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Psychological Morbidity After COVID-19 Critical Illness

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Key Words: Acute Respiratory Distress Syndrome, Coronavirus-19 Pandemic, Post-Intensive Care Syndrome, SARS-CoV-2 Virus

Abbreviations List:

ABCDEF (Assess, prevent, and manage pain; Both spontaneous awakening and breathing trials: Choice of Analgesia and Sedation; Delirium assess, prevent, and manage; Early Mobility and Exercise; Family engagement/empowerment)

Acute Respiratory Distress Syndrome (ARDS)

Coronavirus Disease 2019 (COVID-19)

Hypothalamic-Pituitary-Adrenal (HPA)

Intensive Care Unit (ICU)

Neuromuscular Blockade (NMB)

Post-Traumatic Stress Disorder (PTSD)

23 Serum 100B (s100B)

24 Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

Abstract

Topic Importance: Survivors of intensive care unit (ICU) hospitalizations often experience severe and debilitating symptoms long after critical illness has resolved. Many patients experience notable psychiatric sequelae such as depression, anxiety, and post-traumatic stress disorder (PTSD) that may persist for months to years after discharge. The coronavirus disease 2019 (COVID-19) pandemic has produced large numbers of critical illness survivors, warranting deeper understanding of psychological morbidity after COVID-19 critical illness.

Review Findings: Many patients with critical illness due to COVID-19 experience substantial post-ICU psychological sequelae mediated by specific pathophysiologic, iatrogenic, and situational risk factors. Existing and novel interventions focused on minimizing psychiatric morbidity need to be further investigated in order to improve critical care survivorship after COVID-19 illness.

Summary: This review proposes a framework to conceptualize three domains of risk factors (pathophysiologic, iatrogenic, and situational) associated with psychological morbidity due to COVID-19 critical illness: (1) direct and indirect effects of the COVID-19 virus in the brain; (2) iatrogenic complications of ICU care which may disproportionately affect patients with COVID-19; and (3) social isolation that may worsen psychological morbidity. In addition, we review current interventions to minimize psychological complications after critical illness.

Introduction

Over the past 20 years, cohort studies have demonstrated frequent psychological morbidity among critical illness survivors [1–3]. During the Coronavirus Disease 2019 (COVID-19) pandemic, an unprecedented number of patients experienced critical illness over a short period

of time, which further raised awareness of the psychological sequelae of critical illness [4–6]. It has been hypothesized that patients with critical COVID-19 and associated Acute Respiratory Distress Syndrome (ARDS) may be at increased risk for psychological morbidity compared to other critically ill patients.

In this review, we describe acute and long-term psychological manifestations experienced by patients surviving critical illness from COVID-19 using a framework organized around three distinct risk factors for critical COVID-19-related psychological morbidity: (1) neuro-pathophysiologic changes caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), (2) iatrogenic complications of intensive care unit (ICU) care that may have disproportionally affected patients with critical COVID-19, and (3) situational factors, including social isolation, which has been a characteristic feature of the pandemic (Figure 1). Lastly, we review current therapeutic interventions for psychological sequelae of critical illness and discuss specific features of psychological morbidity after critical COVID-19 that may warrant novel therapies.

Literature Search

Relevant literature identified via PubMed and Ovid searches were reviewed by a single author for inclusion. The search strategy included the following descriptors: “psychiatric morbidity,” “COVID-19 critical illness,” “Post-Intensive Care Syndrome,” “Acute Respiratory Distress Syndrome,” “Depression,” “Anxiety,” and “Post-Traumatic Stress Disorder.” Titles and abstracts were screened for relevance. Relevant articles were read in full. Applicable studies of psychological morbidity in non-COVID-19 ICU survivors were also included to supplement the emerging literature in COVID-19 ICU survivors (Figure 2).

Incidence & Prevalence of Acute and Post-Acute Psychological Morbidity

Standardized measurement tools such as the Hospital Anxiety and Depression Scale and Impact of Events Scaled-Revised are frequently used to measure and quantify psychological morbidity in critically ill patients [7]. In meta-analyses from the pre-COVID-19 period examining psychological outcomes of critical illness survivors using these and other tools, there was a high rate of clinically significant anxiety (25-42%), depression (23-34%), and PTSD (22-50%) persisting as long as one-year post-ICU stay [1–3]. Cohort studies of patients surviving severe COVID-19 likewise showed a high prevalence of symptoms of anxiety (9.5-21.4%), depression (7.1-12.7%), and PTSD (4.7-8.7%), based on the Generalized Anxiety Disorder-7, Patient Health Questionnaire-9, and PTSD Check List-5 questionnaires [8], exceeding population norms (with a prevalence ratio of 1.43 for anxiety and 1.61 for depression) at 6 months post-discharge compared to individuals without a COVID-19 diagnosis [9]. Additional large cohort studies and meta-analyses are needed in patients with COVID-19 critical illness to further describe long-term prevalence and incidence of psychological morbidity.

