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The Long Road to Normalcy Following Survival From COVID-19–Associated Acute Respiratory Distress Syndrome*

KEY WORDS: acute respiratory distress syndrome; coronavirus disease 2019; respiratory failure; return to work; postintensive care syndrome

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Survival from the harrowing experience of critical illness for many patients has been associated with acquired and persistent disabilities affecting multiple domains of cognitive, physical, and psychosocial function (1). Collectively, this has been described as the “postintensive care syndrome” (PICS) and is correlated with the development of anxiety, depression, posttraumatic stress disorder, and decreases in quality of life (2). These disorders can be long lasting and contribute to poor outcomes in long-term follow-up.

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In a recent systematic review, the frequency of cognitive dysfunction following critical illness ranged from a mean prevalence of 35% to 81%, depending on method of assessment at 3 months after discharge, and in one study persisted up to a mean prevalence of 46% at 2 years (3).

Many survivors of the acute respiratory distress syndrome (ARDS) in the pre-coronavirus disease (COVID) era have been burdened with prolonged objective dysfunction following their illness. In one cohort of ARDS survivors at 1 year, scores of the Short Form (SF)-36 assessing health-related quality of life were decreased in all domains (except emotional role) compared with age- and sex-matched controls (4). Additionally, patients had significant weight loss, persistent diffusion defects, and physical weakness with 6-minute walk distances remaining below predicted values at 1-year follow-up. In another cohort of ARDS survivors, quality of life was evaluated using the SF-12 survey at 6 months in comparison with critically ill patients without ARDS. Both appeared to be lower than findings from the general population (5). When directly compared, the long-term limitations in survivors of ARDS appear to be similar to that of survivors of critical illness of non-ARDS etiologies (2).

The use of return to work status as a research endpoint in critical illness survivors is a pragmatic patient-centered measure to assess improvement in many of the PICS domains but also captures the later economic and societal effects. Many survivors of critical illness are unable to return the workforce. This can perpetuate and accentuate many acquired disabilities and create significant economic hardship and stress for patients and their families alike. In a recent study evaluating 10,015 previously employed survivors of critical illness, there was a gradual increase over time of ability to return to work (6). The pooled prevalence (95% CI) at 1–3, 12, and 42–60 months was 36% (23–49%), 60% (50–69%), and 68% (51–85%). However, this was not sustained in all with a sizeable proportion changing their prior occupations (17–66%), working reduced hours or retiring (5–84%), or incurring subsequent job loss (20–36%). In one cohort of U.S. ARDS survivors, the mean (SD) estimated cumulative loss of earnings after 5 years was \$180,221 (\$110,285) (7).

The global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has brought to

light many of the long-term and lasting consequences of infection and critical illness involving nearly every organ system. Postacute COVID symptoms in survivors have included neuropsychiatric effects including depression, fatigue, autonomic dysfunction, cardiopulmonary effects including persistent dyspnea, decline in lung function, chest pain, arrhythmias, as well as coagulopathies and persistent renal dysfunction (8). Although these may represent some unique effects of SARS-CoV-2 infection itself, many of these symptoms have been described in those surviving critical illness in general.

Defining the long-term health consequences of the SARS-CoV-2 pandemic is important to help direct rehabilitation efforts and possibly target therapies to improve outcomes, particularly in those critically ill. Characterization of these consequences in relation to their socioeconomic impact also has implications in the formation of public policy and public health. To date, few studies have been completed specifically to answer these questions. In a hospitalized Italian cohort of 143 patients followed at a mean of 60 days from first symptom, only 12.6% were without any symptoms, and 44.1% had a decrease in quality of life based on the EuroQol scale (9). Fatigue (53.1%), dyspnea (43.4%), and chest pain (21.7%) were among the highest persistent symptoms noted. However, only 12.6% of patients were admitted to the ICU, and 5% required mechanical ventilation, limiting the conclusions of this small study.

