representative A) coronal and B) axial non-contrast CT imaging from the same individual performed at 137 days post discharge following a COVID-19 admission, scored with 52.5% total lung involvement of residual lung abnormality of which 18.3% reticulation and 34.2% ground glass opacity. Peripheral reticulation (arrows) is evident surrounded by faint areas of ground glass density. Representative coronal CT images from the same individual at C) 114 days post discharge scored with 56.8% lung involvement (28.5% reticulation; 28.3% ground glass opacity) and D) 239 days post discharge scored with 49.2% total lung involvement (20.0% reticulation; 29.2% ground glass opacity). Peripheral areas of reticulation (black arrow) and ground glass density (white arrow) in the right lung.

Table 1: UKILD interim cohort demographics

	Interim		C	T score	Tie	er 1	Ti	er 2	χ² pval
	N=3700	percent	n=209	percent	n=1304	percent	n=2396	percent	
Sex									0.091
Male	2247	60.7%	143	68.4%	768	58.9%	1479	61.7%	
Female	1450	39.2%	66	31.6%	535	41.0%	915	38.2%	
Age									0.027
60+	1801	48.7%	99	47.4%	667	51.2%	1134	47.3%	
<60	1895	51.2%	110	52.6%	636	48.8%	1259	52.5%	
Ethnicity									<0.001
White	2804	75.8%	144	68.9%	1015	77.8%	1789	74.7%	
Asian	467	12.6%	40	19.1%	144	11.0%	323	13.5%	
Black	223	6.0%	15	7.2%	56	4.3%	167	7.0%	
Other	131	3.5%	6	2.9%	31	2.4%	100	4.2%	
Missing	75	2.0%			58	4.4%	17	0.7%	
IMD									0.031
1 Most	867	23.4%	38	18.2%	326	25.0%	541	22.6%	
2	817	22.1%	40	19.1%	268	20.6%	549	22.9%	
3	666	18.0%	41	19.6%	251	19.2%	415	17.3%	
4	659	17.8%	38	18.2%	241	18.5%	418	17.4%	
5 Least	667	18.0%	50	23.9%	210	16.1%	457	19.1%	
Missing	24	0.6%			8	0.6%	16	0.7%	
BMI									0.491
<25	262	7.1%	22	10.5%	45	3.5%	217	9.1%	
25 - <30	612	16.5%	59	28.2%	84	6.4%	528	22.0%	
30 - <40	880	23.8%	67	32.1%	121	9.3%	759	31.7%	
>=40	230	6.2%	12	5.7%	30	2.3%	200	8.3%	
Missing	1716	46.4%	49	23.4%	1024	78.5%	692	28.9%	
WHO severity									0.826
No O2 (i)	624	16.9%	35	16.7%	223	17.1%	401	16.7%	
Non-invasive O2 (ii)	1567	42.4%	77	36.8%	557	42.7%	1010	42.2%	
CPAP (iii)	860	23.2%	34	16.3%	306	23.5%	554	23.1%	
IMV (iv)	645	17.4%	63	30.1%	217	16.6%	428	17.9%	
CXR at follow-up									<0.004
Normal	1289	34.8%	70	33.5%	511	39.2%	778	32.5%	

