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Six-Month Impairment in Cognition, Mental Health, and Physical Function Following COVID-19–Associated Respiratory Failure

OBJECTIVES: To determine the prevalence and extent of impairments impacting health-related quality of life among survivors of COVID-19 who required mechanical ventilation, 6 months after hospital discharge.

DESIGN: Multicenter, prospective cohort study, enrolling adults 18 years old or older with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection who received mechanical ventilation for 48 hours or more and survived to hospital discharge. Eligible patients were contacted 6 months after discharge for telephone-based interviews from March 2020 to December 2020. Assessments included: Montreal Cognitive Assessment-Blind, Hospital Anxiety and Depression Scale, Impact of Event Scale-6, EuroQOL 5 domain quality-of-life questionnaire, and components of the Multidimensional Dyspnea Profile.

SETTING: Two tertiary academic health systems.

PATIENTS: Of 173 eligible survivors, a random sample of 63 were contacted and 60 consented and completed interviews.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Mean age was 57 + 13 years and mean duration of invasive mechanical ventilation was 14 + 8.2 days. Six months post-discharge, 48 patients (80%; 95% CI, 68–88%) met criteria for post-intensive care syndrome (PICS), with one or more domains impaired. Among patients with PICS, 28 (47%; 95% CI, 35–59%) were impaired in at least 2 domains, and 12 (20%; 95% CI, 12–32%) impaired in all three domains. Significant symptoms of post-traumatic stress were present in 20 patients (33%; 95% CI, 23–46%), anxiety in 23 (38%; 95% CI, 27–51%), and depression in 25 (42%; 95% CI, 30–54%). Thirty-three patients (55%; 95% CI, 42–67%) had impairments in physical activity; 25 patients (42%; 95% CI, 30–54%) demonstrated cognitive impairment.

CONCLUSIONS: Eighty percent of COVID-19 survivors who required mechanical ventilation demonstrated PICS 6 months after hospital discharge. Patients were commonly impaired in multiple PICS domains as well as coexisting mental health domains.

KEY WORDS: acute respiratory distress syndrome; COVID-19; epidemiology; mechanical ventilation; post-intensive care syndrome

Prior to the emergence of COVID-19, critical illness survivors were known to suffer long-term impairments in physical function, mental health, and cognition (1). Deficits in one or more of these three domains are collectively termed the post-intensive care syndrome (PICS) and may profoundly impact health-related quality of life (1). However, little is known about the long-term impairments experienced by COVID-19 survivors who require mechanical ventilation (MV). These data could inform care at emerging post-COVID clinics and future health policy to support survivors of COVID-19.

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COVID-19 survivors who required MV may be at high risk of PICS due to acute illness-related factors and societal barriers to care unique to the pandemic (2,3). PICS risk factors present during COVID-19–associated respiratory failure include: delirium, prolonged MV, prolonged deep sedation, benzodiazepine administration, and physical isolation (2,3). In addition, unique pandemic elements may impact survivor outcomes including lack of inhospital family presence, limited post-acute care rehabilitation services, and widespread economic recession. Given this context, we hypothesized that survivors of COVID-19 requiring MV would commonly demonstrate elements of PICS even at 6 months post-hospital discharge.

METHODS

Design, Setting, and Participants

We conducted a multicenter prospective cohort study from 2020 March to December 2020 at Beth Israel Deaconess Medical Center (BIDMC) and the Hospital of the University of Pennsylvania. We prospectively maintained a registry of ICU survivors who received at least 48 hours of MV for COVID-19 and were discharged home or to a rehabilitation facility. In September 2020, a list of all registry patients at least 4 months from hospital discharge was generated and letters were mailed to all eligible patients. The list was then sorted in random order and patients were sequentially contacted 2 weeks after letters were mailed. No participants contacted us prior to telephone call to enroll or decline. Thus, a random sample of eligible patients were selected and contacted via telephone. Patients were required to consent and directly answer questions themselves to participate in the study. Medical interpreters were used for patients with limited English proficiency. Sample size of 60 patients was determined by Cochran's formula with finite population correction to achieve a $\pm 10\%$ precision of estimate of the prevalence of impairments (4). Demographics, baseline characteristics, and clinical data were extracted from the electronic medical record.