Pathophysiology of SARS-CoV-2 and the Central Nervous System

While it is widely known that SARS-CoV-2 affects the olfactory cortex causing anosmia via direct viral injury and local inflammation, recent studies show that the virus also has a predilection for replicating in the hippocampus, which may predispose patients to psychiatric symptoms [10–12]. Brain imaging studies in patients without critical illness suggest that the hippocampus and amygdala form fear-associated memory networks, which play an important role in the development of PTSD [13]. Inflammation of the hippocampus, and associated reduction in hippocampal volume, have been postulated to increase vulnerability to psychiatric

disease [14–16], suggesting a mechanism by which SARS-CoV-2 infection may directly contribute to psychological symptoms.

SARS-CoV-2 may also disrupt the hypothalamic-pituitary-adrenal (HPA) axis, leading to alterations in hormone secretion [11,17,18]. While direct viral invasion of the central nervous system is a rare isolated cause of psychiatric morbidity, HPA axis disruption may predispose patients to suicidal ideation [11,17–21]. SARS-CoV-2 enters cells via the angiotensin converting enzyme-2 receptor [11], which is expressed in the respiratory tract, as well as the kidneys, olfactory bulb, hypothalamus, pituitary gland, and adrenal glands—predisposing these organs to SARS-CoV-2-related viral injury [19]. Indeed, small cohort studies suggest there may be insufficient cortisol response and insufficient growth hormone levels in some patients up to 6 months after acute illness [18]. Disruption of the HPA axis has also been implicated in other SARS viruses. For example, a 2005 study of 61 SARS survivors demonstrated that 39% of patients developed hypocortisolism secondary to HPA axis dysregulation three months after acute illness, with a majority recovering to normal cortisol levels within one year [22]. It is possible that the SARS-CoV-2 virus may lead to similar long-term psychiatric consequences of HPA axis dysregulation. Additional studies are needed to better understand the magnitude and duration of suppressed cortisol levels and its nuanced effect in survivors of severe COVID-19.

Finally, neural inflammatory effects of the SARS-CoV-2 may also contribute to adverse mental health outcomes. High levels of inflammatory biomarkers specific to brain tissue such as serum 100B (s100B) and neuron-specific enolase have been correlated with development of PTSD in survivors of non-COVID-19 critical illness [14,23]. A prospective observational study of 69 patients with mild traumatic brain injury demonstrated that increased serum s100B levels

during hospitalization had a statistically significant association with PTSD symptoms at 12 months post-discharge [24]. S100b has also been implicated in COVID-19 infection and is positively correlated with severity of disease [25–27]. A case-control study showed that s100B levels were higher in patients with mild (n=34) or severe COVID-19 (n=30), as compared to 30 healthy controls [26]. The neural inflammation caused by SARS-CoV-2 may increase the risk of detrimental psychiatric outcomes such as PTSD, as described in traumatic brain injury patients. However, the effect of s100B levels on psychological outcomes after COVID-19 have not been reported to our knowledge.

Iatrogenic Causes of ICU Delirium and Subsequent Psychiatric Sequelae

Delirium is a common complication in critically ill patients. A systematic review and meta-analysis of 27,342 patients with non-COVID-19 critical illness from 48 primary studies estimated that 31% of patients experience delirium during an ICU stay [28]. Social isolation, sensory/sleep deprivation, severe medical illness, mechanical ventilation, prolonged sedation, and neuromuscular blockade (NMB) are all important risk factors for the development of delirium [29,30]. An international cohort study of 2088 patients from 69 ICUs demonstrated that delirium was more common and more prolonged in patients with COVID-19 ARDS versus historical controls with non-COVID-19 ARDS and attributed this difference, at least in part, to prolonged duration of benzodiazepine infusions in patients with COVID-19 ARDS [31]. Deeper sedation and NMB are often used to mitigate ventilator desynchrony and facilitate prone positioning in patients with severe ARDS. Guidelines recommend using non-benzodiazepines sedatives (i.e. propofol, dexmedetomidine) over benzodiazepines because they are associated with better patient outcomes [32,33]. However, due to drug shortages, need for prolonged deep

sedation to facilitate NMB, nursing shortages and ICU crowding that limited 1:1 nursing care, benzodiazepine use increased during the pandemic [34,35]. Indeed, in a multicenter cohort of 2088 patients with COVID-19 ARDS, 56% were treated with benzodiazepines [31].

