Determining Cause of Death During Coronavirus Disease 2019 Pandemic

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OBJECTIVES: Controversy exists whether the cause of death due to severe acute respiratory syndrome coronavirus 2 is directly related to the infection or to underlying conditions. The purpose of this study is to assess the relationship of severe acute respiratory syndrome coronavirus 2 infection with the cause of death in hospitalized patients.

DESIGN: Retrospective observational study; deidentified discharge summaries of deceased patients were reviewed by two intensivists and classified as coronavirus disease 2019–related (caused by severe acute respiratory syndrome coronavirus 2) or coronavirus disease 2019–unrelated (not caused by severe acute respiratory syndrome coronavirus 2 or indeterminate) deaths. For classification disagreement, a separate group of three intensivists reviewed the discharge summaries and arbitrated to determine the cause of death.

SETTING: Single-center study performed at the University of Texas Medical Branch.

PATIENTS: All adult patients (> 18 yr) admitted from March 10, 2020, to October 22, 2020, with positive severe acute respiratory syndrome coronavirus 2 test results who expired during their hospitalization were identified.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Patient demographics, comorbidities, prescribed medications, and ventilatory support data were collected. Comparison between groups was performed using *t* test and chi-square test. During the study period, 1,052 patients were admitted within 14 days of severe acute respiratory syndrome coronavirus 2–positive test results, of whom 100 expired during the hospitalization. Deceased patients were predominantly male and older than 65 years. Obesity (body mass index $\geq 30\,kg/m^2$) was present in 41%, and common comorbidities included hypertension (47%), diabetes (30%), and heart failure (20%). Death was classified as directly caused by severe acute respiratory syndrome coronavirus 2 in 85% and not caused by severe acute respiratory syndrome coronavirus 2 in 5%. An indeterminate cause of death in 10% was due to insufficient information or an atypical presentation. The observed interrater agreement on the cause of death classification was 81%.

CONCLUSIONS: In this single-center study, the majority of deaths in severe acute respiratory syndrome coronavirus 2–positive hospitalized patients were related to a typical or atypical presentation of coronavirus disease 2019 disease.

KEY WORDS: death; epidemiology; respiratory failure; viruses

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was declared a pandemic on March 11, 2020, by the World Health Organization (WHO) and designated as coronavirus disease 2019 (COVID-19). The COVID-19 pandemic has spread worldwide to involve over 190 countries, resulting in more than 83 million global cases with the United States recording the greatest number of cases and deaths (1, 2).

To accurately capture the number of deaths, systematic recording of mortality rates is reported by countries using the *International Classification of Diseases* (ICD) and health-related problems. In the United States, the U.S. National Center for Health Statistics, within the Centers for Disease Control and Prevention (CDC), uses the National Vital Statistics System to compile deaths provided by state and local health departments (3).

As COVID-related deaths increased worldwide and to account for mortality related to COVID-19, the WHO introduced a new ICD, 10th Edition code to assign a death related to COVID confirmed by laboratory testing (ICD-U07.1) (4). In April 2020, this code was implemented for reporting by the CDC (5).

In the United States, death certificates are the principal source of mortality statistics. Deaths related to COVID-19 as direct or indirect result of SARS-CoV-2 infection and correct attribution to the pandemic are challenging (6). Furthermore, to enable full analysis of causality and association, it is important to report all other coexisting medical conditions (contributing causes) on the medical certification of cause of death (7).

As the death toll started to increase in the United States, concerns in the lay press that many deaths during the pandemic are being improperly attributed to COVID-19 have emerged (8, 9). Such claims were supported by misinterpreted CDC weekly updates data, that reported additional comorbidities in up to 94% of total COVID-19 mortalities (10).

The purpose of this study was to examine the relationship between SARS-CoV-2 infection and the cause of death in hospitalized patients. We hypothesized that hospitalized patients with SARS-CoV-2 infection who expired during their hospital stay, died as a direct result of the infection (COVID-19–related death) rather than from a comorbidity (COVID-19–unrelated death) (11).

