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Quantifying the Burden of Viral Sepsis During the Coronavirus Disease 2019 Pandemic and Beyond*

KEY WORDS: coronavirus disease 2019; sepsis; severe acute respiratory syndrome coronavirus 2; surveillance; viral sepsis

Claire N. Shappell, MD[1,2]
Michael Klompas, MD, MPH[1,3]
Chanu Rhee, MD, MPH[1,3]

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in millions of deaths worldwide and countless more admissions to hospitals and ICUs. Since its emergence, it has become clear that the pathophysiology of severe COVID-19 involves immune-mediated damage to the lungs and other organ systems, including the CNS, kidneys, liver, heart, and endothelial system (1). Consistent with the Third International Consensus Definitions of Sepsis and Septic Shock (Sepsis-3) that define sepsis as "life-threatening organ dysfunction resulting from a dysregulated host response to infection," there is now a growing consensus that "sepsis" is an appropriate label for SARS-CoV-2–associated organ dysfunction (2–4).

However, there are a paucity of data about the epidemiology of COVID-19–associated sepsis. Most descriptive studies of patients hospitalized with COVID-19 do not comment on sepsis, likely reflecting the common misperception that only bacterial pathogens can cause sepsis. Indeed, the few COVID-19 reports that do include the term "sepsis" have mostly used it to refer to complications of secondary bacterial infections rather than as a direct effect of SARS-CoV-2 infection. The term sepsis was plagued by ambiguity even before the arrival of SARS-CoV-2 due to the multiplicity of different definitions, subjectivity in applying these definitions, and differences between the official definitions versus common bedside use of the term (5). Controversy over whether the term should apply to organ dysfunction associated with severe viral respiratory infections or only to bacterial superinfection has only magnified the ambiguity.

A new study published by Karakike et al (6) in this issue of *Critical Care Medicine* provides welcome data that begin to fill this important knowledge gap. The authors sought to quantify the burden of viral sepsis during the pandemic by performing a systematic review of all cohorts of hospitalized COVID-19 patients published through March 2021 that reported on the diagnosis of

***See also p. 2042.**

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sepsis or any infection-related organ dysfunction or organ replacement. The analysis included 151 studies from several continents, primarily Asia, Europe, and North America. Because so few cohorts directly reported COVID-19–associated sepsis prevalence, sepsis was primarily calculated indirectly using reported Sequential Organ Failure Assessment (SOFA) scores at admission per Sepsis-3 criteria (i.e., SOFA score of 2 or more points) or through surrogates of SOFA scores such as organ dysfunction rates or organ replacement therapies during hospitalization.

The primary finding was that sepsis was present in 78% of ICU patients with COVID-19 and 33% of non-ICU ward patients. This translated into an overall sepsis prevalence rate of 52% among 218,184 hospitalized COVID-19 patients. Acute respiratory distress syndrome was the most common organ dysfunction (present in 88% of ICU patients) followed by septic shock. Correspondingly, invasive mechanical ventilation was the most common organ support therapy (62% of patients), followed by vasopressor use (50%) and renal replacement therapy (20%). Sepsis-related mortality could not be assessed due to the nature of the data, but ICU mortality rates were high at 33%, and mortality rates associated with mechanical ventilation were even higher at 42%.

The findings of Karakike et al (6) that organ dysfunction, and hence sepsis, is common in hospitalized COVID-19 patients—and that mortality rates are high when ICU care or mechanical ventilation is needed—will not be a surprise to many readers. However, the study provides great value as a first step toward affirming COVID-19 as an important cause of contemporary sepsis and beginning to quantify its burden in 2020–2021 and moving forward.

One may wonder how labeling COVID-19 with organ dysfunction as sepsis benefits clinicians and patients. Indeed, some experts object to applying the sepsis label to severe COVID-19, primarily on the grounds that that it fails to recognize the distinctive aspects of severe COVID-19 compared with other sources of sepsis and encourages the reflexive application of unnecessary (and potentially harmful) broad-spectrum antibiotics and aggressive fluid resuscitation (7). Implicit in this argument is the concern that many clinicians only associate sepsis with bacterial infections and that applying the sepsis label encourages monotonic treatment.

Sepsis-3 and previous sepsis definitions, however, have always been agnostic to the specific pathogen type triggering the maladaptive host immune response (3, 8). Beyond conceptual consistency, in our view, the primary benefit of labeling severe COVID-19 as sepsis is that it immediately communicates the severity of a patient's illness and imminent risk of death if left untreated. We share the concern that sepsis is often treated as a monolithic and homogenous entity rather than a heterogeneous syndrome with a wide array of causes, presentations, and optimal treatments. Ideally, the sepsis label should convey severity but still trigger management that is customized for each patient based on their likely sites of infection, pathogens, organ dysfunction types, and comorbidities rather than triggering a "one-size-fits-all" sepsis bundle.

