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Long covid: risk factors, outcomes, and future directions for research

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Closer to identifying those at risk of long covid, but optimal treatment is still unknown

The long term consequences of covid-19 are becoming increasingly apparent. Patients first reported on and conceptualised the condition now commonly known as long covid.[1] The scale and burden of persistent or new symptoms after recovery from initial infection remains difficult to interpret because of high heterogeneity in prevalence estimates in published meta-analyses; however, pooled global prevalence has been estimated to be 43% (95% confidence interval 39% to 46%).[2] Given the high prevalence of ongoing symptoms, identifying individuals at risk of long covid could enhance patient follow-up strategies and treatment options.[3]

In a linked article,[4] Legrand and colleagues determined the risk factors and associations between subphenotypes (based on the severity of patients' hospital course) and outcomes at six months of people admitted to and discharged from hospital after having covid-19. The researchers found that 51% of survivors experienced at least one unresolved symptom six months after hospital admission, which was not mediated by acute covid-19 severity. Patients who were female, received supplemental oxygen in hospital, were not admitted to intensive care, had congestive heart failure, and had a gastrointestinal haemorrhage or thromboembolic event were associated with an increased risk of persistent symptoms.

The authors identified three subphenotypes (least severe, intermediate severity, and most severe), with patients in the more severe subphenotype less likely to return to work and who had impaired function status when compared with the less severe subphenotypes. Legrand and colleagues also showed different quality-of-life outcomes and scores for anxiety and depression between subphenotypes. The number of patients still experiencing at least one persistent symptom did not differ significantly between subphenotypes. The study shows that persistent symptoms occurred regardless of covid-19 severity and did not differ statistically across subphenotypes, yet subjective and objective functional status six months after hospital admission differed significantly between the three subphenotypes. In addition, severity of initial covid-19 disease was not a strong predictor of persistent symptoms at six months. Patients in the subphenotype cluster with the most severe hospital course were less likely to resume their professional occupations.

The main strength of this study was its prospective, multicentre, observational cohort design, which was conducted across 93 hospitals in France. But some study limitations must be acknowledged when interpreting the data. A major limitation was the lack of a test negative control group. A test negative control group is essential for determining the true prevalence of long covid, because many of the symptoms have also been reported by both adults and children who have tested negative for covid-19,[5 6] demonstrating the relative commonness of these symptoms in the population at any given time. While this study advances the understanding of long term symptoms after covid-19 related hospital admission in France, previous research has reported significant differences in long covid prevalence across subphenotypes, with recovery lowest in the severe clusters compared with the moderate and mild clusters.[7] We commend Legrand and colleagues for using validated measurement tools for health related quality of life, depression, anxiety, exercise capacity, and pulmonary function. However, caution is required here given the large amount of missing data (66.1-91.2%), which might reduce statistical power and can complicate the application of clustering algorithms, which aim to group points based on similarity criterion.[8]

The findings of Legrand and colleagues' study have implications for clinical practice in several important respects. Their results could expand on existing data to aid the development of multidisciplinary approaches to manage long covid recovery, although these approaches would be limited to patients who have been in hospital and who have not been vaccinated. While still in its infancy, clustering analysis could inform clinical practice by identifying specific cluster phenotypes that will allow researchers and clinicians to stratify and personalise care. Further work is needed to determine how to translate research on cluster phenotypes into meaningful clinical tools to help healthcare professionals in routine clinical practice. Although we are closer to identifying those individuals at risk of long covid, the question remains—what is the optimal treatment for people with long covid? Several interventional studies are ongoing, and we await their results to identify appropriate treatment strategies tailored to the clustering or severity of symptoms as identified in this analysis.

Symptom cluster phenotyping offers the potential to stratify and personalise care, and it will be interesting to see whether similar cluster analysis results are observed in cohorts of people who were

not in hospital during acute SARS-CoV-2 infection. Multiple ongoing studies by the UK National Institute for Health and Care Research, including routine database studies and prospective cohort studies, will offer further insight into the diagnosis of long covid, alongside treatment, rehabilitation, and recovery.[9] International collaborations are also required to understand trajectories of long covid. Findings from existing test negative controlled studies show a substantial proportion of people with symptomatic covid-19 go on to have persistent symptoms for 12 weeks or more.[10] The Coronavirus Infection Survey showed that 5% of patients with covid-19 reported any of 12 common symptoms 12-16 weeks after infection, as did 3.4% of the test negative control group.[6] In adolescents, similar symptom prevalence was observed in the covid-19 confirmed cohort when compared with the covid-19 negative cohort three months after infection.[5]

This study adds to the evolving evidence base by identifying risk factors that might predispose an individual to long covid; identification of such risk factors could have a fundamental role in the prediction, prevention, and management of long covid. Building on the work of Legrand and colleagues future research should use risk factors to facilitate early identification of patients that are at increased risk of developing long covid and focus on targeted treatments for people living with long term symptoms. Further population based, prospective covid-19 studies of inpatients, outpatients, and test negative comparison groups in adults and children are needed to enhance the current understanding of long covid. Future studies would benefit from having a control group and incorporate robust exposure assessment methods (that is, laboratory confirmed diagnoses); have validated symptom assessment tools that assess key mental, physical, and social outcomes; and provide breakdowns of data across a range of determinants including ethnic origin, socioeconomic deprivation, covid-19 variants, and vaccination status. At present, how long symptoms will persist after disease onset is unknown, but ongoing symptoms two years after acute SARS-CoV-2 infection have also been reported.[11] SARS-CoV-2 is a novel virus about which our understanding is still limited, and similar studies in the longer term will be required with robust study designs to fully understand the epidemiology of long covid.

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