METHODS

Study Design and Participants

This retrospective study identified patients hospitalized at University of Texas Medical Branch (UTMB) health system with a positive nasopharyngeal SARS-CoV-2 test between March 10, 2020, and October 22, 2020, who expired during their hospitalization. Detection of the SARS-CoV-2 nucleic acid from nasopharyngeal swabs was performed via RNA isothermal amplification (ID NOW; Abott Diagnostics Scarborough) or reverse transcription polymerase chain reaction test (Fusion; Hologic, with cycle threshold of ≤ 40).

Patient discharge summaries and death notes were printed and deidentified for review by two blinded board-certified intensivists (J.S., M.Z.,). Each discharge summary was examined, and patient death classified as COVID-19 related (directly caused by SARS-CoV-2) or COVID-19 unrelated (not caused by SARS-CoV-2 or indeterminate). Although some of the cases labeled as "COVID-19 unrelated" may have been indirectly related to SARS-CoV-2 (indeterminate), the previously mentioned terminology was used for simplicity of presentation.

"COVID-19–related death" was defined as a patient who presented with acute respiratory symptoms including fevers, dyspnea, cough, and radiographic infiltrates that required supplemental oxygen or mechanical ventilation. A "death not caused by SARS-CoV-2" was defined as absence of acute respiratory symptoms and radiographic infiltrates. An "indeterminate" cause was defined as acute respiratory failure symptoms without radiographic infiltrates (12, 13). In the event of reviewer discordance, a separate group of senior intensivists arbitrated to determine the cause of death.

Data collection from the patient electronic medical record included demographics and comorbidities including obesity (body mass index [BMI] ≥ 30 kg/m^2), diabetes, hypertension, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease (CKD), end-stage renal disease, stroke, congestive heart failure (CHF), cancer, coronary artery disease (CAD), liver disease, remdesivir and dexamethasone prescriptions, type of respiratory support (invasive vs noninvasive), utilization of comfort care measures, length of stay, and documentation of the ICD-U07.1 code. The study was exempt from review by the Institutional Review Board (IRB) at the UTMB (IRB number 20-0249).

Statistical Analysis

Data are presented as frequency, mean ± SD, and percentage. Comparisons between the COVID-19–related death group and the COVID-19 unrelated death group were performed using independent t test and chi-square test. All analysis was performed with SAS Version 9.4 (SAS, Cary, NC). Significance was two-sided with p value of less than 0.05.

RESULTS

Between March 10, 2020, and October 22, 2020, we identified 15,393 patients who tested positive for SARS-CoV-2, of whom 1,052 were hospitalized. From the hospitalized group, 100 patients expired during their hospitalization, and this group was predominantly male (59%) and greater than 65 years old (71%). The majority of deceased patients were non-White (45% Hispanic; 13% African American), current or former smokers (41%), and, among those with a documented BMI ($n = 91$), 41% were obese (BMI ≥ 30 Kg/m^2). More than half of patients (55%) had at least one comorbidity on record, most commonly hypertension (47%), diabetes (30%), and CHF (20%). CKD was present in 13% of patients, and 2% were dialysis dependent at admission.

Dexamethasone and remdesivir were administered in 46% and 40% of patients, respectively. During their hospital stay, more than half of patients (62%) received invasive mechanical ventilation, and 31% received other forms of oxygen supplementation (low-flow oxygen through nasal cannula or face mask, high-flow nasal cannula). Before their demise, palliative care was initiated with goals of care changed to comfort measures in 54% of patients (**Supplemental Table 1**, http://links.lww.com/CCX/A602).

Most of the patients were medicare beneficiaries (69%), the mean length of stay was 13 ± 10 days, and the mean duration from positive test to death was 17 ±19 days. The majority expired in the ICU (76%) and hospital wards (20%), whereas 4% expired on arrival to the emergency department (ED) or immediately afterwards (within 1 hr) and their nasopharyngeal swab turned positive.

