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The Long-COVID Conundrum

Angus Mackay*

The Brain Health Research Centre, University of Otago, Dunedin, New Zealand

EDITORIAL NOTE

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Corresponding Author:
Shuhei Tanoue
Department of Health Policy and Management
School of Medicine, Keio University,
Tokyo, Japan
shuhei@tanoue.jp

As the COVID-19 pandemic took hold in 2020 (having emerged out of China, it would appear, in late 2019), so it became evident that people who had contracted severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) months previously, were not getting better. Over time, those affected (often referred to as "long haulers") by what was termed Long-COVID grew significantly in numbers, and in Oct 2021 the World Health Organization (WHO) provided a clinical case definition (which still exists) for it, termed Post-COVID Condition (PCC)[1].

"It is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation."

According to the WHO, it is estimated that between 10-20% of those infected by SARS-CoV-2 have experienced (or continue to experience) some form of Long-COVID [1]. This equates to around 70-140 million people worldwide (based on a conservative figure of 700 million confirmed COVID-19 cases worldwide), and around 10-20 million people in the USA (based on a conservative figure of approximately 100 million confirmed COVID-19 cases in the USA). This presents a significant global health problem with profound effects on the economies of countries most affected (which includes the USA).

However, the broad-based, seemingly "catch-all" clinical case definition provided by the WHO, relatively early on in the piece, now seems woefully outdated and inadequate, as the multiple long-term pathophysiological effects of SARS-CoV-2 have become increasingly evident. For example, it is now quite clear that Long-COVID is made up of several major subgroups. There is the significantly sized patient cohort that have been severely afflicted (frequently hospitalized) by SARS-CoV-2, directly attacking and causing long-term damage to various organs; particularly the lungs (primary site of infection), but also other organs including brain, heart, kidneys, liver, spleen, gut and pancreas [2]. It has also become increasingly evident that SARS-CoV-2 infection can potentially trigger a variety of autoimmune diseases, cardio-vascular diseases and diabetes [2] [3]. In addition, another major subgroup has become apparent; that of Long-COVID patients displaying Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) related symptoms [2] [3]. It is estimated that around half of individuals with Long-COVID meet the criteria for ME/CFS [2]. This would equate to around 5-10 million additional (Long-COVID related) ME/CFS patients in the USA, alone. However, no mention of any of these major subgroups (or possible subsets within) is provided by the WHO in their clinical case definition [1]. Consequently, contrasting definitions for Long-COVID have appeared in the literature. Some reviewers perceive it as pertaining only to the subgroup related to long-term ME/CFS-like symptoms[3], whereas others perceive Long-COVID as pertaining to all subgroups and long-term pathophysiological outcomes, some including those with ME/CFS-like symptoms and some without[4].

Although the Centers for Disease Control and Prevention (CDC), in a moderately updated definition of PCC, expands somewhat on the WHO version, it too falls well short of providing any detailed information around these emergent subgroups or potential pathophysiological outcomes [5].

"The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystem; and may present with a relapsing– remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection. Long COVID is not one condition. It represents many potentially overlapping

entities, likely with different biological causes and different sets of risk factors and outcomes."

Likewise, the symptoms reported by both the WHO and the CDC in relation to Long-COVID are generic in nature. In all the WHO recognises that over 200 symptoms have been associated with Long-COVID, another indication that SARS-CoV-2 infection can result in a diverse range of pathophysiological outcomes (but are not described as such by the WHO). The most common symptoms listed by the WHO are chronic fatigue, sleep disorders (including insomnia), cognitive problems (brain-fog), altered smell or taste, persistent cough, chest pain or tightness, dyspnoea (breathlessness), muscle aches (myalgia) and post-exertional malaise (PEM). Some of these symptoms could relate to SARS-CoV-2 afflicted organ damage. For example, a persistent cough, accompanied by dyspnoea and chest pain could well be related to SARS-CoV-2 afflicted long-term lung damage, although "laboured breathing" is a symptom common to ME/CFS sufferers. Other symptoms could be associated with Long-COVID related ME/CFS; in particular chronic fatigue, sleep disorders, brain-fog, myalgia and PEM, are all core symptoms of ME/CFS. In addition, many of the symptoms, such as fatigue, would likely be common across subgroups and, indeed, patients could suffer from not just one, but multiple SARS-Cov-2 related effects (including ME/CFS) further complicating the matter. However, none of these symptom associations with any of the subgroups (and possible subsets within) or particular pathophysiological outcomes are elaborated upon by either the WHO or the CDC. In addition, the "common symptoms" listed by the CDC are overlapping, but also differ from those of the WHO. For example, the CDC includes fever or chills, nausea and diarrhoea as "common symptoms" (but omits PEM), which only adds to the overall confusion and uncertainty.

As a consequence, scientific studies of Long-COVID pathophysiology have been handicapped by the lack of clear guidelines from these directive bodies[6]. Patient cohorts have (like the guidelines) been in the main generic and poorly-characterized containing a possible mixture of patients affected by a diverse range of pathophysiological outcomes: some Long-COVID patients recruited into a study might have been severely affected (hospitalized), with multiple SARS-CoV-2 afflicted pathophysiological effects (as listed above) potentially, while others might have come from milder (non-hospitalized) backgrounds. The latter would be more likely to present only Long-COVID related ME/CFS-like symptoms. A study of 42 Long-COVID (non-hospitalized) patients, was the first to clinically assess a Long-COVID cohort specifically for ME/CFS[7]. Although regrettably this has been a rare occurrence. However, for those studies, which have recruited a generic mix of patients from diverse SARS-CoV-2 afflicted backgrounds potentially causing a range of pathophysiological effects, without utilising any such diagnostic criteria available, results have been inconclusive and impossible to interpret.

In summary, the broad-based clinical case definition of Long-COVID/ PCC, provided by the CDC (and before them by the WHO) and indeed other definitions of Long-COVID available globally require urgent updating and refinement, including the allocation of subgroups (and possible subsets within), the provision of a range of possible pathophysiological outcomes due to SARS-CoV-2 infection, and a shared list of "common symptoms", as agreed upon by all bodies. In particular, ME/CFS diagnostic criteria should be encouraged for use in characterising Long-COVID patients, particularly from the milder, non-hospitalized cases (where longer-lasting organ or system damage was less likely), which would then allow for scientific study biomarker data from these studies to be analysed and interpreted with more relevance, accuracy and confidence.

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