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COVID-19 PANDEMIC

Long COVID – One Year On

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Long COVID is now a recognized complication of acute COVID-19 infection. As the COVID-19 pandemic moves into its third year, the prevalence of Long COVID continues to increase. Many individuals report symptoms lasting longer than a year, and a subset of this group is unable to work. This article will provide an update on Long COVID, with a particular focus on distinguishing it from other clinical entities. It will review several proposed disease mechanisms and will attempt to anticipate the impact on disability insurance.

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Long COVID describes a complex of symptoms that persist for at least 12 weeks following acute COVID-19 infection.[1] Alternative labels abound: the National Institutes of Health has proposed "post-acute sequelae of SARS-CoV-2 infection" (PASC). In the UK, "post-COVID syndrome" (PCS) is popular, while the WHO prefers "post COVID-19 condition." It is unclear which of these will prevail. Long COVID remains the choice of patient advocate groups, and while PASC and PCS may become mainstream in the scientific literature, Long COVID will remain the colloquial favorite.

In October 2021, the WHO proposed a "clinical case definition of Post-COVID-19 condition."[2] "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction, but also others, which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist

from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children."[1]

The definition captures 3 important elements: First, it establishes 3 months from the onset of COVID-19 as the starting point, rather than 4 weeks, which is often used in prevalence reports.

Although arbitrary, this later starting point should help exclude diagnoses other than Long COVID. Second, it stipulates that "symptoms cannot be explained by an alternative diagnosis." This is a key element of the definition, as other illnesses with similar symptoms are currently being conflated with Long COVID (see discussion later in this article). Third, it attempts to quantify the severity of symptoms, by requiring that "they generally have an impact on everyday functioning." The addition of a notion of severity, albeit a somewhat vague one, will help to exclude illnesses of a minor nature and should help to create homogeneous cohorts for clinical research studies.

While this is not the first attempt to define Long COVID, it is the most comprehensive effort to date. The inclusion of clinicians, researchers, patients and policy makers in its formulation has ensured that diverse experiences and expertise have been accommodated. It has also increased the likelihood that the definition will gain widespread approval.

Will this definition help disability adjudicators? Yes, to a degree. In the analysis of disability, a clear diagnostic label is always a plus. However, disability claims are adjudicated on the presence or absence of disabling symptoms, rather than a confirmed diagnosis. In the absence of an objective metric of disability—the definition does not include one—adjudication will continue to be difficult. Although the WHO opined that health and disability insurers might be "primary users" of their definition, the benefit will accrue to the former more than the latter.

CLINICAL PICTURE IS BECOMING CLEARER

Long COVID patients have described many symptoms. However, it is now clear that fatigue, cognitive dysfunction, and dyspnea predominate. The second order of frequency involves palpitations, altered smell/taste, post-exertional malaise, abnormal sleep pattern and muscle pain. And a third tier includes chest pain, joint pain, and headache.

To better characterize Long COVID, one could cluster these symptoms into organ systems as follows:

1. Neurological (fatigue, cognitive dysfunction, smell/taste disorder, memory disorder, abnormal sleep pattern, headache)
2. Cardiorespiratory (dyspnea, palpitations, post-exertional chest pain)
3. Musculoskeletal (muscle pain, joint pain)

Clustering exercises are useful when attempting to elucidate disease mechanisms. For example, the preponderance of neurological symptoms suggests that cerebral function is awry. This has prompted the hypothesis that neuroinflammation or neurovascular damage may be the culprit mechanisms. Similarly, the cardiorespiratory symptoms suggest residual or ongoing lung or heart disease. Pulmonary and/or cardiac inflammation or fibrosis may be plausible explanations for these. Most importantly the identification of different clusters raises the possibility that Long COVID is not a single entity; it may have different phenotypes. It also raises the possibility that "Long COVID" is a label that is being used to describe already existing conditions.

