

# The Impact of COVID-19 on Sepsis-Related Mortality in the United States

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## Abstract

**Background:** Coronavirus disease 2019 (COVID-19)-related organ dysfunction is increasingly considered as sepsis of viral origin. In recent clinical and autopsy studies, sepsis has been present in the majority of decedents with COVID-19. Given the high mortality toll of COVID-19, sepsis epidemiology would be expected to be substantially transformed. However, the impact of COVID-19 on sepsis-related mortality at the national level has not been quantified. We aimed to estimate the contribution of COVID-19 to sepsis-related mortality in the USA during the first year of the pandemic.

**Methods:** We used the Centers for Disease Control Wide-Ranging Online Data for Epidemiological Research (CDC WONDER) Multiple Cause of Death dataset to identify decedents with sepsis during 2015 - 2019, and those with a diagnosis of sepsis, COVID-19, or both in 2020. Negative binomial regression was used on the 2015 - 2019 data to forecast the number of sepsis-related deaths in 2020. We then compared the observed vs. predicted number of sepsis-related deaths in 2020. In addition, we examined the frequency of a diagnosis of COVID-19 among decedents with sepsis and the proportion of a diagnosis of sepsis among decedents with COVID-19. The latter analysis was repeated within each of the Department of Health and Human Services (HHS) regions.

**Results:** In 2020, there were 242,630 sepsis-related deaths, 384,536 COVID-19-related deaths, and 35,807 deaths with both in the USA. The predicted number of sepsis-related deaths for 2020 was 206,549 (95% confidence interval (CI): 201,550 - 211,671). COVID-19 was reported in 14.7% of decedents with sepsis, while a diagnosis of sepsis was reported in 9.3% of all COVID-19-related deaths, ranging from 6.7% to 12.8% across HHS regions.

**Conclusions:** A diagnosis of COVID-19 was reported in less than one in six of decedents with sepsis in 2020, with corresponding less than one in 10 diagnoses of sepsis among decedents with COVID-19. These findings suggest that death certificate-based data may have substantially underestimated the toll of sepsis-related deaths in the USA during the first year of the pandemic.

**Keywords:** COVID-19; Sepsis; Mortality

## Introduction

Sepsis has been estimated to contribute to nearly one in five deaths globally in 2017 [1] and is thus considered a major health burden. Development of organ dysfunction related to the coronavirus disease 2019 (COVID-19) is increasingly considered as sepsis of viral origin [2-5]. However, uncertainties remain about the prevalence of sepsis among patients with COVID-19 and its outcomes. In a recent meta-analysis, sepsis was estimated to be present in 52% of hospitalized patients with COVID-19 [6]. In a retrospective review of medical records of hospitalized patients with COVID-19, sepsis was present in 93% of decedents, and COVID-19 was assessed as causative in all sepsis events [7]. In addition, in autopsy studies of patients with COVID-19, sepsis or COVID-19-related organ failure were reported in nearly 80% of decedents [8, 9].

During the first year of the pandemic, over 375,000 COVID-19-related deaths were reported in the USA [10]. Thus, the epidemiology of sepsis would be expected to be profoundly transformed. We have recently showed that mortality due to the acute respiratory distress syndrome (ARDS), the most common severe pulmonary complication in patients with COVID-19, has increased nearly five-fold in the USA in 2020, though the reported mortality likely underestimated the full toll of ARDS among decedents [11]. COVID-19-related organ dysfunction can affect multiple systems [12] and sepsis-related mortality toll far exceeds that of ARDS [13]. Thus, accurate integration of sepsis-related deaths among decedents with COVID-19 into the tracked dynamics of sepsis-related mortality [14] can provide more complete estimates of the burden of sepsis and its underlying etiologies and can inform clinical and public health efforts geared to its reduction. However, the impact of COVID-19 on sepsis-related deaths at a national level has not been quantified. We aimed to estimate the contribution of COVID-19 to sepsis-related mortality in

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**Table 1.** Sepsis-Related Mortality and the US Population (2015 - 2020)

Variable	Year					
	2015	2016	2017	2018	2019	2020
Sepsis-related mortality	195,522	198,473	204,005	206,251	201,478	242,630
Population	321,418,820	323,127,513	325,719,178	327,167,434	328,239,523	329,484,123

the USA based on death certificates during the first year of the pandemic.

