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Commentary

Recovery after Covid-19

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Worldwide, by mid-June, 2021, there have been more than 177 million registered cases of confirmed SARS-CoV-2 infection, causing Coronavirus disease-19 (Covid-19) [1]. Although Covid-19 has caused nearly four million deaths, the vast majority of cases follow a mild clinical course [2] or survive hospitalization for moderate-to-critical Covid-19 [3]. SARS-CoV-2 vaccination is now clearly decreasing infection rates [4] marking the dawn of the post-Covid-19 pandemic era. Meanwhile, however, after recovery from acute Covid-19, it has been widely recognized that a substantial proportion of people may experience long-lasting symptoms, also termed post-acute sequelae of Covid-19 (PASC), posing serious next challenges.

PASC may occur across Covid-19 severity grades, and covers a wide array of symptoms including fatigue, dyspnea, pain, muscle weakness, concentration problems and more [5-7]. Understanding its prevalence from a population perspective is key; current estimates vary widely, mainly due to the lack of a uniformly applied definition and to variations in Covid-19 severity grade representation among studied samples. The UK National Institute of Care Excellence has proposed a set of definitions to distinguish three phases: acute Covid-19 (symptoms up to 4 weeks after onset), ongoing symptomatic Covid-19 (symptoms lasting beyond 4 weeks up to 12 weeks) and post-Covid-19 syndrome (newly developed symptoms during or after Covid-19 lasting more than 12 weeks and are not explained by an alternative diagnosis) [8]. Given the lack of objective diagnostic criteria, current prevalence estimates are, logically, derived from self-reported data on presence of persisting symptoms.

The relevant study by Liu and colleagues in *The Lancet Regional Health - Western Pacific* adds to the current narrow body of population-based evidence on recovery rate after acute Covid-19 [9]. They longitudinally studied 2904 patients (51% women, mean age 47 years, SD 20) from the public health register in New South Wales Australia, where all regional positively SARS-CoV-2 tested

cases were registered for disease surveillance and outbreak management. The study sample comprised 94% of all registered cases, making this study probably the most inclusive thus far. Of these, 377 (13%) were hospitalized for Covid-19. Through a series of telephone interviews asking whether people still had any symptoms following acute Covid-19, they concluded that 80% of cases had recovered by one month, 90% by 2 months and 93% by 3 months. Excluding deaths from the group who did not recover, yielded an estimated prevalence of ~5% of people with persisting symptoms 3 months after Covid-19. That is, assuming there were no alternative explanations for non-recovery. These prevalence estimates appear in fair agreement with experimental population estimates produced by the UK Office for National Statistics [8]. A typical clinical experience is that a substantial number of affected people relapse after initial recovery. Considering that Liu *et al.* [9] defined self-reported recovery as an end point, true prevalence might be higher. Of note, 87% of those not recovered at last contact had mild Covid-19.

Although the pathophysiology of PASC remains yet largely unresolved, it seems arguable to assume a multifactorial etiology. Indeed, factors involved may include SARS-CoV-2-induced multi-organ manifestations, immune, metabolic or autonomic dysregulation, as well as generic sequelae following intensive care treatment, pneumonia or those seen in other post-infectious syndromes [10]. Disentangling SARS-CoV-2 specific factors from generic factors should be taken into careful consideration both in clinical care and scientific research. Identifying risk factors for non-recovery may contribute to the understanding of PASC pathophysiology. On the population level, older age, female sex, comorbidities, and being symptomatic at diagnosis were risk factors identified by Liu *et al.* [9]. It is, however, also noted in clinical practice [7] and in samples drawn from post-Covid-19 social support groups [11] that those presenting with persisting symptoms after mild Covid-19 are mostly younger and have few comorbidities. At this point, explaining these risk factors would only be speculative.

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The confirmation that the vast majority of people indeed recover quickly after SARS-CoV-2 infection is good news. Yet, PASC is now emerging as a major public health and economic problem for several reasons. First, considering the number of infected people globally, current prevalence estimates suggest PASC affects many million people. Also, at least in a subset, various health status domains in these patients are severely affected [7], [11], and, as corroborated by the plateau phase of the incident recovery curve in the study by Liu *et al.* [9], affected people are mostly recovering only slowly. Third, complicated recovery trajectories are associated with significant loss of productivity [11]. Fourth, clearly there are many knowledge gaps regarding pathophysiology and treatment of PASC for which extensive multidisciplinary research programs, such as those in the UK and USA [12], have been put in place. And, lastly, PASC is posing considerable extra burden on already overloaded health care systems, being challenged to ensure and further develop effective and safe integrated supportive care and rehabilitation. Many efforts across health care levels are being employed to care for individuals with PASC, in which a coordinated response is desirable.

Declaration of Competing Interest

The author declares no competing interests

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