**Residual lung abnormalities following COVID-19 hospitalisation: interim analysis of the UKILD Post-COVID study**

*(Running head) Lung damage burden after COVID-19 hospitalisation*

I Stewart1, J Jacob2, PM George3, PL Molyneaux1, JC Porter4, RJ Allen5,6, S Aslani2, JK Baillie7, SL Barratt8, P Beirne9, SM Bianchi10, JF Blaikley11, J Chalmers12, RC Chambers13, N Chadhuri11, C Coleman14, G Collier15, EK Denneny4, A Docherty7, O Elneima6, RA Evans6, L Fabbri1, MA Gibbons16, FV Gleeson17, B Gooptu5, NJ Greening6, B Guillen Guio5, IP Hall14, NA Hanley11, V Harris6, EM Harrison7, M Heightman18, TE Hillman18, A Horsley11, L Houchen-Wolloff6, I Jarrold19, SR Johnson14, MG Jones20, F Khan14, R Lawson10, O Leavy5, N Lone21, M Marks18, H McAuley6, P Mehta18, E Omer6, D Parekh22, A Parmar6, K Piper Hanley11,23, M Platé18, J Pearl5, K Poinasamy24, JK Quint1, B Raman25, M Richardson6, P Rivera-Ortega11, L Saunders15, R Saunders6, MG Semple26, M Sereno6, A Shikotra6, AJ Simpson27, A Singapuri6, DJF Smith3, M Spears28, LG Spencer29, S Stanel11, D Thickett22, AAR Thompson15, M Thorpe7, SLF Walsh1, S Walker30, ND Weatherley30, M Weeks1, JM Wild30, DG Wootton26, CE Brightling6, LP Ho25, LV Wain5,6, RG Jenkins1

*On behalf of the PHOSP-COVID Study Collaborative Group*

1National Heart & Lung Institute, Imperial College London, 2Centre for Medical Imaging Computing, University College London, 3Royal Brompton and Harefield Clinical Group, Guy’s and St Thomas’ NHS Foundation Trust, 4University College London, 5Department of Health Sciences, University of Leicester, 6Leicester NIHR Biomedical Research Centre, 7University of Edinburgh, 8North Bristol NHS Trust, 9Leeds Teaching Hospitals & University of Leeds, 10Sheffield Teaching Hospitals NHS Foundation Trust, 11University of Manchester, 12Ninewells Hospital and Medical School, 13Respiratory Medicine, University College London, 14University of Nottingham, 15University of Sheffield, 16Royal Devon and Exeter NHS Foundation Trust, 17Oxford University Hospitals NHS Foundation Trust, 18University College London Hospital, 19Asthma UK British Lung Foundation, 20Faculty of Medicine, University of Southampton, 21Usher Institute, University of Edinburgh, 22University of Birmingham, 23Manchester University NHS Foundation Trust, 24British Lung Foundation, 25University of Oxford, 26University of Liverpool, 27Newcastle University, 28Perth Royal Infirmary, NHS Tayside, 29Liverpool University Hospitals NHS Foundation Trust, 30Sheffield Teaching NHS Foundation Trust

**Corresponding author**:

Dr Iain Stewart, National Heart & Lung Institute

iain.stewart@imperial.ac.uk

**Author Contributions**

Conceptualisation: IS, JJ, JMW, JCP, PLM, PMG, RJA, JKB, SLB, PB, SMB, JFB, NC, GC, EKD, AD, LF, MAG, FVG, BG, IPH, NAH, MH, TEH, SRJ, MGJ, FK, RL, PM, MP, KP, JKQ, PRO, MS, AJS, DJFS, MS, LGS, SS, DRT, AART, SLFW, NDW, MEW, DGW, CEB, RCC, LPH, KPH, LVW, RGJ. Data curation: SA, EMH, MS, OL, HM, IS, JJ, NL, AB, JKQ. Formal analysis: IS, JJ, JKQ. Funding acquisition: CEB, LVW, RAE, JC, LPH, AH, MM, KP, BR, OL, MR, OE, HM, ASh, MS, RS, VH, LH, NG, RGJ. Project administration: ASh, MW, AS. Writing - original draft: IS, JJ, PMG, RGJ. Writing - review & editing: IS, JJ, PMG, PLM, JCP, RJA, JKB, SLB, PB, SMB, JFB, JC, RCC, NC, CC, GC, EKD, AD, OE, RAE, LF, MAG, FVG, BG, NJG, BGG, IPH, NAH, VH, EMH, MH, TEH, AH, LHW, IJ, SRJ, MGJ, FK, RL, OL, NL, MM, HM, PM, EO, DP, KPH, MP, JP, KP, JKQ, BR, MR, PRO, LS, RS, MGS, MS, ASh, AJS, AS, DJFS, MS, LGS, SS, DT, AART, MT, SLFW, SW, NDW, JMW, DGW, CEB, LPH, LVW, RGJ.

