Post–Intensive Care Syndrome in COVID-19 versus Non–COVID-19 Critical Illness Survivors

More Similar than Not?

At the outset of the coronavirus disease (COVID-19) pandemic, some observers reported differences between COVID-19 acute respiratory distress syndrome (ARDS) and non–COVID-19 ARDS. In COVID-19 ARDS, early impairment in gas exchange may be disproportionately worse than impairment in lung compliance (1), and acute inflammation in COVID-19 acute lung injury was labeled a "cytokine storm" (2). Subsequent studies, however, have revealed considerable overlap in the respiratory mechanics, inflammatory response, subphenotypes, and short-term mortality of mechanically ventilated patients with COVID-19 and non–COVID-19 ARDS (3–7). Accordingly, long-term outcomes after COVID-19 and non–COVID-19 ARDS might also be similar.

Yet, patients with COVID-19 ARDS often have a longer dependence on mechanical ventilation (7), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may cause pulmonary fibrosis (8), especially among survivors of mechanical ventilation (9). "Long COVID" impairments in physical, psychological, and cognitive function that are the hallmarks of post-intensive care syndrome (PICS) are often observed in COVID-19 survivors who were never mechanically ventilated (10). These observations raise concern that COVID-19 PICS could be worse than non–COVID-19 PICS.

In this issue of the *Journal*, Hodgson and colleagues (pp. 1159–1168) report a study comparing long-term outcomes of COVID-19 and non–COVID-19 survivors of critical illness (11). Study patients, who were adults in Australia requiring at least 24 hours of mechanical ventilation, were drawn from two prospective observational studies, one of patients with COVID-19 during the pandemic and one of patients without COVID-19 before the pandemic. The primary exposure was the presence or absence of COVID-19 at the time of mechanical ventilation. The authors showed that COVID-19 and non–COVID-19 PICS at 6 months after ICU admission are at least phenotypically similar (11). At the 6-month follow-up, the investigators prospectively assessed survivor disability, anxiety, depression, cognitive impairment, and health-related quality of life and asked survivors to recall their disability and health-related quality of life just before their ICU hospitalization. After adjusting for baseline differences in demographics, frailty, disability, and severity of critical illness, they found that the incidence of new disability and the prevalence of severe disability, anxiety, depression, and cognitive impairment at 6 months were similar between the non–COVID-19 and COVID-19 critical illness survivors.

Underlying these striking similarities at 6-month follow-up, COVID-19 critical illness survivors appeared to have less disability and higher health-related quality-of-life before their ICU hospitalization. This difference in pre-ICU function among COVID-19 and non–COVID-19 critical illness survivors may yet be clinically relevant, as those with less pre-ICU frailty and disability typically have better long-term outcomes (12) and are generally considered better candidates for rehabilitative interventions.

The results of this study should be interpreted in the context of important potential limitations. First, the selection of a non–COVID-19 comparator group is critical here. Contemporary comparator groups are usually best because they avoid the introduction of confounding secular trends. But critical care during the COVID-19 pandemic was so dramatically disrupted that the contemporary care and patient mix of non–COVID-19 critical illness during the pandemic may be sufficiently different as to render it a poor comparator group. The authors reasonably opted for a historical comparator group from the recent prepandemic period. But of note, the non–COVID-19 comparator group was drawn from a significantly smaller number of hospitals, with 64% of the comparator patients coming from a single hospital's ICU. As such, any unique aspects of patient characteristics (e.g., 23% vs. 2.5% with heart failure in the non–COVID-19 vs. COVID-19 cohorts), care, or outcomes for that hospital's patients would have an oversized impact on the whole comparator group's outcomes.

Second, the primary outcome of new disability at 6 months required a patient-provided retrospective assessment of pre-ICU function, which is susceptible to recall bias. Third, and perhaps more importantly, the results could be affected by the fact that COVID-19 survivors had higher levels of pre-ICU function and health-related quality of life than non–COVID-19 survivors. While incident disability was similar between the cohorts, the type of new disability may be different, and its effects on health-related quality of life may be greater in patients with COVID-19 only because they had more to lose. Finally, the 18–21% dropout rates at 6 months (and 27–66% missingness of various 6-month outcome survey measures) in both cohorts raise concern for bias from differential loss to follow-up. While these dropout rates are higher than other major ARDS long-term outcomes studies (13), the overall low mortality rate after hospitalization suggests that at least survival bias (i.e., confounding by death) is likely small.

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Still, this is arguably the best comparative study of COVID-19 and non–COVID-19 critical illness survivors to date for several reasons. First, the authors compare prospective multicenter COVID-19 and non–COVID-19 cohorts who had identical schedules of measurements that included validated and recommended surveys for acute respiratory failure survivors (14). The COVID-19 critical illness survivor sample size is comparable to other major COVID-19 critical illness survivor studies (10, 15, 16). The non–COVID-19 comparator cohort was enrolled from 2017 to 2019, likely limiting the potential for substantial bias from secular trends or COVID-19-related care disruptions. They sought to minimize loss to follow-up via opt-out consent. ICU strain during COVID-19 is associated with worse outcomes (17); importantly, Australian ICUs were not overwhelmed in 2020 and 2021, and thus the quality of critical care was likely similar for the non–COVID-19 and COVID-19 cohorts.

This study by Hodgson and colleagues has important clinical and research implications. Since COVID-19 and non–COVID-19 critical illness survivors appear similarly debilitated at 6 months, COVID-19 critical illness survivors will likely need similar post-ICU care. This will create a huge demand for post-ICU clinics and other post-ICU care infrastructure, which remain largely underfunded (18). If COVID-19 critical illness survivors indeed have less baseline disability and higher quality of life than non–COVID-19 survivors, they might be more resilient and have more to gain from post-ICU physical therapy and other rehabilitation interventions after hospitalization, which to date, have failed to demonstrate benefit (19). Accordingly, rehabilitation trials in COVID-19 critical illness survivors are urgently needed. Lastly, while most recovery after critical illness plateaus after 6 months (20), further improvement in physical function can occur over 1 year (13). Whether lung fibrosis, ICU-acquired weakness, or cognitive impairment after COVID-19 critical illness is fundamentally different than that seen after non–COVID-19 critical illness, and whether it modifies longer-term trajectories of recovery remains unknown and warrants further study. ■

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