MORE THAN ONE ILLNESS

Long COVID is, likely, a composite term that aggregates multiple conditions. It is highly likely that any one or more of the following diagnostic alternatives is being subsumed under the Long COVID umbrella:

1. Amongst survivors of hospital stays for COVID-19, organ damage such as pulmonary fibrosis or cerebrovascular disease may provide a perfect explanation for Long COVID symptoms. In this instance organ-specific diagnoses should replace "Long COVID."
2. Post-Intensive Care syndrome (PICS) affects up to 50% of patients discharged from an intensive care unit.[3] It is characterized by cognitive, physical, and psychiatric symptoms that are strikingly similar to those of Long COVID. A label of PICS may be more appropriate in this instance.
3. Pre-morbid chronic illnesses, such as chronic lung diseases, polymyalgia rheumatica and/or psychological disorders may worsen following COVID-19 infection. It may be more appropriate to ascribe Long COVID symptoms to one of these pre-morbid illnesses.
4. "Postviral fatigue syndrome" or "Post Infectious Fatigue Syndrome" is used to describe a complex of symptoms that persist following many viral infections, such as Epstein-Barr virus (EBV), SARS and Ebola amongst others.[4,5] The symptom list is markedly similar to that of Long COVID; one could argue that it is a fitting label for many individuals with Long COVID.
5. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is also a condition characterized by many of the symptoms that Long COVID sufferers describe. Fatigue and cognitive dysfunction are prominent among these.[6] Indeed the similarities between ME/CFS and Long COVID are such that many are predicting a substantial increase in ME/CFS prevalence in the next few years.[7] (see fuller discussion later in article)
6. Somatic symptom disorder, which is characterized by protracted somatic complaints without an explanatory illness may be an appropriate diagnosis for some Long COVID individuals. This disorder can also travel under the label "functional disorder" or "psychosomatic illness." Traditionally, it is assigned after all other etiologies have been excluded. It can be a controversial label for patients as it implies that symptoms are not "real" or are being discounted. Further, the application of a psychiatric diagnosis for a condition that appears "physical" can be distressing.

ARE ME/CFS AND LONG COVID THE SAME?

Increasingly, comparisons are being drawn between ME/CFS and Long COVID.[7,8] The emergence of debilitating fatigue as a prominent symptom of Long COVID, and its persistence beyond 6 months (a defining feature of ME/CFS) has triggered this comparison. Similarly, the cognitive symptoms and post-exertional malaise described in Long COVID are shared with ME/CFS.

However, other symptoms such as dyspnea, chest pain and anosmia are common in Long COVID, but rare in ME/CFS. And multiplicity of symptoms is a striking feature of Long COVID; in contrast, those of ME/CFS are more limited. However, for a cohort of Long COVID individuals the symptom similarities are such that ME/CFS will be the correct diagnosis. This may not sit well as ME/CFS has many negative connotations. Over the past 40 years, 9 different sets of diagnostic criteria have been published, disease pathogenesis has not been finalized and most importantly, there is no effective treatment. This is not a cohort that Long COVID individuals will be anxious to join.

In fact, for this cohort, Long COVID more closely resembles Postviral Fatigue Syndrome than it does ME/CFS. Long COVID is clearly precipitated by infection with SARS-CoV-2. The ICD-10 descriptors for Postviral Syndrome and ME/CFS are virtually identical; the key difference is definite evidence of a precipitating infection, which establishes the former.[4,9] In contrast, evidence of previous infection in ME/CFS is not required.

HOW WILL THIS SORT ITSELF OUT?

In this confusing scenario, where will Long COVID land? When organ damage can be proven, when a protracted intensive care stay has occurred, or if a pre-COVID illness can be established it will be appropriate to quit using Long COVID as the diagnostic descriptor. When the symptom fit is close, it will be possible to assign other Long COVID individuals to "post viral fatigue" syndrome or to ME/CFS. The allocation of "somatic symptom disorder" will be applicable to a further subset. If one can successfully complete this exercise, one will be left with a residual cohort where the label "Long COVID" is most appropriate. It is in this group that the discovery of a unique pathogenesis would solidify Long COVID as a new diagnosis and increase the chances for an effective remedy.