Another distinct but equally import reason to label COVID-19–associated organ dysfunction as sepsis is that it allows for more accurate accounting of the global and local burden of sepsis prevalence and outcomes. In this regard, the high degree of heterogeneity in estimates of COVID-19 sepsis prevalence among the published studies is another important take-home point in the study by Karakike et al (6). This likely reflects not only underreporting of viral sepsis and variable and changing hospital and ICU admission thresholds and use of organ support therapies for COVID-19 patients but the general lack of standardization in how hospitals and researchers report organ dysfunction. The prevalence of SOFA scores of 2 or greater was directly reported in only five studies and obtained through correspondence with the study authors for an additional seven cohorts. For the remaining studies, the authors were forced to make pragmatic decisions according to the reporting method of each article to define organ dysfunction to arrive at conservative estimates of sepsis prevalence.

This challenge of accurately and consistently identifying sepsis in COVID-19 patients for rigorous case counting purposes is certainly not new. Prior work has demonstrated that diagnosis and coding practices for sepsis and organ dysfunction are highly variable and changing over time, confounding estimates of sepsis prevalence, mortality, and trends derived from administrative data and prospective registries (9–11).

These limitations may largely be overcome by the growing movement to conduct sepsis surveillance using objective clinical markers of infection and organ dysfunction that can be extracted from electronic health record (EHR) systems (12). Several recent studies have

demonstrated the feasibility and accuracy of applying SOFA scores and Sepsis-3 criteria to EHR datasets to generate local estimates of sepsis epidemiology (13, 14). However, the SOFA score is complicated to implement electronically, and some data elements, such as Glasgow Coma Scale scores, urine output, blood pressure measurements, Pao_2/Fio_2 ratios, and vasopressor doses, are not readily available in many datasets. The "eSOFA" criteria used in the Centers for Disease Control and Prevention's Adult Sepsis Event definition were designed to overcome these challenges and facilitate consistent application across diverse EHR systems by simplifying the criteria for each type of organ dysfunction (namely, new vasopressors, initiation of mechanical ventilation, elevated lactate levels, or changes in patients' baseline creatinine, platelet count, or bilirubin levels) and removing Glasgow Coma Scale scores given their subjectivity and inconsistent measurement (15). The Adult Sepsis Event currently requires evidence of "presumed serious infection"—defined by a blood culture draw and administration of at least 4 consecutive days of antimicrobial therapy—combined with one or more concurrent eSOFA criteria, but eSOFA could also be paired with positive SARS-CoV-2 test results to facilitate more standardized reporting of COVID-19 sepsis. Additional work is needed, however, to adapt, optimize, and validate the Adult Sepsis Event criteria or other EHR-based sepsis definitions specifically for COVID-19.

The COVID-19 pandemic has reinvigorated long-standing debates around how best to define sepsis. It is critical, however, that we move beyond the definition controversy, so that we can start to quantify the enormous impact of COVID-19 on the global epidemiology of sepsis. Karakike et al (6) have taken an important first step toward quantifying the burden of COVID-19–associated sepsis via systematic review and meta-analysis by attempting to apply a uniform definition to very heterogenous data. Moving forward, a more rigorous and consistent surveillance approach for viral sepsis caused by COVID-19, as well as for other current and future pathogens, will be critical in informing better prevention and treatment strategies and guiding research, policy, and resource allocation decisions to combat sepsis.

1 Department of Population Medicine, Harvard Medical School/Harvard Pilgrim Health Care Institute, Boston, MA

2 Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA

3 Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital, Boston, MA

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Sodium Rising: Deciphering the Code*

KEY WORDS: hypernatremia; hyponatremia; intensive care unit; mortality; sodium

Nicolás Serrano, MD, MSc, PhD

Sodium is one of the commonest serum laboratory tests in ICU patients, with frequent abnormal results. Dysnatremia, the generic name for either hyponatremia or hypernatremia, is associated with worse outcomes in the ICU setting. Several studies have shown the impact of dysnatremia on mortality of ICU patients in a wide variety of clinical situations (1–13).

Funk et al (1) in a retrospective study with a database of 151,486 adults from 77 ICUs in Austria found both hypo- and hypernatremia present on ICU admission as independent risk factors for poor prognosis (1). Similar results in surgical patients were reported from another large database by Leung et al (2, 3) where apart of increased hospital mortality were also independently associated with length of hospital stay and complications (2, 3).

New evidence suggests that even mild deviations from normal and simple variability of normal sodium values may also be a significant independent predictor of increased hospital mortality (4–7).

Thus, subtle changes in serum sodium concentration were found as independent mortality risk factors. Darmon et al (5) in another large database with 11,125 patients found that both moderate and severe hyponatremia and mild, moderate, and severe hypernatremia were independently associated with day-30 mortality. They suggest that even mild abnormalities of serum sodium concentration present on ICU admission predict mortality (5).

Furthermore, two independent retrospective studies conducted by Sakr et al (6) and Marshall et al (7) including 10,923 and 8,600 surgical ICU patients, respectively, revealed that fluctuations in serum sodium concentrations were also independently associated with an increased risk of death, even in patients who remained normonatremic during the ICU stay (6, 7).

These results indicate that variability of sodium concentrations, including changes within the normal range, is linked to an increased risk of death (4–7).

The effect of organ dysfunction on dysnatremia and mortality was investigated by Güçyetmez et al (8) in a retrospective analysis on 1,060 critically ill medical and postsurgical patients. The impact of hypo- and hypernatremia on mortality was influenced by the simultaneous presence of organ dysfunction, and the authors found that the impact on mortality is more severe when concomitant organ dysfunction is present (8).

***See also p. 2070.**

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