Outcome Measures

We used the Society of Critical Care Medicine international consensus recommendations for PICS assessment in the three domains of mental health, cognition, and

physical function (5). All instruments were administered via telephone with patients. We assessed symptoms of anxiety, depression, and post-traumatic stress disorder (PTSD) using the Hospital Anxiety and Depression Scale (HADS) and Impact of Event Scale-6 (IES-6), respectively (5). Significant symptoms of depression and anxiety were defined as HADS score of 11 or greater, based on standard scoring criteria. Significant post-traumatic stress symptoms was defined as mean score across all items on IES-6 greater than 1.75 (6). Physical function was assessed via the EuroQual 5 domain questionnaire. The Montreal Cognitive Assessment-Blind determined cognitive impairment defined as a score of 18 or less. PICS was defined as impairment in one or more domain—mental health, cognition, or physical function.

Concurrent to the PICS assessment, the BIDMC cohort also underwent dyspnea assessment using quantitative and qualitative aspects of the Multidimensional Dyspnea Profile (7). This measure provides both quantitative assessment of dyspnea, as well as the qualitative emotional impact of this sensation on patients, which was of interest given a focus on mental health impairments in this study.

Statistical Analysis

Descriptive data are reported as means with SD or number with percent, where appropriate. 95% CIs are reported for proportions. Analyses were conducted using R, Version 3.6.1 (R Project for Statistical Computing, Vienna, Austria).

Ethical Review and Reporting

The study was approved by the institutional review boards at BIDMC (protocol 58757) and the University of Pennsylvania (protocol 84320) and follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

RESULTS

Of 173 eligible survivors, 63 were identified for recruitment via random sampling. Of the 63 survivors contacted, three declined, while 60 consented and completed interviews a mean of 182 days (SD, 15 d) after hospital discharge. Mean age was 59 years (SD, 13 yr) and 52 patients (86.7%) resided at home prior to admission. Duration of invasive MV was 14 days (SD, 6.5 d) and $\text{PaO}_2\text{:FIO}_2$ ratio at intubation was 164 (SD, 42) (Table 1). Delirium developed in 39 patients

TABLE 1.
Baseline Characteristics of Enrolled Patients

Characteristics	Patients Surveyed (<i>n</i> = 60)
Enrollment site, <i>n</i> (%)	
Beth Israel Deaconess Medical Center	40 (66.7)
Penn Medicine	20 (33.3)
Admission location, <i>n</i> (%)	
Home	52 (86.7)
Nursing facility ^a	8 (13.3)
Mean timing of follow-up after hospital discharge, d	182 ± 15
Mean age (range), yr	59 ± 13 (24–88)
Sex, <i>n</i> (%)	
Male	29 (48.3)
Female	31 (51.7)
Race/ethnicity ^b , <i>n</i> (%)	
Asian	6 (10)
Black	12 (20)
Hispanic	26 (43.3)
White, non-Hispanic	16 (26.7)
Mean body mass index, kg/m ²	31.2 ± 5.2
Coexisting conditions, <i>n</i> (%)	
Anxiety	3 (5)
Chronic kidney disease	6 (10)
Chronic obstructive pulmonary disease	7 (11.7)
Coronary artery disease	11 (18.3)
Current tobacco smoker	11 (18.3)
Dementia	1 (1.7)
Diabetes mellitus	16 (26.7)
Hypertension	17 (28.3)
Obstructive sleep apnea	9 (15)
Pregnancy	1 (1.7)
Depression	4 (6.7)
Delirium in ICU ^c	39 (65)
Delirium day of ICU discharge	12 (20)
Mean duration of invasive mechanical ventilation, d	14 ± 6.5
Mean length of hospital stay, d	23.5 ± 8.6
Mean Sequential Organ Failure Assessment score at intubation	5 ± 1
Mean Pao ₂ :Fio ₂ at intubation	164 ± 42
Medications in ICU, <i>n</i> (%)	
Antipsychotics	10 (16.7)
Benzodiazepines	14 (23.3)
Opioids	60 (100)
Neuromuscular blockade	17 (28.3)
Corticosteroids	0 (0)