Other	325	8.8%	19	9.1%	140	10.7%	185	7.7%	
Abnormal	162	4.4%	21	10.0%	45	3.5%	117	4.9%	
Missing	2139	57.8%	36	41.4%	677	52.2%	1462	60.8%	
CT at follow-up									
Linked records	255	6.9%	209	100.0%	35	2.7%	220	9.2%	<0.001
Scored	209	5.6%	209	100.0%	29	2.2%	180	7.5%	<0.001
Symptoms at follow-up									0.636
Present - worsen	850	23.0%	74	35.4%	21	1.6%	829	34.6%	
Present - no change	319	8.6%	21	10.0%	11	0.8%	308	12.9%	
Not present/improved	359	9.7%	24	11.5%	9	0.7%	350	14.6%	
Missing	2172	58.7%	90	43.1%	1263	96.9%	909	37.9%	
ppFVC at follow-up									-
80%+	786	21.2%	53	25.4%			773	32.3%	
<80%	297	8.0%	29	13.9%			294	12.3%	
Missing	2617	70.7%	127	60.8%	1288	98.8%	1329	55.5%	
ppDLco at follow-up									-
80%+	333	9.0%	37	17.7%			333	13.9%	
<80%	177	4.8%	25	12.0%			175	7.3%	
Missing	3190	86.2%	147	70.3%	1302	99.8%	1888	78.8%	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Age	59	50, 68	58	52, 67	60	51, 70	59	50, 67	
ppFVC	90.3	78.6, 101.7	87.0	75.0, 98.8	-	-	90.2	78.6, 101.6	-
ppDLco	87.6	74.2, 101.3	84.7	69.9, 96.2	-	-	87.5	74.0, 101.3	-
Time to follow-up	127	91, 173	140	106, 170	101	82, 138	141	100, 180	
Small and the second of the second of the second of the second terms of the second of									

Small numbers <5 have been suppressed. Chi-squared ( $\chi^2$ ) performed between Tier 1 and Tier 2 on non-missing categories. IMD: index of multiple deprivation in quintiles, BMI: body mass index, WHO: modified World Health Organisation severity score, CXR: chest X-ray, CT: computed tomography – chest, Symptoms: Patient Symptom Questionnaire breathless or cough, ppFVC: percent predicted forced vital capacity, ppDLco: percent predicted diffusion capacity across the lung for carbon monoxide.

Table 2: Risk factors of residual lung abnormalities on CT

Characteristic	Risk factor present (%)	Risk factor absent (%)	Univariate risk ratio	95% Credible Interval	Estimated mean difference (%)	95% Credible Interval	Adjusted mean difference (%)	95% Credible Interval
Male	87.4%	62.1%	1.42	(1.17; 1.77)	12.46	(5.76; 19.59)	11.26	(4.24; 18.04)
Age 60+	87.9%	71.8%	1.22	(1.06; 1.40)	8.29	(2.11; 14.44)	8.57	(3.61; 16.16)
Non-white	78.5%	79.9%	0.97	(0.84; 1.12)	3.48	(-3.78; 10.88)	3.84	(-4.95; 9.37)
IMD (Q1/2)	87.2%	74.4%	1.17	(1.02; 1.34)	6.91	(0.38; 13.33)	6.28	(-0.31; 12.91)
BMI >30	87.3%	71.6%	1.22	(1.04; 1.45)	3.93	(-3.70; 11.52)	4.54	(-2.40; 11.65)
CPAP/IMV	93.8%	67.0%	1.40	(1.23; 1.63)	20.56	(14.80; 26.36)	20.14	(14.34; 25.69)
aCXR	100.0%	73.0%	1.40	(1.22; 1.61)	14.96	(3.89; 25.78)	11.54	(0.53; 21.59)
ppFVC <80	86.2%	79.3%	1.07	(0.85; 1.31)	10.40	(-0.90; 22.00)	11.99	(-0.14; 23.52)
ppDLco <80	96.0%	75.7%	1.26	(1.02; 1.58)	19.04	(7.65; 30.71)	15.31	(2.84; 28.06)
PSQ worse	78.4%	80.0%	0.99	(0.81; 1.21)	4.49	(-4.58; 13.54)	4.71	(-4.31; 13.87)

Percentage of non-missing case observations reaching >10% threshold of residual lung abnormalities according to risk factor being present or absent. Univariate risk ratio (RR) of >10% threshold of residual lung abnormalities and 95% credible interval derived from binomial regression, mean effect difference in % lung involvement where risk factor present relative to risk factor absent estimated from univariate linear regression and adjusted for sex and index of multiple deprivation. Index of multiple deprivation (IMD); Body mass index (BMI); continuous positive airway pressure or invasive mechanical ventilation (CPAP/IMV); abnormal chest x-ray (aCXR); percent predicted forced vital capacity (ppFVC); percent predicted diffusion capacity across the lung for carbon monoxide (ppDLco); Patient Symptom Questionnaire (PSQ).