## Materials and Methods

We used the Centers for Disease Control Wide-Ranging Online Data for Epidemiological Research (CDC WONDER) Multiple Cause of Death dataset [15] to obtain mortality and US population data. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. We have identified decedents with a diagnosis of sepsis during 2015 - 2019, and with a diagnosis of sepsis, COVID-19, or both in 2020. Sepsis was defined by previously reported International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code taxonomy (A02.1, A20.7, A22.7, A26.7, A32.7, A40.0-A40.9, A41.0-A41.9, A42.7, B37.7) [14, 16]. The ICD-10-CM coding of the causes of death in CDC WONDER does not include codes for severe sepsis (R65.20) or septic shock (R65.21). COVID-19 was identified by ICD-10-CM code U07.1. We used negative binomial regression with log-link and robust standard errors on the 2015 - 2019 data with population offset to forecast the number of sepsis-related deaths in 2020 and expressed the yearly changes as annual percent change (APC). We then compared the number of observed vs. expected sepsis-related deaths in 2020, expressing the difference as a ratio and its 95% confidence interval (95% CI), and examined the frequency of a diagnosis of COVID-19 among decedents with sepsis. In addition, we examined the proportion of a reported diagnosis of sepsis among all decedents with a diagnosis of COVID-19. We then repeated the latter analysis within each of the 10 Department of Health and Human Services (HHS) regions. These regions represent state-based divisions of the USA for the purpose of public health promotion. Data analysis was performed using R 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). The study was not subject to institutional review due to use of publicly available data.

## Results

The annual sepsis-related mortality and population data for 2015 - 2020 are detailed in Table 1. Sepsis-related mortality in the USA rose between 2015 and 2019 from 195,522 to 201,478, but this change was not statistically significant when adjusted for the US population (APC +0.4 (95% CI: -0.3 - +1.2);  $P = 0.2397$ ). In 2020, there were 242,630 sepsis-related deaths, 384,536 COVID-19-related deaths, and 35,807 deaths with both in the USA. The predicted number of sepsis-related

deaths for 2020 was 206,549 (95% CI: 201,550 - 211,671), with the ratio of observed to expected deaths 1.17 (95% CI: 1.16 - 1.18). COVID-19 was reported in 14.7% of decedents with sepsis. A diagnosis of sepsis was reported in 9.3% of all COVID-19-related deaths, ranging from 6.7% (HHS region 2) to 12.8% (HHS region 9). The data on the proportion of a diagnosis of sepsis among decedents with COVID-19 within each HHS region are presented in Table 2.

## Discussion

In this study we found that a diagnosis of COVID-19 was reported in less than one in six sepsis-related deaths in the USA during the first year of the pandemic. The number of sepsis-related deaths in 2020 increased substantially by nearly 36,000 beyond that expected based on pre-pandemic data. This large change was, however, relatively low, when considering the number of all decedents with COVID-19.

The observed limited contribution of COVID-19 to sepsis-related mortality was driven by the corresponding infrequent diagnosis of sepsis among the former. Our study shows that sepsis was reported in less than one in 10 COVID-19-related deaths in the USA in 2020. Given the reported estimates of sepsis prevalence among decedents with COVID-19 in clinical and autopsy studies [7, 8], our findings suggest that death certificate-based data may have substantially underestimated the occurrence of sepsis among patients with COVID-19 in the USA who died during the first year of the pandemic. The causes of this gap are unclear. However, they may reflect clinicians' uncertainties about the syndromic interpretation of COVID-19-related organ dysfunction during the first year of the pandemic. This may have led in turn to low levels of documentation of sepsis in death certificates, with resultant effect on coding of these deaths. Such uncertainties can be expected, given the initially limited data on the pathogenesis of illness among affected patients. In addition, although several reports in 2020 have considered COVID-19-related organ dysfunction as sepsis and a key risk for death, suggesting potential interventions to mitigate mortality in affected patients [17-19], they were rare and challenging to fully track among the surge in research reports and opinion pieces on COVID-19, while some of the key reports on conceptualizing COVID-19-related organ dysfunction as sepsis and quantifying its prevalence were published only after the first year of the pandemic [2, 3, 6].