(Continued)

**TABLE 1. (Continued).
Patient Characteristics**

Characteristics	Patients Surveyed (n = 60)
Tracheostomy, n (%)	6 (10)
Extracorporeal membrane oxygenation, n (%)	2 (3.3)
Discharge disposition, n (%)	
Home	33 (55)
Nursing/post-acute rehabilitation facility ^a	27 (45)
Thirty-d hospital readmission	1 (1.7)

^aIncluding skilled nursing facility, acute rehabilitation facility, and long-term acute care hospital.

^bPatient self-identified race at hospital admission.

^cDelirium was assessed by Confusion Assessment Method-ICU performed bid as routine nursing care.

(65%). Common comorbidities present at baseline included hypertension (28%), diabetes mellitus (26%), coronary artery disease (18%), and chronic obstructive pulmonary disease (12%). Thirty-three patients (55%) were discharged to home, while 27 patients (45%) were discharged to a rehabilitation setting including skilled nursing facility, acute rehabilitation facility, or long-term acute care hospital.

Approximately 6 months after hospital discharge, 48 patients (80%; 95% CI, 68–88%) met criteria for PICS,

with one or more domains impaired (**Fig. 1A**). Among patients with PICS, 28 (47%; 95% CI, 35–59%) were impaired in at least two domains, and 12 (20%; 95% CI, 12–32%) impaired in all three domains. Thirty patients (50%; 95% CI, 38–62%) had impairment in at least one mental health domain—PTSD was present in 20 patients (33%; 95% CI, 23–46%), anxiety in 23 (38%; 95% CI, 27–51%), and depression in 25 (42%; 95% CI, 30–54%). Thirty-three patients (55%; 95% CI, 42–67%) had impairments in physical activity, including performing

