EDITORIAL

Disentangling the Postacute Sequelae of SARS-CoV-2
E Unibus Pluram (From One, Many)

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Early in the COVID-19 pandemic, patients and clinicians reported the persistence of initial symptoms and the onset of new symptoms after the acute phase of SARS-CoV-2 infection, collectively referred to as *postacute sequelae of SARS-CoV-2 infection* (PASC), or more colloquially called *long COVID*.[1]

Related article

Persistent anosmia as well as debilitating physical symptoms, such as chronic cough, gastrointestinal symptoms, fatigue, malaise, myalgias, pain, and lack of clarity of thought ("brain fog"), with or without obvious organ dysfunction, were prominent ailments identified by numerous patients after acute COVID-19.[1,2] This phenomenon has been a major focus of research. Investigators have sought to determine the pathogenesis of illness with a goal of designing effective interventions to mitigate or resolve the symptoms.

To optimize our understanding of the long-term impact of post-COVID-19 sequelae and to design and assess potential interventions, it is critically important to establish validated case definitions. Erroneous case definitions, and the resultant misclassification bias, could delay the correct diagnoses by clinicians, will decrease the likelihood of identifying the biological mechanisms underpinning these symptoms, might threaten the ability to demonstrate the efficacy of interventions, and could lead to misdirected, ineffective treatments. However, before developing a case definition for PASC, it is important to consider whether these sequelae represent a single pathophysiologic process or rather multiple different conditions triggered by antecedent SARS-CoV-2 infection.[3] In addition, it is important to know whether they are direct sequelae of infection itself or are mediated by specific organ injury and dysfunction. For example, severe SARS-CoV-2 infection that requires intensive care unit admission can result in a well-described postintensive care syndrome with many features that overlap with postacute sequelae.[4] Thus, it may be inaccurate to define PASC as a single syndrome classified by a score on a diagnostic algorithm. If these sequelae represent multiple different processes, each might require separate definitions and treatments.

To begin classifying postacute sequelae of SARS-CoV-2 infection, the RECOVER Consortium established an adult longitudinal cohort. They prospectively collected post-COVID-19 clinical data and banked biosamples to determine the incidence of various sequelae, including clinical symptoms and organ dysfunction and their natural history over time, and to investigate biological mechanisms underlying the pathogenesis of the various phenotypes of PASC. In this issue of *JAMA*,[5] the RECOVER adult cohort investigators report the initial results of this cohort study. Across 85 sites in the US, they enrolled 8646 participants with evidence of prior COVID-19 and 1118 uninfected individuals. Enrollment of patients occurred at different times after SARS-CoV-2 infection, incorporating an acute cohort that included patients diagnosed within 30 days after acute infection and a postacute cohort diagnosed more than 30 days to up to 3 years after acute infection. Additionally, participants were enrolled during different phases of the pandemic starting before and continuing after the Omicron variant became the most common strain. Uninfected participants were identified as having no evidence of current or prior SARS-CoV-2 infection.

The study compared symptoms between those with and without SARS-CoV-2 infection to identify the symptoms most likely to characterize postacute sequelae. Symptoms that emerged most prominently included postexertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, palpitations, change in sexual desire or capacity, loss of or change in smell or taste, chronic cough, thirst, chest pain, and abnormal movements. Each symptom was assigned a value and the total was summed to yield an individual's score. A cutoff point of 12 on the PASC score classified 23% of the overall SARS-CoV-2–infected cohort as meeting the definition. The study found that the proportion meeting this definition was, in general, higher among unvaccinated than fully vaccinated participants and in the Omicron cohorts, higher among reinfected participants compared with those with 1 reported infection. Importantly, the authors then clustered individuals into groups with similar symptoms and degrees of disability to explore whether there might be different phenotypes of postacute sequelae. The most severe clusters shared symptoms of postexertional fatigue and central nervous system dysfunction. Anosmia was prominent in the least severely affected cluster.

It was notable that nearly 4% of people without a history of COVID-19 met the score cutoff for PASC. This is almost certainly due to overlap of the PASC score criteria with other common chronic symptomatic conditions, such as depression, a disorder whose incidence has risen globally during the COVID-19 pandemic.[6] Interestingly, many of the symptoms included in the PASC score are similar to those of myalgic encephalomyelitis/chronic fatigue syndrome.[7] Of course, because chronic symptomatic conditions can subsequently cause depression, it may be impossible to determine whether the symptoms are due to late sequelae of SARS-CoV-2 infection or another condition and may therefore remain as a limitation that decreases the positive predictive value of any final PASC score. In light of the results of the cluster analyses

suggesting different degrees of disability for subgroups and the misclassification of those without SARS-CoV-2 infection as having PASC, a single overall PASC score may have limited clinical and research utility.