In a larger cohort of 1,733 hospitalized Chinese patients with SARS-CoV-2, the outcomes and long-term health consequences at 6 months found that 76% of patients complained of persistent symptoms with the most common being fatigue or muscle weakness (63%) and sleep difficulties (26%) (10). In those with more severe disease requiring greater oxygen support, there was an increased difficulty with mobility (odds ratio [OR], 2.48; 95% CI, 1.12–5.48) and chronic pain (OR, 1.94; 95% CI, 1.19–3.16), high proportion of abnormal lung diffusion (OR, 4.6; 95% CI, 1.85–11.48), and decreased 6-minute walking distances compared with normal indices (OR, 2.18; 95% CI, 1.18–4.03). However, the severity of disease in this report was low with only 4% of patients requiring ICU admission and 1% requiring invasive mechanical ventilation, extracorporeal oxygenation, or both making inferences about outcomes in critically ill inconclusive.

In this issue of *Critical Care Medicine*, Carenzo et al (11) performed a prospective study evaluating rates of returning to work and health-related quality of life in a cohort of critically ill patients with moderate to severe ARDS related to SARS-CoV-2 at 6-month follow-up. In this group, 71 patients had follow-up, and of them, 45 (63%) were gainfully employed before contracting SARS-CoV-2. The major findings were of the previously employed patients, 33 (73%) were able to regain entry to the work force at 6 months. However, 20 of these patients (85%) subjectively reported reduced effectiveness, and six (18%) required significant changes to their work duties related to their illness. The remaining patients either retired ($n = 2$) or remained unemployed ($n = 10$). In those remaining unemployed, they self-reported a significant worsening in health-related quality of life based on the Italian EQ-5D-5L survey. These patients specifically appeared to have more severe disease with organ dysfunction scores, worse lung injury indices, longer days of mechanical ventilation, increased utilization of neuromuscular blockade, and a longer ICU length of stay. It is tempting to conclude that these variables affected the outcome, but the study was not designed nor powered to specifically answer this question. Specific causes of reduced effectiveness or changes to work duties were not assessed, and the study was underpowered to directly compare the severity of these long-term measures compared with non-SARS-CoV-2 critical illness.

Despite these limitations, the study by Carenzo et al (11) describes a quality of life metric that can arise in survivors of COVID-19 ARDS. The full spectrum of specific related disorders and disabilities resulting from infection and critical illness remains to be completely described; however, similarities may be predicted from previous beta coronavirus outbreaks. In a 6-month follow-up of patients surviving severe acute respiratory syndrome, patients requiring ICU admission had increased incidences of restrictive lung disease, gas diffusion impairments, and persistent abnormal chest radiographs, which led to decreases in quality of life (12). Pulmonary imaging of survivors of the Middle East Respiratory Syndrome-coronavirus, at a median of 43 days, revealed evidence of pulmonary fibrosis in 33% of this cohort (13). Emerging data suggest that SARS-CoV-2 infection has similar effects on lung function in those with severe disease (14).

Identification of underlying mechanisms and interventions to improve long-term outcomes from critical illness remains a challenge to all critical care practitioners. For critically ill patients due to SARS-CoV-2, the complex interplay of tissue injury, intense inflammatory responses, and processes of care have substantial impact on survivors. The latter may include prolonged sedation regimens to maintain lung-protective ventilation, prone positioning, use of neuromuscular blocking agents, corticosteroids, and or other immunomodulatory agents. It may be intuitive that best practices pertaining to the quality of care these patients receive are impactful on long-term outcomes; others have noted that in patients with ARDS, there was poor association between long-term outcomes and indicators of quality of care (15).

Early and aggressive rehabilitation may also be effectual for improvement in outcomes. In the study by Carenzo et al (11), only 47% of surviving patients were discharged to a rehabilitation center, a scarce resource during a surge in SARS-CoV-2 cases. The relationship rehabilitation and outcomes in this study is uncertain, yet other studies of early and standardized physical therapy regimens in recovered patients from critical illness were unable to show differences in functional outcomes (16, 17).

Future studies will hopefully identify evidence for best practice during treatment of acute phase of infection to mitigate some of these long lasting effects as well as factors to help maximize rehabilitation efforts to help survivors to return to life as it once was.

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