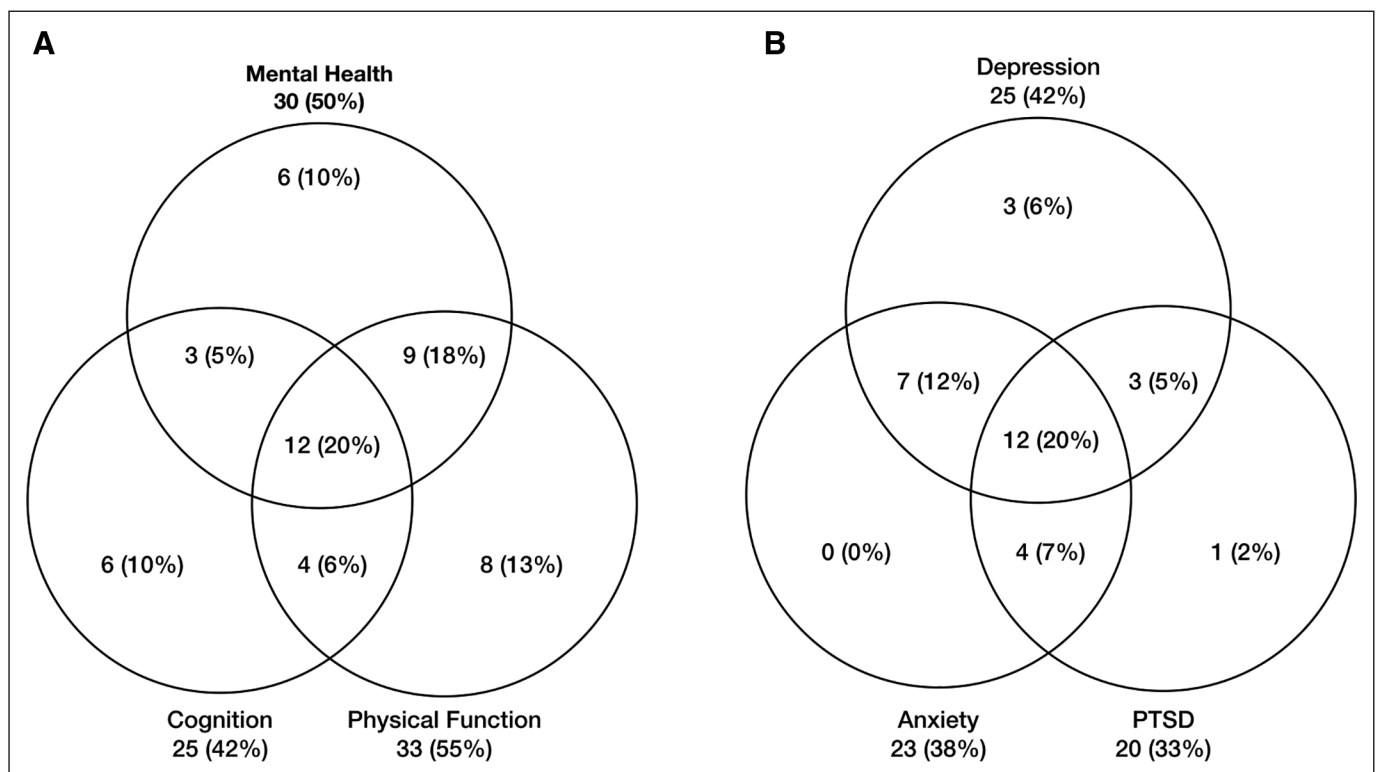


Figure 1. Patient outcomes at 6 mo. Prevalence and coexistence of (A) post-intensive care syndrome (PICS) impairments and (B) mental health conditions at 6-mo assessment. Values outside of the figures show total number (%) of patients experiencing impairment in a PICS domain, and values within regions show number (%) of patients with isolated or coexisting impairments. PTSD = post-traumatic stress disorder.

activities of daily living (29 patients and 48%; 95% CI, 36–60%) and impaired mobility (30 patients and 50%; 95% CI, 37–62%). Twenty-five patients (42%; 95% CI, 30–54%) demonstrated cognitive impairment. Two or more concomitant mental health impairments—*anxiety*, *depression*, and/or *PTSD*—were present in 26 patients (43%) (**Fig. 1B**). Patient characteristics stratified by presence of PICS and individual impairments are provided in **Supplemental Table 1** (<http://links.lww.com/CCX/A961>).

Among the 40 patients at BIDMC, all of whom completed dyspnea assessment at 6 months, 25 (63%; 95% CI, 47–76%) experienced any dyspnea, and 13 (33%; 95% CI, 14–44%) had moderate to severe dyspnea (10-point severity scale score > 4). Among patients with persistent dyspnea at 6 months, the majority reported that fear (60%), anxiety (57.5%), or frustration (52.5%) were associated with breathing discomfort.

DISCUSSION

Impairments in cognition, mental health, and physical function were common 6 months after surviving COVID-19 requiring MV. Nearly half of patients had impairments in at least two PICS domains. Patients with mental health impairments also commonly experienced a combination of disorders—most often anxiety, depression, and PTSD combined. Dyspnea was also experienced by most assessed patients at 6 months post-hospital discharge.

The prevalence of PICS in our study appears broadly similar to that reported in studies prior to the COVID-19 pandemic (8). However, co-occurrence of long-term impairments may be more common in COVID-19 survivors, especially those who required invasive MV (8,9). We present a detailed description of coexisting impairments using the PICS framework to better inform post-acute care surveillance and therapeutic intervention to pursue recovery. Prior to our study, the largest multicenter study to examine the coexistence of PICS impairments before COVID-19 found that 25% of patients had two or more impairments at 3 months. Concerningly we discovered coexisting impairments in 47% of patients after 6 months (8). The increased prevalence may reflect greater severity of illness, difference in practice patterns, and/or the influences of those practices. These risk factors could include prolonged deep sedation and ventilation course, a large proportion of patients experiencing

delirium, limited interaction between staff and patients due to infection control measures, and public health and safety measures at the time that impaired patient-and-family-centered care approaches.