Table 3: Risk stratification of residual lung abnormalities in unscored UKILD interim cohort

Interim cohor	rt			
Strata	Unscored (N=3491)	Percent	Sensitivity (n=2219)	Percent
Very high	14	0.4%	14	0.6%
High	143	4.1%	123	5.5%
Moderate	116	3.3%	94	4.2%
Low	1256	36.0%	767	34.6%
Very low	1962	56.2%	1221	55.0%
Linked CT: un	scored			
	Interim (n=46)	Percent	Sensitivity (n=40)	Percent
At-risk	8	17.4%	8	20.0%
Low risk	38	82.6%	32	80.0%

Risk strata: very high – all three risk factors present (abnormal CXR, ppDLco <80%, severe admission requiring CPAP or IMV). High – at least two risk factors present. Moderate – either abnormal CXR or ppDLco<80% present. Low – severe admission present only. Very low – risk factors not present. Missing data were imputed at the reference category. Percent denominator is interim cohort without linked, scored CT (n=3491) and sensitivity analysis within Tier 2 research visit participants (n=2219). Moderate to very-high risk combined to at-risk; low to very-low risk combined to low risk, quantified in people with unscored linked CT.

Table 4: Prevalence estimate of residual lung abnormalities >10% following COVID-19 hospitalisation

Model	Prevalence (%)	95% CrI	Prior	a	b	DIC
1	8.51	(7.56; 9.51)	Uniform	1	1	9.38
1-i	8.48	(7.52;9.49)	Jeffreys	0.5	0.5	9.45
1-ii	6.49	(5.75; 7.27)	Skeptical	1	1000	28.67
1-iii	7.37	(6.53; 8.24)	Power	1	1000	14.99
2	11.67	(10.28; 13.14)	Uniform	1	1	9.20
2-i	11.61	(10.19; 13.04)	Jeffreys	0.5	0.5	9.27
2-ii	7.74	(6.79; 8.72)	Skeptical	1	1000	45.97
2-iii	9.32	(8.17; 10.54)	Power	1	1000	20.91

Estimated prevalence of >10% residual lung abnormalities on CT following hospitalization for COVID-19, derived from posterior mean and 95% credibility interval using binomial distributions of at-risk vs low-risk numbers in interim UKILD cohort. Model 1, overall; Model 2, Tier 2 research visit participants. Uniform priors and in sensitivity analysis with Jeffreys non-informative (i), skeptical informative priors (ii) and skeptical informative priors with power weighting (iii). Beta prior distributions defined using cases (a) and non-cases (b). Deviance information criterion (DIC) presented to interpret model.

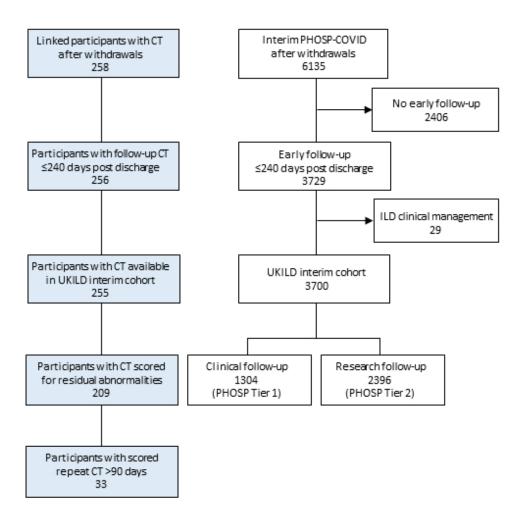


Figure 1. CONSORT Flow diagram of UKILD interim cohort definition.

White boxes derived from PHOSP-COVID database. Blue boxes represent CT sample linked with PHOSP-COVID identifiers a radiological database.