Main Outcome

In the 100 deceased patients, mortality was assessed as directly related to COVID-19 in 85%; in 10% of patients, there was insufficient information or atypical presentation, such that the cause of death could not be definitely classified (indeterminate) as related to COVID-19 infection. Only 5% of the deaths were determined as not attributed to SARS-CoV-2 infection.

In the primary review, the agreement between the two blinded physicians was strong, with concordant decisions in 81% of cases. Classification of death as COVID-19 related was noted in 72% and not caused by SARS-CoV-2 in 5%, whereas 4% were classified as indeterminate.

For the 19 cases with classification discordance, the second group of physicians determined the death to be related to COVID-19 in 13 cases (68.4%), and six cases (31.4%) were indeterminate.

Analyzing Characteristics

In patients classified with COVID-19–related mortality, the length of stay was greater compared with those with COVID-19 unrelated mortality, 14.2 and 8.2 days, respectively ($p = 0.005$). No difference was noted between groups in the use of supplemental oxygen or mechanical ventilation (**Supplemental Table 2**, http://links.lww.com/CCX/A603).

After excluding two patients who expired before the ICD-U07.1 implementation (April 1, 2020), the code was documented by bedside providers in 70% of all deaths. Among 83 deaths classified as COVID-19 related mortality, the ICD-U07.1 code was reported in 62 deaths (74.7%), and in the 15 deaths classified as COVID-19–unrelated mortality, this code was reported in seven (46.7%). No difference was noted between the groups regarding the ICD code documentation ($p = 0.07$).

DISCUSSION

In our single-center study, overall, 85 of 100 deaths were attributed to COVID-19 among patients who tested positive for SARS-CoV-2 and died during hospitalization. Only one of 20 deaths in otherwise test positive cases was not caused by SARS-CoV-2.

COVID-19–Related Death

A challenge in management of this respiratory infection is that patients with COVID-19 present with a broad clinical spectrum ranging from asymptomatic

infection to multiple organ failure with death (12). Patients classified with a COVID-related death had characteristic clinical features of COVID-19 pneumonia with acute onset of respiratory symptoms (fever, cough, and/or dyspnea), progressive hypoxemic respiratory failure, and bilateral radiographic infiltrates (13–15). These patients fulfilled the criteria for acute respiratory distress syndrome, defined as severe hypoxemia, bilateral lung infiltrates, and pulmonary edema not due to volume overload or acute heart failure. Similar to other reports, the presence of diabetes, hypertension, and obesity was recorded in 30–47% of this deceased study cohort. Interestingly, no comorbid conditions were recorded in 45% of the cohort, indicating that age, viral load, and social determinants are important contributing factors to critical illness and death (13–16).

Consequently, the mean length of stay of 14 days was similar to the findings of a systematic review that reported the length of stay to range from 4 to 21 days in patients with severe COVID-19 who died during hospitalization (17).

The increased length of stay likely reflects the severity of the underlying disease process and prolonged course of respiratory failure as well as nosocomial infections and complications, especially for those requiring invasive mechanical ventilation. Accurate data regarding the duration of mechanical ventilation in patients with COVID-19 pneumonia are limited. One observational study from Italy reported a mean duration of 14 days before liberation from ventilatory support (18).

COVID-19–Unrelated Death

Among the 15 cases classified as "COVID-19 unrelated death," five patients (5% of the total cohort) had a nonrespiratory disease that led to their death with little or no contribution from the original infection. One patient with a history of end-stage liver cirrhosis was admitted for a perforated duodenal ulcer, had exploratory laparotomy and repair, and died 3 days after the surgery from refractory peritonitis and septic shock. Another patient, admitted with massive upper gastrointestinal bleeding and hemorrhagic shock, was unstable for intervention and expired 2 days later. The third patient, a resident of a long-term care facility who had multiple comorbidities, was admitted with

severe ileus and abdominal compartment syndrome, underwent surgical decompression, and his course was complicated by anuric renal failure. His family decided against dialysis, and he expired 6 days after admission. The last two patients both had a history of multiple strokes, were nursing home residents and bed-bound at baseline, and were admitted for multidrug resistant urinary tract infection with septic shock; their families decided against life-sustaining measures and opted for hospice care. Both patients expired shortly after admission.

