

COVID-19, Critical Illness, and Sleep*

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SARS-COV-2 IS BAD FOR SLEEP, AND SO IS THE ICU

While acute respiratory distress syndrome has been the most-reported severe complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, there is mounting evidence that this infection can affect the nervous system. This includes excessive daytime sleepiness, anxiety, depression, fatigue, muscle weakness, and elevated scores on the Pittsburgh Sleep Quality Index (PSQI). Sleep problems affect between 30% and 60% of COVID-19 patients (1).

In an international survey of over 25,000 people that compared pre-pandemic sleep to intra-pandemic sleep, the prevalence of disrupted sleep increased from 14% to 28%. For those patients with self-reported COVID infection (800 patients), it was increased from 14% to 32%. Excessive sleepiness increased to 40% from 18% in post-infection patients (2).

As most practicing intensivists already know, critically ill patients have significant sleep disruptions that contribute to ICU delirium. While many zeitgebers and interventions like vital sign checks, noise, procedures, and sedation have been implicated, invasive mechanical ventilation has a disproportionate contribution (3). These disruptions have been shown to persist up to a week after ICU discharge. While they do improve over time, they do not appear return to normal, even after 12 months (4). The natural question then arises, is there an additive effect of critical illness, mechanical ventilation, and SARS-CoV-2 infection?

COVID-19 CRITICAL ILLNESS DISRUPTS SLEEP AND CIRCADIAN RHYTHM

In this issue of *Critical Care Medicine*, Benítez et al (5) followed 172 consecutive patients admitted to their ICU in Spain with COVID-19 infection. No experimental interventions were made. The usual demographic and clinical data were obtained (e.g., age, ventilator days, ICU length of stay [LOS], etc.). Study-specific data were collected during a research visit with surviving patients at day 90: PSQI (seven category subsets of 19 questions); Epworth Sleepiness Scale; Satisfaction Alertness Timing Efficiency Duration (sleep quality survey); actigraphy (7 d with total sleep time [TST], intradaily variability [IV] for sleep fragmentation, and interdaily stability [IS] for circadian rhythm); carbon monoxide diffusion coefficient; chest CT scan; Hospital Anxiety and Depression Scale (HADS); and 6-minute walk test for distance (6MWD). The statistical analysis was appropriate.

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Most patients (67%) were male with a median age of 61. Half had obesity or hypertension; one-fourth had diabetes. Median LOS was 23 days with ICU LOS 11 days with approximately half the patients undergoing mechanical ventilation. The PSQI noted poor sleep quality was identified in 60% of the patients—sleep efficiency and duration were the most affected. Notably, the PSQI data were quantitatively confirmed by actigraphy, which showed a reduction in total sleep time, increased wake after sleep onset, and high circadian rhythm (IS) variability. The 6MWD showed a 13% reduction from predicted distance when adjusted for sex, age, height, and weight. Depression and anxiety were also noted at 6% and 14%, respectively. The most prevalent symptoms were muscular fatigue (22%) and cough (18%). In subgroup analysis, mechanical ventilation resulted in increased IS at 3 months when compared with those without invasive mechanical ventilation. The PSQI at 90 days correlated with depression and anxiety scores from the HADS, but it did not correlate with sleep fragmentation (IV), IS, or relative amplitude of the actigraphy.

It should be noted that the actigraphy was performed on a random subset of patients whose demographic and outcome characteristics were no different than the larger 172 patient population. The study by Benítez et al (5) is further limited, as are most critical care studies, by a lack of precritical illness baseline data. Finally, the study Benítez et al (5) is observational, and can therefore not confirm causal relationships, nor can it differentiate the effects of critical care interventions from the effects of SARS-CoV-2 infection (5).

WHAT ABOUT NON-COVID CRITICAL CARE?

In a multicenter study of 109 patients with comparable demographics by Wilcox et al (4), 6-month follow-up showed actigraphic sleep fragmentation (IV) of 68% and sleep rhythm (IS) 0.62. Both findings are comparable to this project's IV of 84% and IS 0.52. The study by Wilcox et al (4) took place prior to the SARS-CoV-2 pandemic, which allows us to infer that perhaps these complications are those of critical illness as opposed to SARS-CoV-2 (4).

Compared with Benítez et al (5), Wilcox et al (4) found a greater disruption at 7 days with significant improvement by 6 months that was maintained at 12 months. When should we consider screening patients

for potential sleep interventions? Perhaps 90 days, as in the current study by Benítez et al (5), is the right time.

We do not yet know if SARS-CoV-2 infection specifically disrupts sleep beyond the effects of critical illness either acutely or in the long term. However, there are multiple plausible inflammatory pathway-mediated mechanisms for this infection to affect the chronobiology (6).

Sleep and depression are intricately intertwined. Depression often manifests as sleep disruption. Treatment of disordered sleep has been shown to reduce the prevalence of depression. These are challenging symptoms and diagnoses to parse. The advent of actigraphy, home sleep testing, and the improved awareness of and reliability of screening tools for depression will be critical in differentiating these separate but related phenomena in the ICU survivor environment (7).

RECOMMENDATIONS

Beyond the acute intensive care that we provide our patients with acute SARS-CoV-2 infection, this project does not offer a specific and effective intervention to prevent the sleep disrupting sequelae of intensive care. It cannot differentiate causality of these sleep disruptions between critical care and SARS-CoV-2 infection.

However, the Clinical Practice Guideline (CPG) from the Society of Critical Care Medicine for the management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep offers a standardized best practice for current interventions (8). This CPG offers pharmacologic and non-pharmacologic interventions. Perhaps, since the study by Benítez et al (5) reports that invasive mechanical ventilation has a higher association with sleep disruption, the relatively harmless pharmaceutical melatonin could be a way to reinforce the circadian rhythm that we disrupt in the process of providing intensive care (9).

Finally, as the authors note, the development of depression and anxiety after hospital discharge may be a strong indicator of disruptions in sleep efficiency and rhythm. Since the PSQI and HADS did not correlate with the actigraphic measurements, actigraphy, sleep diaries, and perhaps even polysomnography should be considered as part of the medical evaluation of those patients with these mental health markers. Certainly, ICU survivors should be evaluated for these and other issues after discharge.

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Dr. Chatterjee is employed by Wake Forest School of Medicine and the Department of Defense (DoD, U.S. Navy Reserve). His opinion is his alone and does not represent those of the DoD.

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

KEY WORDS: disability; Long COVID; frailty

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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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