109x119mm (118 x 118 DPI)

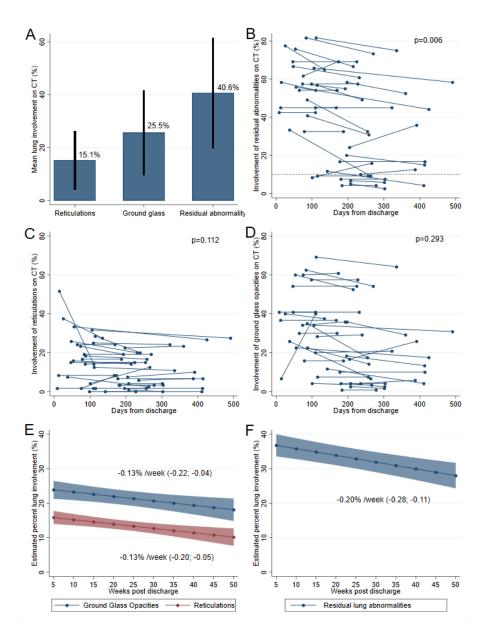


Figure 2. Extent of residual lung abnormalities on linked CT.

A) Mean percentage lung involvement of reticulations, ground glass opacities, and residual abnormalities within 240 days of discharge with visually scored involvement >10%, presented with standard deviation (n=166). Percentage lung involvement of B) residual abnormalities, C) reticulations and D) ground glass opacities at initial and repeat CT scans with >90days between (n=33), with p-values from paired t-test. E) Estimated percent lung involvement of ground glass opacities (top, blue) and reticulations (bottom, red) from linear mixed effects by weeks post discharge (n=209, scans=242), F) estimated percent lung involvement of residual abnormalities from linear mixed effects by weeks post discharge, presented with mean weekly effect and 95% confidence intervals (n=209, scans=242).

149x199mm (118 x 118 DPI)

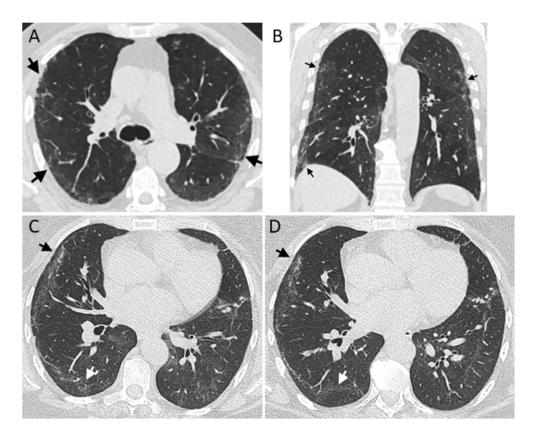


Figure 3. Representative CT images of residual lung abnormalities.Representative A) coronal and B) axial non-contrast CT imaging from the same individual performed at 137 days post discharge following a COVID-19 admission, scored with 52.5% total lung involvement of residual lung abnormality of which 18.3% reticulation and 34.2% ground glass opacity. Peripheral reticulation (arrows) is evident surrounded by faint areas of ground glass density. Representative coronal CT images from the same individual at C) 114 days post discharge scored with 56.8% lung involvement (28.5% reticulation; 28.3% ground glass opacity) and D) 239 days post discharge scored with 49.2% total lung involvement (20.0% reticulation; 29.2% ground glass opacity). Peripheral areas of reticulation (black arrow) and ground glass density (white arrow) in the right lung.

49x39mm (300 x 300 DPI)