NMB was also used frequently in patients with critical COVID-19 [36]. In a prospective observational cohort study of 1462 ICU patients without COVID-19, NMB was one of the strongest independent risk factors for developing delirium [37]. In a New York City cohort study of 258 ICU patients with COVID-19, 25% received early NMB within 48 hours of being placed on mechanical ventilation [36,38]. Though NMB may be useful in certain scenarios, data suggest that NMB may have been used more often in COVID-19 ARDS compared to other etiologies of ARDS. In a single center cohort study of patients with COVID-19 ARDS, 60% of 267 mechanically ventilated patients received NMB, whereas in the multicenter, international LUNG SAFE study, only 38% of 12,906 patients with non-COVID-19 ARDS received NMB [39,40].

Patients with COVID-19 also experience prolonged mechanical ventilation with a mean ventilator duration of 14.6 days compared to 5.9 days in ICU patients without COVID-19 [41,42]. As the individual risk factors of prolonged neuromuscular blockade, sedation, and mechanical ventilation compound in patients with COVID-19 ARDS, the overall risk of developing ICU delirium increases.

Importantly, the presence and duration of delirium are associated with subsequent development of neuropsychiatric and neurocognitive sequelae [4,43,44]. A prospective study of 381 non-ICU patients with COVID-19 demonstrated that 30% of patients developed PTSD within four months of acute illness and attributed in-hospital delirium as an independent risk factor [4]. Another multicenter retrospective cohort study in 4033 medical-surgical ICU patients without

COVID-19 across 14 ICUs demonstrated that patients who experienced at least one calendar day of ICU delirium were more likely to develop clinically diagnosed neuropsychiatric disorders (Risk Ratio = 1.14) and neurocognitive disorders (Risk Ratio = 1.59) at 1 year after ICU discharge [43]. Correlation between duration of delirium and likelihood of subsequent neuropsychiatric disorders was not reported and may have helped to identify a dose-dependent relationship. Additional studies are needed to assess long-term psychiatric outcomes in critical COVID-19 survivors specifically, as these patients have multiple risk factors to experience a prolonged duration of delirium.

Conversely, a pre-existing diagnosis of anxiety or depression has been shown to increase the risk of developing ICU delirium. A retrospective study of 286 patients with ARDS demonstrated that in patients who experienced ICU delirium, 49.2% of patients had pre-existing psychiatric conditions (Odds Ratio = 1.94, p = 0.01) [45]. Subgroup analysis demonstrated that pre-existing depression and anxiety were statistically significant contributing factors (Odds Ratio = 1.76 and 1.88, respectively) [45].

Large-scale, population-based surveys demonstrated that prevalence of depression and anxiety increased during the COVID-19 pandemic [46,47]. Fear and anxiety about contracting SARS-CoV-2 and spreading it to family members were especially prevalent during the early months of the COVID-19 pandemic [48,49]. Prevalence of depression was also increased due to social isolation, especially in older adults [50]. An international study based on online questionnaires to assess psychiatric symptoms demonstrated marked increases in anxiety, acute stress, and depression in the general worldwide population [46]. Another cross-sectional study conducted in the Guangdong province of China during the early months of the pandemic found that 20% of

179 respondents (n = 98) experienced severe depression symptoms based on Patient Health
180 Questionnaire-9 data [47]. While selection bias and unknown pre-pandemic psychological history
181 of respondents may limit interpretation of these data, the findings suggest that patients who
182 develop critical COVID-19 are at increased risk for pre-existing psychological diagnoses due to
183 circumstances created by the pandemic, which may compound the risk of developing ICU
184 delirium and subsequent post-ICU psychological sequelae.

185 **Situational Effects of COVID-19 in the Critical Care Setting**

186 During the pandemic, hospitals restricted visitation to inpatient areas in order to
187 minimize spread of SARS-CoV-2. There are limited data regarding the psychological effects of
188 restricted visitation in ICU patients with COVID-19. A pre-pandemic clinical trial demonstrated
189 that flexible versus restricted visitation policy had no effect on the incidence of ICU delirium [51],
190 but did not examine delirium duration or severity. However, a multicenter cohort study in ICU
191 patients with COVID-19 found that family visitation decreased the incidence of next-day
192 delirium by 27%, suggesting that visitation may reduce duration of delirium [31].