Several studies have examined symptoms and quality of life after COVID-19 in cohorts with mixed severity of illness, including hospitalized patients who did not experience critical illness (10). Huang et al (10) reported the largest follow-up study of a hospitalized population from early in the pandemic, although only 1% were mechanically ventilated and 25% did not require any supplemental oxygen. Despite a lower severity of illness, they found, at 6 months, that 26% had dyspnea, 23% had anxiety or depressive symptoms, 52% had persistent fatigue or weakness, and 6% had impaired mobility. The prevalence of impairments remained similar, or increased, in these domains at 1 year.

Breathing discomfort, an important and distressing symptom that impacts quality of life, has not been well-described after critical illness in past studies. A 2011 post-acute respiratory distress syndrome landmark study found that predicted spirometry and diffusion capacity was reduced at 1 year (11). Those impairments correlated with a 66% reduction in 6-minute walk distance as well. Steinbeis et al (12) reported longitudinal measures of respiratory symptoms and lung function over 1 year in a cohort of COVID-19 survivors spanning from mild acute illness to ICU survivors. Among all patients, 43% reported dyspnea at 12 months, although data specific to ICU survivors alone were not presented. Among survivors of MV, 65% had reduced carbon monoxide diffusion capacity and 62% had restrictive ventilatory defect on pulmonary function testing. Our patients commonly experienced persistent dyspnea that was often tied to strong emotional responses including fear and anxiety. This component of ICU recovery is likely under-assessed but may substantially impair post-acute care recovery and quality of life.

Our findings, in the context of existing literature, support the need for a coordinated effort within healthcare to support ICU recovery and survivorship. Optimizing long-term outcomes begins in the ICU, with evidence-based strategies for early mobility, minimization of sedation, family engagement, and protocolized liberation from the ventilator (13). A reduction in the application of these ICU practices during the pandemic, including isolation from family, may have played a role in the high rate of PICS in our

study. Routine PICS screening for patients surviving MV appears warranted in the post-acute care setting, given that the majority of patients in our study and existing literature have ongoing impairment in physical function, cognition, and/or mental health. The high prevalence of dyspnea, its adverse emotional impact, and past studies demonstrating pulmonary function impairments in this population support the need for routine assessment and evaluation of dyspnea among this population, as well. Coordinated multidisciplinary teams within post-ICU clinics are one appealing model of care, to provide the comprehensive screening and management that ICU survivors need, although this is an area that requires more study to define the optimal approach (14). While data evolve regarding the ideal interventions to support recovery, it is clear that the substantial burden of impairments across all domains of PICS warrant urgent and thoughtful attention.

Our multicenter study has important limitations. This is a cross-sectional study with a limited sample of patients. Recruitment of patients was greater at BIDMC, although both sites recruited a random sample of eligible patients to limit bias. We assessed preexisting impairments in the electronic medical records, however, did not have baseline assessment of patients prior to critical illness. As patients needed to answer all questions themselves, the accuracy of answers to mental health or physical function instruments that require recall may be impacted by coexisting cognitive impairment. Additionally, we enrolled those hospitalized early in the pandemic, the epidemiology of long-term impairments among survivors of severe COVID-19 may differ over time as a result of changes in intensive and/or post-acute care practices. For example, corticosteroids were not used in our institutions until randomized trials later supported their use, all of which occurred after the study period. Last, patients were typically cared for in the hospital for a longer period of time prior to discharge, due to limitations in capacity of rehabilitation facilities, and may have been discharged to home with fewer post-acute rehabilitation services available to them given health system strain at this point in the pandemic.

CONCLUSIONS

Impairments in mental health, cognition, and physical function—including breathing discomfort—are common after COVID-19–associated respiratory failure.

Coexistence of multiple domains of impairments appears common as well, including multiple aspects of mental health. These identified impairments inform the proper alignment of post-acute care services, including multidisciplinary post-ICU clinics, with the needs of COVID-19 survivors.

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