# Residual lung abnormalities following COVID-19 hospitalization: interim analysis of the UKILD Post-COVID study

(Running head) Lung damage burden after COVID-19 hospitalization

Iain Stewart, Joseph Jacob, Peter M George, Philip L Molyneaux, Joanna C Porter, Richard J Allen, Shahab Aslani, J Kenneth Baillie, Shaney L Barratt, Paul Beirne, Stephen M Bianchi, John F Blaikley, James D Chalmers, Rachel C Chambers, Nazia Chadhuri, Christopher Coleman, Guilhem Collier, Emma K Denneny, Annemarie Docherty, Omer Elneima, Rachel A Evans, Laura Fabbri, Michael A Gibbons, Fergus V Gleeson, Bibek Gooptu, Neil J Greening, Beatriz Guillen Guio, Ian P Hall, Neil A Hanley, Victoria Harris, Ewen M Harrison, Melissa Heightman, Toby E Hillman, Alex Horsley, Linzy Houchen-Wolloff, Ian Jarrold, Simon R Johnson, Mark G Jones, Fasihul Khan, Rod Lawson, Olivia Leavy, Nazir Lone, Michael Marks, Hamish McAuley, Puja Mehta, Dhruv Parekh, Karen Piper Hanley, Manuela Platé, John Pearl, Krisnah Poinasamy, Jennifer K Quint, Betty Raman, Matthew Richardson, Pilar Rivera-Ortega, Laura Saunders, Ruth Saunders, Malcolm G Semple, Marco Sereno, Aarti Shikotra, A John Simpson, Amisha Singapuri, David JF Smith, Mark Spears, Lisa G Spencer, Stefan Stanel, David Thickett, A A Roger Thompson, Mathew Thorpe, Simon LF Walsh, Samantha Walker, Nicholas David Weatherley, Mark Weeks, Jim M Wild, Dan G Wootton, Chris E Brightling, Ling-Pei Ho, Louise V Wain, R Gisli Jenkins

**ONLINE DATA SUPPLEMENT** 

## Supplementary Table 1: Comparison of demographics between visually scored >10% residual abnormalities and at-risk group

	Inte	erim	At-	risk	>10% inv	olvement	χ² pval
	N=3700	percent	N=273	percent	N=166	percent	
Sex							0.295
Male	2247	60.7%	193	70.7%	125	75.3%	
Female	1450	39.2%	80	29.3%	41	24.7%	
Age							0.155
60+	1801	48.7%	162	59.3%	87	52.4%	
<60	1895	51.2%	111	40.7%	79	47.6%	
Ethnicity							0.567
White	2804	75.8%	199	72.9%	115	69.3%	0.00
Asian	467	12.6%	41	15.0%	31	18.7%	
Black	223	6.0%	15	5.5%	11	6.6%	
Other	131	3.5%	sn	sn	sn	sn	
	75	2.0%	sn	sn	sn	sn	
Missing IMD	/3	2.070	311	311	311	311	0.076
1 Most	867	23.4%	72	26.4%	32	19.3%	0.076
	817	23.4%	63	23.1%	36	21.7%	
2	666	22.1% 18.0%	48	23.1% 17.6%		21.7% 18.7%	
3					31		
4	659	17.8%	54	19.8%	28	16.9%	
5 Least	667	18.0%	35	12.8%	37	22.3%	
BMI	252	<b>=</b> 40/		10.50/	4 =	0.00/	0.416
<25	262	7.1%	29	10.6%	15	9.0%	
25 - <30	612	16.5%	90	33.0%	43	25.9%	
30 - <40	880	23.8%	81	29.7%	58	34.9%	
>=40	230	6.2%	20	7.3%	11	6.6%	
Missing	1716	46.4%	52	19.0%	39	23.5%	
WHO severity							0.123
No O2 (i)	624	16.9%	21	7.7%	16	9.6%	
Non-invasive O2 (ii)	1567	42.4%	100	36.6%	59	35.5%	
CPAP (iii)	860	23.2%	73	26.7%	30	18.1%	
IMV (iv)	645	17.4%	79	28.9%	61	36.7%	
CXR							<0.001
Normal	1289	34.8%	40	14.7%	50	30.1%	
Other	325	8.8%	21	7.7%	15	9.0%	
Abnormal	162	4.4%	141	51.6%	21	12.7%	
Missing	1924	52.0%	71	26.0%	80	48.2%	
CT							<0.001
Performed	255	6.9%	8	2.9%	166	100.0%	
PSQ: cough/breathless			-	- / -			0.277
Present - worsen	850	23.0%	116	42.5%	58	34.9%	
Present - no change	319	8.6%	22	8.1%	19	11.4%	
Not present/improved	359	9.7%	34	12.5%	17	10.2%	
Missing	2172	58.7%	101	37.0%	72	43.4%	
ppFVC	21/2	30.770	101	37.070	12	75.770	0.920
• •	786	21.2%	97	35.5%	42	25.3%	0.320
80%+	297	8.0%	56	20.5%	25	25.5% 15.1%	
<80%							
Missing	2617	70.7%	120	44.0%	99	59.6%	10.004
ppDLco	222	0.00/	12	/ 00/	20	16.00/	<0.001
80%+	333	9.0%	13	4.8%	28	16.9%	
<80%	177	4.8%	151	55.3%	24	14.5%	
Missing	3190	86.2%	109	39.9%	114	68.7%	

