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Persistent pulmonary disease after acute covid-19

Lingering pathology contributes to a wider picture of poor health after hospital discharge

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It has been over a year since the first patients were discharged from UK hospitals following treatment for covid-19. Hospital admission was largely dictated by the requirement for supplementary oxygen and additional respiratory support.¹ Acute imaging commonly showed multifocal airspace opacification, and venous thromboembolism was recorded in around a quarter of adults admitted to critical care.² This led to concern about the long term respiratory consequences of covid-19, particularly interstitial lung disease and pulmonary vascular disease.³

Fifteen months later, our understanding of the complications after hospital treatment for covid-19 is improving. A UK study of 47 780 discharged patients reported all cause mortality of 12% and readmissions in one third after 140 days of follow-up.⁴ Interestingly, although respiratory disease was diagnosed in 29.6% after discharge, rates of extrapulmonary complications, including diabetes, adverse cardiovascular events, and liver and kidney dysfunction were also increased compared with those in population matched controls, indicating that the effect of covid-19 extends far beyond the lungs.

Outcome data from single centre cohorts have shown that the lungs are often physiologically and radiologically impaired 3-4 months after hospital discharge. In one prospective study from Italy, the diffusion capacity for carbon monoxide (DLCO, a marker of pulmonary-vascular integrity) was below normal range in 52% of 238 patients at four months.⁵ A study from Canada (n=60) found that 55% of patients who had follow-up computed tomography (CT) had persisting radiological abnormalities 12 weeks after discharge.⁶ A French cohort study reported similar findings, with evidence of fibrosis in 12% (15/121) and 37% (19/49) of non-intubated and intubated patients, respectively. However, only one patient had abnormalities affecting more than 25% of the lung.⁷

In a cohort from Wuhan, China, severity of acute infection correlated with percentage of patients with DLCO impairment six months after discharge (22% in those who did not require oxygen compared with 56% requiring respiratory support or intensive care). Three quarters of patients remained symptomatic, with fatigue, muscle pains, and sleep disturbance most frequently reported.⁸

Concordance among these studies suggests the findings are likely to be applicable to hospital treated patients more generally. Indeed, lung abnormalities persisting a few months after other viral pneumonias are recognised.⁹ Interestingly, however, while most patients in these studies had persisting symptoms (particularly fatigue, memory problems, and psychological sequelae), only a minority reported

dyspnoea (5.5%, 20%, 16%, and 26% in the studies from Italy, Canada, France, and Wuhan, respectively⁵⁻⁸).

Data on longer term post-covid sequelae remain sparse, although a small prospective study from Wuhan (n=83) looked at respiratory outcomes over the course of a year after hospital discharge.¹⁰ The percentage of patients with radiological abnormalities fell from 78% at 3 months to 27% (22/83) by 9 months and remained unchanged at 12 months. Only four patients reported dyspnoea one year after discharge and functionally, patients recovered well with normalisation of six minute walk distance. These findings are reassuring, but wide extrapolation should be avoided: participants had a median age of 60 but had no pulmonary and cardiac comorbidities, had never smoked, and 46% did not require respiratory support during the acute infection.

The follow-up studies use various radiological descriptions, but “ground glass opacification” is often reported.^{5-8 10 11} In the absence of dilated bronchi, this can indicate a potentially reversible cellular (inflammatory) infiltrate.¹² However, in the year long Wuhan study,¹⁰ ground glass opacification noted at nine months was still present at 12 months, raising the possibility it may in part represent fine fibrosis. This distinction is important as it could influence use of immunomodulatory therapy in patients with persisting ground glass opacification (which will have no effect if fibrosis is the underlying cause). Currently, the benefit of such treatment remains unclear, with only a single study from the UK reporting improvement in dyspnoea scores, lung function, and imaging with a tapering course of corticosteroids starting six weeks after discharge for patients with persistent inflammatory change on CT.¹¹ However, this was an uncontrolled observational study of just 30 patients, and since outcome studies have shown improvement in these measures over time without use of corticosteroids,^{5-8 10 11} it is difficult to draw conclusions.

Pulmonary emboli are common in patients in hospital with covid-19.² Analysis of healthcare claims in the US also found an increased incidence of venous thromboembolism 200 days after the acute illness,¹³ although little is known about the burden of chronic thromboembolic disease. Interestingly, a small pilot study from the UK (n=9) using hyperpolarised xenon magnetic resonance imaging of the lungs found regional diffusion abnormalities persisting for three months after hospital discharge, even in those with near normal appearances on computed tomography.¹⁴ These findings may indicate enduring pulmonary vascular abnormalities after acute covid-19, but

further investigation is required. The clinical significance of these abnormalities remains unknown.

To summarise, studies to date show that persisting respiratory complications do occur and that the severity of infection and prior health status are probably the main determinants of radiological and functional impairment longer term. Interstitial abnormalities do not seem to progress (although evidence is sparse) and improve over time.^{5-8 10}

Importantly, many studies^{4-8 10 15} highlight the extent of non-respiratory physical and psychological symptoms after acute covid-19, and follow-up studies report all-cause mortality exceeding 10% in the six months after discharge.^{4 15} Thus, while persisting lung damage may be substantial for some, for many, morbidity and mortality after covid-19 are influenced most by pre-existing conditions, infection severity, and the extra-pulmonary complications of SARS-CoV-2.

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