193 Longer-term detrimental effects on mental health, coping mechanisms, and overall
194 wellbeing may also be impacted by restricted visitation in patients with COVID-19. A
195 prospective cohort study of 88 ICU patients with COVID-19 assessed in-hospital psychiatric
196 symptoms and found that 83% and 73% experienced symptoms of anxiety and depression,
197 respectively [52]. Out of 33 patients who completed the three-month follow-up questionnaire,
198 73% reported a negative psychological impact of restricted visitation [52]. While the study is
199 limited in interpretation due to self-reported data and low retention rate, it is an informative
200 starting point to conduct additional, large cohort studies in survivors of critical COVID-19 illness.

Restricted visitation may also have an impact on patients with COVID-19 ARDS who are admitted to the ICU and monitored on maximum non-invasive ventilatory support. Not only do these patients experience significant dyspnea, but they face challenging decisions regarding mechanical ventilation and goals of care without having family members physically present. Several studies have demonstrated that dyspnea in itself is a pathophysiologic trigger for panic attacks [53,54]. Long-term consequences of emotional distress in the peri-intubation period have not been documented in the literature and warrant additional studies. It will be helpful to conduct such studies with and without family presence to better understand whether restricted visitation has a compounding effect on psychological distress.

Intubated patients with COVID-19 may face a similar challenge related to restricted visitation. Patients experience heightened levels of anxiety, agitation, and stress while mechanically ventilated [55,56]. Patients with long-term ventilator dependence also experience feelings of helplessness and depression as they are consciously aware of being sustained by a breathing machine [57]. Family support during ventilator weaning has been correlated with ease of emotional distress as evidenced by patient interviews [56]. Pandemic-related restrictions do not allow patients with critical COVID-19 to access an important protective mechanism against acute mental health effects which may have long-term sequelae that are currently unknown.

The use of ICU diaries in minimizing psychiatric complications has been studied and validated in the literature [1,58,59]. A randomized control trial in 352 ICU patients without COVID-19 demonstrated a statistically significant reduction of PTSD symptoms 1-month post-ICU discharge in patients who were randomized to the ICU diary group [59]. Data regarding the use of ICU diaries in patients with COVID-19 are lacking. In part, this may be secondary to restricted

visitation as ICU diaries are often maintained and read to patients by family members. With restricted visitation policies in place, fewer patients with critical COVID-19 may be able to psychologically benefit from sustained ICU diary use.

Current Interventions and Future Directions

Interventions to minimize psychological morbidity during and after critical illness have been studied in both the inpatient and outpatient setting, mostly in non-COVID-19 patients (Table 1). Implementation of the ABCDEF Bundle (Assess, prevent, and manage pain; Both spontaneous awakening and breathing trials: Choice of Analgesia and Sedation; Delirium assess, prevent, and manage; Early Mobility and Exercise; Family engagement/empowerment) has had a significant effect in reducing in-hospital delirium and subsequent psychological and cognitive impairment [60,61]. Results of the ICU Liberation Collaborative in over 15,000 patients across 68 ICUs demonstrated that performing elements of the ABCDEF bundle resulted in a significantly reduced readmission rate and length of ICU stay, thereby minimizing iatrogenic risk factors for psychological morbidity [60]. Inpatient use of ICU diaries has also improved long-term psychiatric morbidity, mainly by significantly minimizing PTSD symptoms after ICU discharge [62].

A number of other interventions have been tested to mitigate psychological morbidity but have not been found beneficial. The POPPI multicenter, cluster-randomized clinical trial of 1353 patients treated in 24 ICUs in the United Kingdom tested a nurse-led, post-ICU preventive psychological intervention, but found no difference in PTSD symptoms at six months after ICU discharge [63]. The SMOOTH clinical trial of 291 ICU patients with non-COVID-19 sepsis tested an enhanced primary care follow-up intervention but found no difference in mental health outcomes compared to usual PCP care [64]. Likewise, a Cochrane review of post-ICU clinics found

insufficient evidence to determine whether these programs are effective [65]. Nonetheless, post-ICU clinics are consistently liked by patients and provide an important venue for both learning about post-ICU sequalae and pilot-testing interventions. For these reasons, the 2021 Surviving Sepsis Campaign Guidelines suggest referral to post-critical illness clinics where available [66].

Data regarding interventions to minimize adverse mental health effects in patients with critical COVID-19 specifically are limited. An international study conducted in 262 ICU patients with COVID-19 ARDS demonstrated a significantly lower implementation rate of the ABCDEF Bundle and ICU diaries in patients with COVID-19 compared to the reported pre-pandemic implementation rate [67]. Use of the ABCDEF Bundle and ICU diaries were low in all ICU patients regardless of COVID-19 status during the pandemic, suggesting that the driving factor was resource constraints and staffing shortages [68]. Additional interventions such as the creation of tailored programs to minimize ICU discomfort in patients with COVID-19 ARDS are currently being evaluated to determine effects on long-term mental health outcomes (NCT03991611).