The data suggest that anosmia may define a unique subgroup with less severe symptoms. This difference highlights the importance of further disentangling the different phenotypes of the postacute sequelae. It may not be appropriate for an individual debilitated by fatigue and brain fog and another individual who is highly functioning despite loss of taste and smell to similarly be labeled as having the same single entity of PASC. The creation of definitions for individual phenotypes of post–COVID-19 sequelae could enhance the ability to accurately study mechanisms and develop interventions to improve function and quality of life for the key subgroups.

This research should be considered within the context of some important limitations. There was an overrepresentation of women and those with higher levels of education in the cohort than in the US population. The self-referral nature of a subset of the cohort could have led to selection bias. Given the methodological limitations and differences in rates of postacute sequalae for those enrolled during different phases of illness (acute vs postacute) and different eras (pre-Omicron vs Omicron), the estimates of the prevalence of postacute sequelae syndromes reported by the RECOVER adult cohort should not yet be interpreted as definitive.

An important strength of the RECOVER adult cohort's initial analyses is the clustering of different symptoms into postacute sequelae phenotypes. Subgroupings of clusterings could lead to more fruitful future analyses of the biological mechanisms causing these symptoms and, ultimately, to intervention studies demonstrating differential effects of treatments that can return those affected back to health. Another potential benefit of the RECOVER adult cohort study would be if future work finds characteristic biomarkers for the different phenotypes of postacute sequelae, and if those signatures are similar to biosignatures in other conditions, particularly of myalgic encephalomyelitis/chronic fatigue syndrome. This would create an opportunity to conduct studies relevant to that complex disorder with sample sizes not previously feasible, accelerating the ability to rapidly test various treatment strategies for this previously identified disabling condition.[8] Additional benefits of this work may be years in the making if it ultimately changes our understanding of how and why different individuals respond differently to infections and why abnormalities persist in some but not others. Future prevention studies, beyond vaccination, could also be identified to avert what appear from this study to be multiple different debilitating conditions caused by a single novel infectious pathogen.

This first RECOVER adult cohort study report provides an important initial framework for defining the sequelae that manifest after acute SARS-CoV-2 infection. The research exemplifies the benefits of multidisciplinary collaboration informed by extensive input from patient representatives. These efforts will continue to be needed to determine whether this phenomenon represents one entity with a single definition or multiple phenotypes that arise after COVID-19 infection requiring separate case definitions (ie, *E unibus pluram* [from one, many]). Addressing this question and finalizing the definitions of these postacute sequelae should facilitate more robust research that ultimately leads to high-quality care and treatment for patients with late effects of SARS-CoV-2 infection.

ARTICLE INFORMATION

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REFERENCES

1. Danesh V, Arroliga AC, Bourgeois JA, et al. Symptom clusters seen in adult COVID-19 recovery clinic care seekers. *J Gen Intern Med*. 2023;38(2):442-449. doi:10.1007/s11606-022-07908-4

2. Huang C, Huang L, Wang Y, et al. 6-Month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220-232. doi:10.1016/S0140-6736(20)32656-8

3. Reese JT, Blau H, Casiraghi E, et al; N3C Consortium; RECOVER Consortium. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes. *EBioMedicine*. 2023;87:104413. doi:10.1016/j.ebiom.2022.104413

4. Baldwin MR, Anesi GL. Post-intensive care syndrome in COVID-19 versus non-COVID-19 critical illness survivors: more similar than not? *Am J Respir Crit Care Med*. 2022;205(10):1133-1135. doi:10.1164/rccm.202202-0396ED

5. Thaweethai T, Jolley SE, Karlson EW, et al; RECOVER Consortium Authors; RECOVER Consortium. Development of a definition of postacute sequelae of SARS-CoV-2 infection. *JAMA*. Published May 25, 2023. doi:10.1001/jama.2023.8823

6. COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet*. 2021;398(10312):1700-1712. doi:10.1016/S0140-6736(21)02143-7

7. Komaroff AL, Lipkin WI. Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. *Trends Mol Med*. 2021;27(9):895-906. doi:10.1016/j.molmed.2021.06.002

8. Jason LA, Benton MC, Valentine L, Johnson A, Torres-Harding S. The economic impact of ME/CFS: individual and societal costs. *Dyn Med*. 2008;7:6. doi:10.1186/1476-5918-7-6