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Frailty and Disability: Predictors or Outcomes or Both in Post COVID-19*

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The COVID-19 pandemic may rival the 1918 influenza pandemic in loss of life, morbidity, and impact on society and healthcare. Although vaccines, antivirals, and other therapies offer hope, emerging quietly is a “lasting legacy” or Long-COVID (1). Yes, some post-COVID-19 symptoms have clear pathology related to acute infection. However, many post infection symptoms are complex and difficult to explain. At this time, relatively little is known about Long-COVID symptom makeup, severity, expected clinical course, impact on functional status, and return to baseline health (1, 2).

At this time, there is no universally agreed upon definition for Long-COVID that is a problem for practice and research. Current literature and social media describe many symptoms such as fatigue, breathlessness, arthralgia, sleep difficulties, and chest pain and long-term sequela of cutaneous, respiratory, cardiovascular, musculoskeletal, mental health, neurologic, and renal involvement (3). Post-COVID-19 symptom names include postacute sequelae severe acute respiratory syndrome coronavirus (SARS-CoV) 2 infection, post-COVID-19 syndrome, or Long-COVID (4). Clinicians have seen these lingering post-viral symptoms before SARS-CoV-1 and the Middle East respiratory syndrome coronavirus (4, 5). But, the lack of a universally accepted definition and nomenclature for Long-COVID makes diagnosis, management, and research difficult (3).

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COVID-19 viral illness is facilitated by its receptor angiotensin-converting enzyme 2 expression, immune dysregulation, inflammation with cytokine storm, endothelial damage, microvascular injury, and hypercoagulable state (5). Emerging evidence suggests that persons experiencing Long-COVID (referred to as COVID-19 long-haulers) report prolonged, multisystem involvement and significant disability (2, 5). Symptom burden appears to vary by age, race, and gender and is greater in persons with poorer baseline health and those with more severe infection. It is estimated that Long-COVID may be around 7% for hospitalized and 4.4% for those not hospitalized which translates into millions of persons worldwide (4). All of this suggests underlying disease pathology that persists beyond acute infection, immune response, or mediating inflammatory activity (5). Multiple observation studies worldwide have documented symptoms experienced post COVID-19 infection. However, there is a gap in that all these findings have not been organized and structured in relationship to “patient outcomes.”

Considering the continuing increases in prescriptions for analgesia, antidepressants, antihypertensives, and oral hypoglycemics with Long-COVID (6) and the estimated number of over 2002 reported symptoms suggest that Long-COVID has a significant impact on quality of life, work, and return to baseline health. Perhaps a different examination is needed to understand and manage Long-COVID in survivors (2, 7).

In this issue of *Critical Care Medicine*, this original and rare clinical investigation by Taniguchi et al (8) explores patient-centered outcomes following acute COVID-19 infection by examining frailty and disability transitions in critical care survivors in Latin America. This article provides a unique framework to assess and evaluate Long-COVID patient outcomes within constructs of frailty and disability. Findings suggest frailty is a predictor of COVID disease outcomes as well as a consequence for some surviving acute COVID-19 infection. Additionally, frailty is identified as an independent factor for future disability (8).

This prospective cohort study of 428 survivors (mean age 64 yr) following COVID-19 ICU admission examined frailty and disability before COVID-19 infection and 90 days post hospital discharge. Fourteen percent were frail at baseline, and 31% were frail at

day 90, 70% of whom were previously nonfrail. The number of disabilities also increased (mean difference =2.46; 95% CI = 2.06–2.86), in subjects who were nonfrail before COVID-19. At day 90, 135 patients (34%) were either frail or disabled. Results suggest many COVID-19 critical care survivors transition to poorer health states, and there is overlap between frailty and disability both of which require long-term symptom management (8).

Although the study by Taniguchi et al (8) has limited generalizability related to use of one site and an older age sample requiring ICU admission, this research perhaps provides a framework that can be expanded to organize Long-COVID symptoms related to patient-centered outcomes: examining frailty and disability across the COVID-19 infection spectrum. Further cohort studies like this are needed to understand the trajectory and consequences of COVID-19 infection in diverse populations, in other countries, and in both hospitalized and nonhospitalized with particular attention to minority ethnic groups and older survivors who generally experience greater negative outcomes with infection (9).

The final wave of this pandemic may be Long-COVID (10). Ongoing symptoms after the infection phase are bringing many survivors back into health-care systems with finite resources. Even with control of the pandemic, Long-COVID patients will continue to seek care which will further impact employers, insurance companies, and communities.

Governments are now coordinating surveys to examine Long-COVID which will increasingly occupy primary care practice. Substantial financial support (\$1.15 billion over 4 yr) has been appropriated by the U.S. Congress for research for this next wave. Research areas include symptom expression, spectrum of recovery, who is at most risk for Long COVID as well as the biological mechanisms. This multidisciplinary research will be challenging and perhaps more difficult than defining the pathophysiology of acute COVID-19 infection (11).

FINAL THOUGHTS

Another rare article also exploring frailty in relationship to Long-COVID emerged in the European literature less than a month ago. In a sample of 254 persons, frailty (and other symptoms) was associated with

symptom persistence and increased risk of somatic symptoms at 12 months (12).

Finally, it has been proposed that frailty in Long-COVID may be related of inflammaging defined as an accelerated state of chronic subclinical systemic inflammation often observed in aging. COVID-19 infection appears to increase inflammaging through excessive oxidative stress, metabolic derangement, and DNA damage which actuates cellular senescence. Senescence-associated secretory phenotype molecules including cytokines, chemokines and chemokines lead to proinflammatory responses in multiple tissues. This immune response against the virus contributes to chronic inflammation. Inflammaging is characterized by increased morbidity, disability, and “frailty” (13).

Science has a steep and complex research agenda going forward, and the possibility exists that morbidity from COVID-19 infection will not fully disappear. This article (8) from Brazil is a good beginning for the next focus of COVID-19 research.

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