Although the majority of patients with severe COVID-19 have progressive respiratory failure and radiographic lung infiltrates, some develop thromboembolic complications as well as acute cardiac, renal, CNS, and liver injury (19). In 10 of the COVID-19–unrelated cases (10% of the total cohort), the direct cause of death was indeterminate, mostly due to atypical presentations with a lack of the typical signs of COVID-19 pneumonia (absence of radiographic infiltrates or acute respiratory symptoms) (13–15).

In the current report, atypical presentations included patients with cardiac arrhythmias with a prior history of CAD. Two patients presented with encephalopathy from acute ischemic stroke and new onset seizures, whereas another presented with a thromboembolic event. Similarly, cardiovascular, neurologic, and thromboembolic complications of COVID-19 have been previously reported (20–23).

From the 10 patients in the indeterminate group, three expired in the ED. Two patients arrived with cardiopulmonary resuscitation in progress, and one patient was on home hospice; all three died shortly after their presentation to the ED. There was insufficient information to determine the underlying cause of death in this group.

Strengths and Limitations

Reviewing the discharge summaries of hospitalized patients who expired with a positive SARS-CoV-2 test allowed us to assess the events leading up to their demise. In most cases, respiratory failure was the presenting event, and coexisting conditions contributed to the mortality (24–26). Our data are consistent with previous observational studies demonstrating that most of the hospitalized patients with a positive SARS-CoV-2 test die as a result of infection complications

(27). The review was done by board-certified intensivists who cared for patients with COVID-19 during the pandemic. There was high agreement between the reviewers on both the causality and association of COVID-19 with mortality.

This study also highlighted the potential underestimation of the total number of mortalities related to COVID-19 using the ICD-U07.1 code. Of our entire cohort, providers assigned the death to COVID-19 in 70% of cases, and of those classified as direct COVID-19–related mortality, only 74.7% were coded as COVID-19 deaths (ICD-U07.1). A study by Stokes et al (28) estimated that up to 26.3% of excess deaths attributable to the COVID-19 pandemic were not assigned to COVID-19 on death certificates.

In a recent study by Ketcham et al (29), pulmonary dysfunction and septic shock were the most common immediate causes of death among COVID-19 decedents. However, the purpose of this study was to determine whether COVID-19 was the underlying cause of death in hospitalized patients who tested positive for SARS-CoV-2.

We acknowledge several limitations of our study. The small sample size is unlikely to be fully representative of the general population. However, it provides an estimate of the true number of mortalities directly related to the pandemic.

Our testing protocol evolved over the study period, initially testing was limited to only those with respiratory symptoms, potentially introducing selection bias. Conversely, as testing became more available, all patients were screened for SARS-CoV-2 before admission; with the test's high cycle threshold (≤ 40) and inability to distinguish between live and dead organisms, it is possible that some patients have recovered from a remote COVID-19 infection and retained nasopharyngeal positivity at admission (30).

Second, the relatively low rate of the ICD-U07.1 documentation can possibly reflect an overall underutilization of ICD codes by bedside providers, rather than failure to appropriately attribute the deaths to COVID-19. Similarly, data regarding comorbidities were collected from the problem lists using the diagnoses' ICD codes and may be underestimated due to incomplete documentation or undiagnosed conditions.

Finally, the reviewers cared for this group of patients, and although they were blinded to patient identifiers, their decision may have been subjected to recall bias and documentation flaws. Furthermore, autopsy data were available in only 3% of our cohort, all of which were in cases categorized as COVID-19 related and were concordant with the reviewers' classification; without autopsy findings, the underlying cause of death may remain inconclusive (31).

CONCLUSIONS

We found that, among deceased patients hospitalized with a positive COVID-19 test, 85% died because of infection complications and 10% had atypical presentation. Of 20 COVID-19 mortalities, one was possibly not caused by the infection.

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