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**9.23 Interstitial Lung Disease**

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**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 hospitalised 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 were linked by PHOSP-COVID identifiers and scored for percentage involvement of residual abnormalities (ground glass opacities and reticulations). Risk factors in linked CT were estimated with Bayesian binomial regression and used to generate risk strata. Numbers of cases within strata were used to estimate post-hospitalisation prevalence using Bayesian binomial distributions. Sensitivity was performed in research follow-up participants.

**Measurements and Main Results.** The interim cohort comprised 3700 people. Of 209 linked CTs (median 119 days, interquartile range 83-155), 164 people (79.6%) had >10% involvement of residual lung abnormalities. Major 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). Moderate to very-high risk was classified in 7·8% of the remaining 3491 people, post-hospitalisation prevalence was estimated at 8.5% (95%CI CrI 7.6%; 9.5%) rising to 11.7% (95%CrI 10.3%; 13.1%) in sensitivity analysis.

**Conclusions.** Prevalence of residual lung abnormalities were estimated in up to 11% of people discharged following COVID-19 related hospitalisation. Health services should monitor at-risk individuals to elucidate long term functional implications.

1. **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 aetiology, [7, 8] circulating biomarkers, [9, 10] similarities in pulmonary function and radiological features.[11] Viral insult is considered an exposure of lung fibrosis, and chronic infection been shown in meta-analysis to be associated with developing IPF.[12] Some survivors of COVID-19 may therefore 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 interstitial lung damage or 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 hospitalisation following completion of an early follow-up visit of the prospective Post-HOSPitalisation COVID-19 (PHOSP-COVID) Study. [13]

1. **Methods**
	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. The PHOSP-COVID dataset includes a core set of demographics, tests of physical and pulmonary performance, symptom questionnaires, and biochemical tests, previously described in detail.[14]

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 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] All CTs were scored by one radiologist, a random sample of 100 were tested for inter-rater agreement (kappa) with a second radiologist. The primary outcome was visually scored residual abnormalities >10% lung involvement on CT.[15]

Demographics 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 (mask or nasal cannula); 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 on the greater of two recordings using GLI reference equations. These risk factors have been implicated in worse outcomes following COVID-19 hospitalisation for individuals with ILD.[16]

2.3 Statistical analysis

Risk factor data were presented descriptively overall, according PHOSP-COVID Tier, and within the subsample with linked CTs scored. 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 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.

Univariate relative risk ratios of threshold >10% residual abnormalities and continuous involvement on CT were modelled with dichotomised exposure variables in the subsample of CT scored participants. 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 hospitalisation. 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. Effect sizes for an inflammatory biomarker panel of 368 proteins (Olink) sampled in plasma at follow-up,[17] were tested between at-risk groups using t-tests with Welch’s correction and presented on volcano plots, top hits were selected using nominal p<0.01.

Bayesian inference with binomial distribution of at-risk cases and non-cases,[18] was used to estimate the prevalence of suspected residual lung abnormalities Post-COVID hospitalisation within 240 days of discharge, reported with the 95%CrI. MCMC simulations 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 sceptical and power priors informed by published population studies of ILD.[19, 20] 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.

1. **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, a total of 209 (82.0%) were visually scored (median 113 days; IQR 69 to 166, Supplementary Figure 1), inter-rater reliability κ. 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% was visually scored in 166/209 participants (79.4%). Visual scoring of involvement indicated ground glass opacities affected a mean 25.5% ±15.9 of the lung, reticulation a mean 15.1% ±11.0, with residual abnormalities involved in a mean a 40.6% ±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).

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 dyspnoea since discharge in Tier 2. ILD diagnostic criteria of lung function (ppFVC and ppDLCO), CXR and symptoms was frequently missing, particularly in Tier 1 (Supplementary Figure 2). In Tier 1, 578/1304 (44.3%) were missing data on all four characteristics at interim, whilst in Tier 2, 362/2406 people (15.0%) 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 abnormality involvement >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 and corticosteroid treatments pre-admission, renal comorbidities, intensive care unit stays, complications of acute respiratory distress syndrome (ARDS) and unscheduled emergency visits post discharge (Supplementary Table 2). At-risk participants had elevated levels of 13 inflammatory biomarkers at follow-up compared to low-risk participants (p<0.01), of which LAMP3 and PRSS8 were replicated in analysis of participants with residual abnormalities >10% compared to those with lower scored involvement (Figure 3). No biomarkers reached bonferroni threshold in the CT sample.