Another potential contributor to clinicians' uncertainties in interpreting COVID-19-related organ dysfunction may have been the early guidelines by professional organizations on management of severely ill patients with COVID-19, that is, those with organ dysfunction. In the 2020 guidelines issued by the Surviving Sepsis Campaign, the authors noted that the rec-

**Table 2.** Frequency of a Diagnosis of Sepsis Among Decedents With COVID-19, Stratified by HHS Region in 2020

HHS region	Number (%) of sepsis diagnoses among decedents with COVID-19
HHS region #1 (CT, ME, MA, NH, RI, VT) <sup>a</sup>	1,379/19,725 (7.0)
HHS region #2 (NJ, NY)	3,797/56,707 (6.7)
HHS region #3 (DE, DC, MD, PA, VA, WV)	2,912/34,918 (8.3)
HHS region #4 (AL, FL, GA, KY, MS, NC, SC, TN)	7,530/70,574 (10.7)
HHS region #5 (IL, IN, MI, MN, OH, WI)	5,062/66,484 (7.6)
HHS region #6 (AR, LA, NM, OK, TX)	6,276/52,638 (11.9)
HHS region #7 (IA, KS, MO, NE)	1,424/18,521 (7.7)
HHS region #8 (CO, MT, ND, SD, UT, WY)	880/11,281 (7.8)
HHS region #9 (AZ, CA, HI, NV)	5,936/46,549 (12.8)
HHS region #10 (AK, ID, OR, WA)	611/7,139 (8.6)

<sup>a</sup>The parenthesized acronyms within each HHS region represent the states in that region. HHS: Health and Human Services; COVID-19: coronavirus disease 2019; AL: Alabama; AK: Alaska; AZ: Arizona; AR: Arkansas; CA: California; CO: Colorado; CT: Connecticut; DE: Delaware; FL: Florida; GA: Georgia; HI: Hawaii; ID: Idaho; IL: Illinois; IN: Indiana; IA: Iowa; KS: Kansas; KY: Kentucky; LA: Louisiana; ME: Maine; MD: Maryland; MA: Massachusetts; MI: Michigan; MN: Minnesota; MS: Mississippi; MO: Missouri; MT: Montana; NE: Nebraska; NV: Nevada; NH: New Hampshire; NJ: New Jersey; NM: New Mexico; NY: New York; NC: North Carolina; ND: North Dakota; OH: Ohio; OK: Oklahoma; OR: Oregon; PA: Pennsylvania; RI: Rhode Island; SC: South Carolina; SD: South Dakota; TN: Tennessee; TX: Texas; UT: Utah; VT: Vermont; VA: Virginia; WA: Washington; WV: West Virginia; WI: Wisconsin; WY: Wyoming; DC: District of Columbia.

ommendations were based on pre-pandemic sepsis data. However, the term “sepsis” was not mentioned in the guideline in relation to COVID-19 [20], likely reflecting the uncertainties of the authors on this topic at the time. This contrast between the mission of the organization issuing the guideline and its content likely has sent a mixed message and may have added to the uncertainties of clinicians at the bedside.

This hypothesis is supported by the nearly two-fold variability in the frequency of a diagnosis of sepsis among COVID-19-related deaths across HHS regions, possibly reflecting variation in clinicians’ consideration of a diagnosis of sepsis in these patients.

The postulated clinicians’ uncertainties about COVID-19-related organ dysfunction appear to be shared in earlier research reports. In the abovementioned meta-analysis on sepsis prevalence among patients with COVID-19, the term “sepsis” was found only in nine out of the 151 analyzed studies [6].

Thus, our findings represent the real-world collective judgment of bedside clinicians in the USA during the first year of the pandemic on the causes of death of their patients with COVID-19. However, given the abovementioned uncertainties by clinicians and researchers alike, the “correct” number of sepsis-related deaths among decedents with COVID-19 in 2020 in the USA remains unknown.

This study is limited by the data source, precluding confirmation of its accuracy and misclassifications can result from inaccuracies in the documentation on the death certificates. However, death certificate data remain the primary source for national and regional estimates of cause-specific mortality.

While there is a growing consensus that COVID-19-related organ dysfunction represents sepsis [3, 4], further insights into its pathobiology are much needed and can inform future studies on the prevalence of sepsis in COVID-19 and management of sepsis in these patients and would lead to more precise estimates of its death toll in the USA and in other

countries and regions.

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None to declare.

### Financial Disclosure

None to declare.

### Conflict of Interest

None to declare.

### Informed Consent

Not applicable.

### Author Contributions

LO has performed the design of work, acquisition of data, analysis and interpretation, composition, drafting, revising, editing, and final approval. JG has performed analysis and interpretation, revising, editing, and final approval.

### Data Availability

The data used in this study are publicly available at <https://>

wonder.cdc.gov/controller/datarequest/D77.

## Abbreviations

COVID-19: coronavirus disease 2019; HHS: Health and Human Services; ICU: intensive care unit

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