Background Persistent breathlessness is commonly reported following recovery of acute COVID-19 infection. Our previous study identified residual lung abnormalities (RLA) on CT, and suggested up to 11% of COVID-19 hospitalisations were at high risk of RLA. Whether RLA represents persistent epithelial damage or inflammation is unknown.

Methods Plasma was sampled from the PHOSP-COVID cohort at five months post-hospitalisation. Epithelial injury biomarkers Krebs von den Lungen-6 (KL6), matrix metalloproteinase 7 (MMP7), surfactant protein-D (SPD) and surfactant protein-A (SPA) were assayed for hypothesis testing. An O-link Explore inflammatory panel of 384 biomarkers was included in exploratory analysis. Confirmed RLA was defined as ≥10% combined involvement of ground glass opacity and reticulation on follow-up CT. High RLA risk in those without a CT was defined by percent predicted DLCO <80% and/or abnormal chest X-ray.

Results A total of 868 people with biomarker profiles were included, 111 people with CT scores (85 confirmed RLA, 77%), 757 people with no CT (81 high risk, 11%). KL6 and MMP7 were significantly higher in people with confirmed RLA than those without, SPD and SPA did not reach significance (table 1). Epithelial injury biomarkers correlated with reticulation (KL6 $r_s=0.36$, $p<0.001$; MMP7 $r_s=0.40$, $p<0.001$; SPD $r_s=0.29$, $p=0.002$; SPA $r_s=0.22$, $p=0.029$), but only KL6 and MMP7 correlated with ground glass opacities. All epithelial injury biomarkers were significantly elevated in people at high risk of RLA compared to low risk (table 1). No O-link Explore inflammatory biomarkers were reproducibly higher in both confirmed RLA and high risk participants after correction for multiple testing.

Conclusion All epithelial injury biomarker levels increased with greater reticulation on follow-up CT and were elevated in those at high risk of RLA, whilst KL6 and MMP7 were significantly elevated in people with CT-confirmed RLA. Limited inflammatory biomarkers were elevated in either confirmed RLA or high risk, and none at reproducibly significant levels. Findings suggest RLA is characterised by persistent epithelial injury after acute COVID-19 infection.

REFERENCE

Abstract S82 Table 1 Epithelial biomarker concentration according to residual lung abnormality

<table>
<thead>
<tr>
<th>RLA ≤10%</th>
<th>RLA ≥10%</th>
<th>$p$</th>
<th>RLA low risk</th>
<th>RLA high risk</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>KL6 (RU/mL)</td>
<td>269.04 (170.34 – 377.58)</td>
<td>380.33 (281.40 – 608.06)</td>
<td>0.0020</td>
<td>364.60 (260.36 – 526.44)</td>
<td>407.72 (295.53 – 641.50)</td>
</tr>
<tr>
<td>MMP7 (ng/mL)</td>
<td>10.27 (8.21 – 13.20)</td>
<td>16.38 (10.78 – 22.56)</td>
<td>0.0001</td>
<td>12.55 (9.54 – 17.42)</td>
<td>17.76 (10.93 – 25.02)</td>
</tr>
<tr>
<td>SPD (ng/mL)</td>
<td>44.10 (33.27 – 62.89)</td>
<td>53.99 (32.70 – 70.98)</td>
<td>0.2802</td>
<td>45.36 (29.76 – 73.88)</td>
<td>69.36 (39.42 – 99.72)</td>
</tr>
<tr>
<td>SPA (ng/mL)</td>
<td>31.27 (22.16 – 39.70)</td>
<td>33.90 (24.99 – 41.09)</td>
<td>0.3528</td>
<td>39.51 (21.22 – 39.16)</td>
<td>34.71 (26.35 – 45.75)</td>
</tr>
</tbody>
</table>

Median concentrations presented with interquartile range. P-values calculated with Wilcoxon rank sum test. RLA: residual lung abnormality. Confirmed RLA threshold scored as overall involvement on CT scans, risk defined by clinical risk factors of DLCO <80% predicted and/or abnormal chest X-ray.
intracytoplasmic cilia up to 12 months post infection. There was no correlation with any ongoing nasal symptoms or symptoms of long COVID. In contrast, ciliogenesis was normal in the Omicron infected, vaccinated cohort, and no mislocalised basal bodies or intracytoplasmic cilia were seen. Defects in cilia function were present in both cohorts compared to pre-pandemic controls: reduced cilia beat frequency (FOLLOW p<0.01), reduced amplitude per second in both: (FOLLOW p<0.01, ULTRON p<0.01).

This ciliogenesis defect led us to explore FOXJ1 expression post-COVID: qRT-PCR showed a significant reduction of FOXJ1 mRNA levels 6 months (p<0.001) and 12 months (p=0.002) following pre-Omicron variant infections compared with healthy volunteers; however, there was a significant improvement between 6-months and 12-months.

Conclusion Cilia loss and defective ciliogenesis linked to reduced FOXJ1 expression persisted for a year following infection with early SARS-CoV-2 variants. No such defects were seen in vaccinated individuals infected with the Omicron variant despite some functional ciliary defects. This work illuminates novel long-term effects of viral infection on human epithelial function through altered expression of a key ciliary regulator gene.

**S84 SINGLE-CELL LANDSCAPE OF BRONCHOALVEOLAR CELLS IN INFLAMMATORY AND FIBROTIC POST-COVID RESIDUAL LUNG ABNORMALITIES**


Background Approximately 10% of patients hospitalised with COVID-19 have residual lung abnormalities (RLAs) at 12 months. In clinical practice, CT scan appearances are often used to guide management. Whether such radiological changes reliably reflect immunopathomechanisms, and can therefore inform the treatment approach, is unclear and an important clinical question.

Methods We compared the single cell transcriptomic and T cell receptor (TCR) profiles of bronchoalveolar lavage cells from patients with Post-COVID RLAs with either predominantly inflammatory or fibrotic radiological appearances.

Results We generated a dataset of 55,776 cells. CD4 central memory T cells (TCM) and CD8 effector memory T cells (TEM) were significantly increased in the inflammatory subphenotype. Both patient groups were transcriptionally similar and exhibited clonal expansion and high TCR clustering, without enrichment for SARS-CoV-2 reactive sequences.

Conclusions We describe the first comparison of purported radiological subphenotypes in patients with Post-COVID RLAs, which may actually represent different manifestations of the same disease. Antigen-specific immune responses to unidentified T cell targets, imply a breach of immune tolerance in the lung and a potential role for T-cell directed therapies in these patients, agonistic of radiological appearance.

Please refer to page A285 for declarations of interest related to this abstract.