Based on the distribution of at-risk cases, the prevalence of residual abnormalities post-COVID hospitalisation 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 sceptical priors based on ILD population prevalence estimated at 1 in 1,000 (Supplementary Table 3, Supplementary Figure 3).[19, 20] In sensitivity analyses based on Tier 2 distribution, the prevalence of residual lung abnormalities post-COVID hospitalisation 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 sceptical priors.

1. **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 hospitalisation. The extent of involvement of residual lung abnormalities suggested slow decline over time, whilst minimal resolution was observed in paired subsequent scans. 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 CT scored, 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 hospitalisation, which increased to 10.4% in sensitivity analysis on those with protocolised research follow-up. Based on Bayesian modelling, we estimate the prevalence of suspected residual abnormalities with >10% lung involvement to be up to 11.7% in people hospitalised with acute COVID-19 infections before March 2021.

This UKILD Post-COVID interim analysis of residual abnormalities in patients hospitalised for COVID-19 offers the largest assessment of prevalence in hospitalised 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.[21-24] At the time of this interim analysis it is not possible to determine whether the observed residual 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.[25] 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 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 hospitalised cohort in order 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.[26] 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, renal comorbidity, and further unscheduled emergency visits post discharge. A number of inflammatory biomarkers were significantly upregulated in sampling at follow-up, with replication of Lamp3 and Prostasin in those with >10% residual lung abnormalities. Lamp3 is a lysosomal associated membrane protein that has been observed to be upregulated earlier in COVID-19 infection with high levels at admission associated with greater 28-day mortality.[27, 28] Prostasin is a serine proteinase expressed in organ tissues including lung that may lead to enhanced viral infectivity in COVID-19.[29] Elevated levels of such inflammatory biomarkers after acute infection may be consistent with persistence of lung abnormalities in COVID-19.

The interim findings highlight residual lung abnormalities Post-COVID are not uncommon in the hospitalised population and may persist. Considering approximately 459,000 people were hospitalised with COVID-19 in the UK National Health Service by end of March 2021 with two-thirds surviving the admission,[30] these results emphasise 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 hospitalisation, and we used informative sceptical priors and power priors for more conservative estimates of prevalence, which continued to suggest a substantial burden of residual abnormalities Post-COVID hospitalisation. 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 prioritisation 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.

We recognise 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 dichotomised 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.

Finally we recognise that these findings may not be generalisable to all populations especially people not admitted to hospital. Severe admissions requiring CPAP or IMV were over-represented in the PHOSP-COVID dataset relative to hospitalised 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 anaemia 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.

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**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 and reticulations from linear mixed effects by weeks post discharge, 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.

**Figure 3. Differences in inflammatory biomarker panel for at-risk participants**

Mean difference in levels of Olink inflammatory panel (368 proteins) sampled in plasma at follow-up plotted against –log10 pvalue from t-test. A) 844 linked participants with no CT scored, including 104 at-risk participants and 740 low-risk participants. B) 91 linked participants with CT scored, including 72 reaching >10% threshold of residual lung abnormalities and 19 who did not. Dashed line indicates nominal p<0.01 threshold, dotted line indicates bonferroni threshold (p<0.000136). LAMP3 (A 0.25, p=0.001; B 0.48, p=0.004) and PRSS8 prostasin (A 0.28, p<0.001; B 0.42, p<0.001) were replicated across subsamples at the nominal threshold.

**Table 1: UKILD interim cohort demographics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Interim | CT score | Tier 1 | Tier 2 | χ² pval |
|  | N=3700 | percent | n=209 | percent | n=1304 |  | 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 numbers <5 have been suppressed. Chi-squared (χ²) 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 | Percent of exposed | Percent of unexposed | 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 exposed and unexposed cases from non-missing case observations reaching >10% threshold of residual lung abnormalities. Presented with univariate risk ratio (RR) and 95% credible interval derived from binomial regression, mean effect difference in % lung involvement between unexposed and exposed from univariate linear regression and adjusted for sex and index of multiple deprivation**.** Interstitial lung damage (ILDam);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 cohort |
| 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 unscored CT |
|  | 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; Tier 2 sensitivity 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.

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



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



**Figure 3. Differences in inflammatory biomarker panel for at-risk participants**