A potentially novel area of study could explore the outcomes of group-based therapy. Studies in psychology have demonstrated that group therapy for patients who have undergone shared trauma can substantially reduce depression, anxiety, and feelings of isolation [69]. Trauma-focused cognitive behavioral therapy has been extensively studied in children and adolescents with a known benefit of reducing psychiatric symptoms (56). Trauma-focused cognitive behavioral therapy in critically ill patients with COVID-19 both individually and in group settings may demonstrate clinical benefit as many patients share similar experiences related to the pandemic and view their ICU stay as a source of trauma [70]. It will be beneficial to study these interventions in ICU patients with and without COVID-19.

Additionally, it will be important to determine whether effective post-discharge treatment can be provided in primary care settings or if cognitive and behavioral therapy should be provided by mental health experts. Unfortunately, the current literature demonstrates that non-specialist interventions by nurses and primary care physicians have been unsuccessful [64,71].

Conclusion

As critical illness has increased during the COVID-19 pandemic, there is an urgent need to expand and improve ICU survivorship care. Many patients with critical illness due to COVID-19 experience significant psychological burden, driven by pathophysiologic, iatrogenic, and situational factors. The direct inflammatory effects of the SARS-CoV-2 virus in the brain may inherently increase patients' risk of psychiatric sequelae. Prolonged mechanical ventilation, sedation, and paralysis due to severe ARDS increase the risk of ICU delirium, which may subsequently increase the risk of long-term mental health effects. The added burden of restricted visitation, staffing shortages, and resource constraints during a pandemic interferes with the delivery of evidence-based interventions such as the ABCDEF bundle.

Patients with critical COVID-19 undoubtably face a complicated and psychologically challenging recovery. Though it is currently unknown whether these complications occur at a greater incidence or with greater severity compared to other critical illness, the pandemic has given importance to further understanding the psychological aftermath of critical illness. The specific features of patients with COVID-19 ARDS such as prolonged mechanical ventilation and social isolation pose a challenge in generalizing data from patients with other critical illness. Additional studies regarding pre-ICU admission psychiatric co-morbidities, in-hospital

interventions, and outpatient follow-up in ICU patients with and without COVID-19 are necessary to make conclusions that have therapeutic implications. Given the limitations of current data and the growing number of patients who will experience psychological morbidity due to COVID-19 as a result of lasting effects of ICU stays and ongoing discovery of novel variants with unknown susceptibility to vaccines, additional research is warranted to identify unique risk factors, pathogenesis, and targeted therapies for post-ICU psychiatric sequelae.

Summary

Survivors of COVID-19 critical illness are at risk for experiencing significant psychiatric morbidity. The risk factors for developing post-ICU psychological sequelae in patients with critical COVID-19 can be conceptualized in three main domains: pathophysiological effects of the virus, iatrogenic effects of prolonged ICU hospitalizations, and situational effects of a global pandemic. Additional research is necessary to determine the severity and duration of psychological morbidity in survivors of critical COVID-19, and whether current and novel interventions will benefit this growing patient population.

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504 **Table 1-** Summary of studies evaluating acute and post-acute psychological morbidity

Study Title	Study Aim	Setting	Study Population Inclusive of Patients with COVID-19	Improvement in Psychiatric Morbidity
Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative	Assessed complete and partial utilization of ABCDEF bundle as it relates to ICU length of stay, delirium, pain, and mechanical ventilation.	Inpatient	NO	YES
Intensive Care Unit (ICU) Diaries as a Therapeutic Intervention for Post Traumatic Stress Disorder (PTSD) Following Critical Illness (RACHEL II)	Assessed efficacy of ICU diary usage in reducing post-discharge PTSD symptoms	Inpatient	NO	YES
Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI): protocol for a cluster-randomised clinical trial of a complex intervention	Evaluated clinical effectiveness of nurse-led preventative psychological interventions in reducing PTSD symptom severity and psychological morbidity	Inpatient	NO	NO
The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial	Compared nurse-led follow up programs to standard follow-up in improving post-ICU quality of life.	Outpatient	NO	NO
Effect of a Primary Care Management Intervention on Mental Health-Related Quality of Life Among Survivors of Sepsis: A Randomized Clinical Trial	Compared enhanced PCP follow-up to usual PCP follow-up in improving mental-health related quality of life after ICU discharge	Outpatient	NO	NO

505

506 **Figure Legends:**

507 Figure 1- HPA = hypothalamic-pituitary-adrenal, PTSD = Post-Traumatic Stress Disorder