Small numbers  $\leq 5$  have been suppressed. Chi-squared ( $\chi^2$ ) performed on non-missing categories. IMD: index of multiple deprivation in quintiles, BMI: body mass index, WHO: modified World Health Organisation severity score, CXR: chest X-ray, CT: computed tomography – chest, PSQ:

Patient Symptom Questionnaire, ppFVC: percent predicted forced vital capacity, ppDLco: percent predicted diffusion capacity across the lung for carbon monoxide.

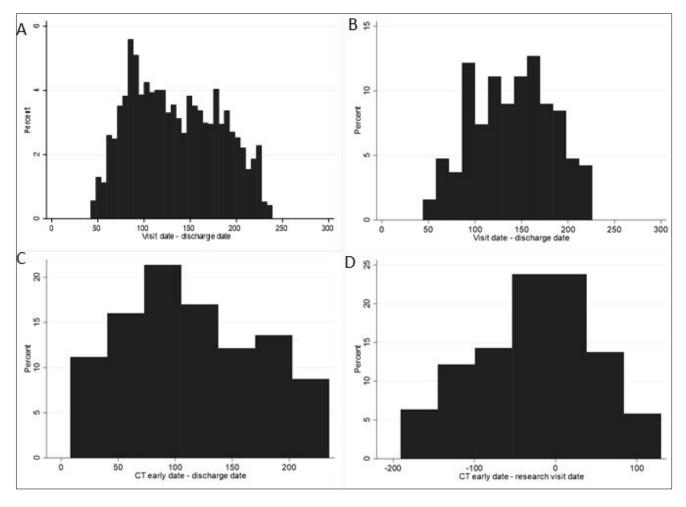
### **Supplementary Table 2: Comparison of hospital admissions**

	No C	T scored (n=	3491)	Abnorma	alities score	d (n=209)
	At-risk	Low-risk	χ² pval	>10%	<10%	χ² pval
Pre admission						
Treatment for infection	23.4%	14.7%	0.004	19.6%	11.5%	0.342
Immunosuppressant	18.3%	9.9%	0.001	10.3%	3.9%	0.305
Corticosteroid treatment	35.3%	26.5%	0.019	33.3%	23.1%	0.318
Renal replacement therapy	9.0%	3.8%	0.002	9.7%	0.0%	0.099
Ionotrope treatment	25.2%	12.7%	< 0.001	24.7%	7.7%	0.059
Admission						
Muscle aches	27.9%	24.7%	0.374	26.3%	50.0%	0.020
Headache	13.0%	16.9%	0.212	11.1%	19.2%	0.270
Sore throat	9.1%	8.8%	0.888	11.1%	0.0%	0.075
Intensive care unit	50.0%	33.4%	< 0.001	50.0%	15.4%	0.002
Invasive therapy	35.5%	20.1%	< 0.001	41.9%	7.7%	0.001
Oxygen	89.7%	79.4%	0.002	85.0%	61.5%	0.009
Complications						
Anaemia	15.1%	11.1%	0.138	23.9%	3.9%	0.023
Acute Respiratory Distress Syndrome	25.0%	13.7%	< 0.001	17.4%	11.5%	0.473
Liver dysfunction	7.9%	5.2%	0.157	12.0%	7.7%	0.540
Discharged home	44.7%	44.9%	0.937	48.2%	60.5%	0.151
Post discharge						
≥1 unscheduled emergency visit	34.8%	25.2%	0.001	15.7%	11.6%	0.507
≥1 unscheduled emergency visit*	24.5%	16.2%	< 0.001	13.3%	sn	0.258
Symptoms of emergency visit			n=906			n=31
Shortness of breath	33.7%	24.3%	0.046	34.6%	sn	0.818
Cough	14.7%	9.7%	0.129	sn	sn	0.656