THE SEARCH FOR MECHANISMS IS UNDERWAY

In the meantime, the search for a mechanism(s) to explain Long COVID symptoms has begun. A starting hypothesis is that the pathophysiology that underpins acute COVID-19 may also explain Long COVID. Thus, viral or viral remnant persistence, and/or a dysfunctional immune response are of particular interest. In favor of the former, virus has been observed in lung, brain, liver, kidney and intestinal tissues many weeks following resolution of acute COVID-19.[10] In favor of the latter, many abnormalities of both innate and adaptive immune responses have been recorded that suggest ongoing low-grade immunological activity. In this vein, the discovery of a multiplicity of autoantibodies that appear to be virally induced has generated particular interest.[11,12]

Given the preponderance of Long COVID neurological symptoms (fatigue, anosmia, dysgeusia, sleep disorder, brain fog, etc.), abnormalities of cerebral anatomy and function are under special scrutiny. Chronic neuroinflammation due to viral invasion and immune dysregulation could explain the neurological symptoms. Abnormal brain PET scans and functional MRI studies have provided evidence to support the former;[13] viral invasion of olfactory cells supports the latter, as do signs of abnormal immune activity in the brainstem.[14]

Disruption of the microbiome by SARS-CoV-2 with downstream effects on metabolic, immune and neuroendocrine function is a further area of interest as is endothelial cell damage, which may explain both neurological and cardiopulmonary symptoms.[15]

CAN WE IDENTIFY RISK FACTORS FOR LONG COVID?

Hospitalization is the strongest predictor of Long COVID. Amongst the hospitalized, mechanical ventilation, female sex and obesity are major risk factors.[17] In the non-hospitalized, the age band 35-69, female sex, BMI >30 and a pre-morbid health condition or disability are overrepresented. Healthcare workers and educators are also at higher risk.[18] Caution again is needed; this data is largely derived from self-reports. Further, it is also apparent that most individuals with Long COVID do not appear to have any risk factors.

THE PREVALENCE OF LONG COVID DISABILITY IS A GUESS

Prevalence reports suggest that between 2% and 71% of COVID-19 survivors have Long COVID symptoms following a COVID-19 infection. This wide range is explained by different study design, different study populations (hospitalized vs non-hospitalized), different time-point counting (eg, 4 weeks vs 12 weeks), different counting techniques (eg, self-reports vs clinic visits) and different statistical methods. In most studies, the absence of control groups combined with limited knowledge of pre-COVID-19 health status is a major impediment to accurate results. As a result, the

prevalence of Long COVID, and by extension, Long COVID disability remains quite speculative.

The most comprehensive tabulations of Long COVID prevalence have been provided by the UK Office of National Statistics. It has produced 9 prevalence studies since April 2021, based on large population surveys. In a recent publication (September 1, 2021), Long COVID symptom prevalence at 12 weeks among PCR-positive survivors was 3%.[16] In contrast, the UK PHOSP-COVID study reported that 71% of individuals who had been hospitalized remained symptomatic at 1 year.[16] This underscores that Long COVID is closely correlated with COVID-19 disease severity.

Neither of these reports provides an answer to the question: how many long-term disability claims can life insurers anticipate? In contrast to the populations surveyed in the previously mentioned studies, insured populations are younger (disability coverage typically stops at age 65), healthier, more likely vaccinated and less likely to have been hospitalized. Thus, one can reasonably anticipate fewer to develop Long COVID. And, of those that do, only a subset will be disabled to a degree that prompts a disability application.

It seems reasonable to anticipate that the correct number will be less than the 3% reported in the UK population analysis and perhaps closer to 1%. Claims experience to date suggests that the impact of Long COVID in Canada has been minimal (according to Munich Re internal data), but this is preliminary and may well change. At the time of this writing, Omicron is the dominant SARS-CoV-2 strain in North America. Its impact on Long COVID is entirely unknown. Omicron's increased transmissibility has caused many more infections, but most of these have been mild. To what extent either or both observations is relevant to Long COVID remains to be seen. Preliminary evidence should become available in summer 2022.

CONCLUSION

Long COVID is now a recognized complication of acute COVID-19 infection. The World Health Organization has recently proposed definition, so this should permit a more accurate case counting. Despite the multiplicity of reported symptoms, neurological and cardiopulmonary complaints predominate, with fatigue and cognitive dysfunction emerging as the most limiting. Reports of Long COVID prevalence vary between 1% and 25% of survivors. Hospitalization, and in particular an intensive care unit stay, is the clearest risk factor. However, the vast majority of Long COVID individuals have not been hospitalized; amongst these, the risk factor profile is less clear. The prevalence of disability, and in particular the inability to resume employment, is unknown. Given the demographics and health status of the insured population, it is likely that the impact will be relatively small. However, at the time of this writing, the impact of Omicron on Long COVID is unknown. Further, the emergence of new variants may substantially alter this prediction.

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