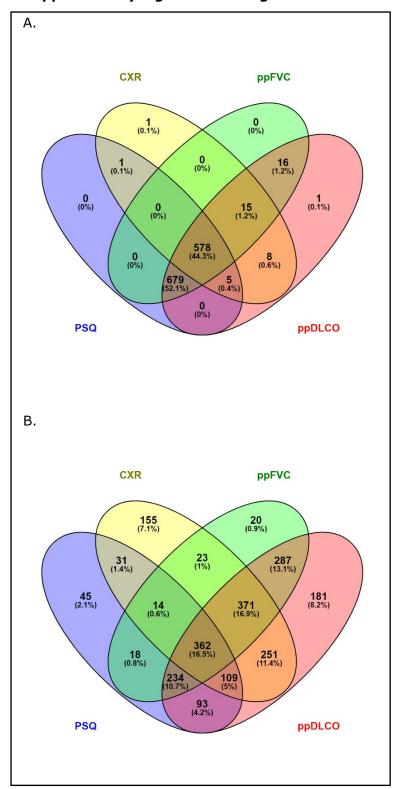
Percentages based on small numbers have been suppressed (sn). Index admission variables from linked ISARIC4C dataset were selected from a list of 61 using least absolute shrinkage and selection operator, using last lamda for at-risk associations (8 non zero coefficients) and >10% involvement associations (6 non-zero coefficients). Post discharge recorded in PHOSP-COVID Study. \*indicates participants with a minimum of 12 months research follow-up completed.

### Supplementary Figure 1. Histograms of follow-up time.

Where CTs were performed and linked. The time from discharge to follow-up visit in the interim cohort (A) and in those with CT scored (B) are plotted. Time between CT date and discharge date (C), and CT date to follow-up visit (D) are plotted.



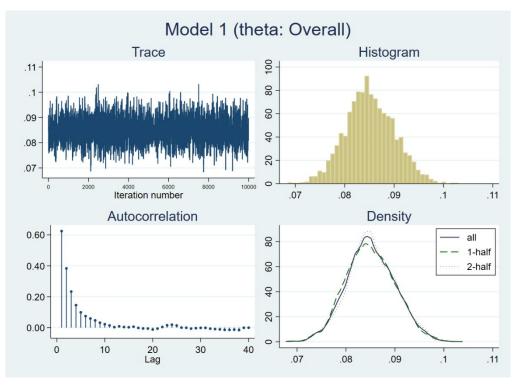
#### Supplementary Figure 2. Missing records in ILD diagnostic indicators

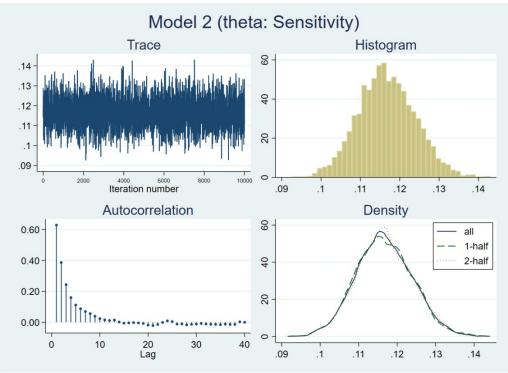


Missing data and representative percentage of missing data are reported for A) Tier 1 (n=1304) and B) Tier 2 (n=2396, of which 2194 had a missing value in one of the records) according to ppFVC (percent predicted forced vital capacity), ppDLco (percent predicted DLco gas transfer), PSQ (patient symptom questionnaire, cough and/or breathlessness), CXR (chest X-ray). Venny (2007-2015) https://bioinfogp.cnb.csic.es/tools/venny/index.html

#### **Supplementary Figure 3. Convergence traces**

Bayes convergence diagnostics provided for prevalence of suspected Post-COVID ILDam in hospitalised participants <240 days with non-informative flat priors (Model 1), and sensitivity based on cases in Tier 2 alone (Model 2).





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