Cause of death in fatal cases associated with positive COVID-19 PCR tests

Christopher J Peterson MS , John Makram Fanous MD, Haneen Mallah MD, Shengping Yang PhD, Gilbert Berdine MD

ABSTRACT

The response to the COVID-19 pandemic is heavily influenced by reported fatalities from the virus and, by implication, the criteria used to determine those fatalities. Given complications, such as the presence of comorbidities and limitations in testing, the World Health Organization (WHO) guidelines recommend counting both confirmed and suspected COVID-19 deaths as fatalities. While easily implementable, this method does little to indicate the degrees of certainty for a COVID-19 death, and thus concerns have arisen that this may overcount the number of COIVD-19 fatalities. In response, we developed and implemented a scoring system to determine the likelihood that COVID-19 contributed to patient death. Three reviewers independently assessed records of 47 patients who reportedly died from COVID-19. Greatest consensus was observed at the ends of the scoring spectrum, with twelve patients having complete consensus among reviewers. Intraclass correlation among the three reviewers was 0.52 (95% CI, 0.25–0.72). Middle scores had the greatest variability, possibly due to plausible alternative diagnoses, suggesting the potential for variability in death certification and the need for a scoring system that reports degrees of certainty. Although scoring rules can guide reviewers toward greater consensus about cause of death, in the absence of an objective criteria for COVID-19 disease, the determination of cause of death in paitents with positive PCR tests for SARS-CoV-2 who also have significant comorbid conditions will remain subjective.

Keywords: COVID-19; fatality; cause of death

INTRODUCTION

During the COVID-19 pandemic, determining the mortality rate has been both an area of emphasis and controversy. The World Health Organization guidelines recommend that a confirmed or suspected COVID-19 death be counted as a COVID-19 fatality.[1] While this is relatively straightforward for patients who test positive for SARS-CoV-2, have no comorbidities, and have a typical clinical presentation, other confounding factors can make determining the cause of death more complicated. The presence of comorbidities, limitations in testing, and secondary causes, such as limited healthcare resources due to the pandemic, can make the relationship to COVID-19 less clear.[2–4] Although these could arguably be classified as "suspected" COVID-19 deaths, this classification is subjective and potentially overcounts COVID-19 fatalities.

Another method to determine COVID-19 mortality is to use "excess mortality," or deaths greater than what would normally be expected for the population given historical data. It is argued that since some fatalities may not be correctly attributed to COVID-19, the total increase in fatalities above what is normally

Corresponding author: **Gilbert Berdine**
Contact Information: Gilbert.Berdine@ttuhsc.edu
DOI: 10.12746/swrccc.v9i40.903

expected for a population elucidates the best approximation of COVID-19 deaths.[5] This method is limited, however, by the accuracy of previous historical data, other confounding causes of mortality, and potentially significant margins of error.[6] Furthermore, it does not differentiate between direct causes of COVID-19 fatality (such as respiratory failure) and secondary causes, and could therefore falsely inflate the fatality rate of a SARS-CoV-2 infection.[3]

Finally, deaths during the summer of 2020 and winter of 2020-2021 show no excess of respiratory deaths (which would be expected for a respiratory virus) but rather an excess of deaths from other causes, such as cardiovascular disease, dementia, suicide, and drug overdose.[7,8] Given that only 6% of reported COVID-19 deaths are in patients without comorbidities, there is potential for significant overlap between COVID-19 presentation and other medical conditions.[9] While it is argued that COVID-19 can exacerbate preexisting conditions and that these patients would not have died "but for" COVID-19, it is also possible that deaths from comorbidities are being misattributed to COVID-19.[6] As COVID-19 deaths can frequently be determined by clinical acumen rather than by quantitative analyses, the potential exists for misattributing fatalities to COVID-19 rather than comorbidities.[10] With the recommendation for "suspected" COVID-19 cases being vague, as well as reported COVID-19 deaths failing to differentiate between confirmed and suspected fatalities, we submit that more rigor is needed to determine which deaths can correctly be attributed to COVID-19. Here we assess the charts of 47 patients who reportedly died from COVID-19, using a scoring system to determine the likelihood that COVID-19 contributed to the cause of death.

Methods

Patients admitted to University Medical Center (UMC) in Lubbock, TX between April 1, 2020 and August 1, 2020 with a final diagnosis of COVID-19, and a disposition of death were included in the study. There were 47 patients who met these criteria. All patients were PCR positive for COVID-19 by time of discharge. The medical records were reviewed by the three independent reviewers (G, J, and H). Cause of death was stratified into one of five categories based on the likelihood that COVID-19 was the actual cause of death. Category 0 considered COVID-19 to be an incidental finding. Patients in this category had a clinical presentation inconsistent with COVID-19 disease. An example would be deterioration of a chronic degenerative central nervous system disease. Category 1 considered COVID-19 to be a possible cause of death, but COVID-19 was less likely than some other cause of death. Patients in this category had illnesses consistent with COVID-19 but had pre-existing conditions known to cause the same clinical presentation and past history of similar events. An example would be a patient with end stage renal disease and cirrhosis who missed two dialysis sessions due to a positive PCR test for COVID-19. Category 2 considered COVID-19 to be a possible cause of death and approximately equal likelihood to some other cause of death. Patients in this category had pre-existing conditions capable of causing the clinical picture but without a past history of similar events. An example would be a patient with a past history of congestive heart failure using home oxygen but without previous hospitalizations for acute respiratory failure. Category 3 considered COVID-19 to more likely be the cause of death than some other cause of death. Patients in this category had pre-existing conditions associated with the clinical picture but of clinical severity not likely to cause a sudden decompensation with death. An example would be a patient with past history of hypertension and congestive heart failure but who had never required home oxygen. Category 4 considered COVID-19 to be the only plausible cause of death. Patients in this category had no past histories of other illnesses that could have plausibly caused the clinical picture. An example would be a patient who died from acute lung injury with no significant past medical history and no plausible environmental exposures other than COVID-19. The reviewers scored the records independent of each other. Each reviewer was blinded to the scores of the other reviewers. Body mass index (BMI) and age at time of admission were recorded. This project was reviewed and approved by the Institutional Review Board (IRB# L21–131).

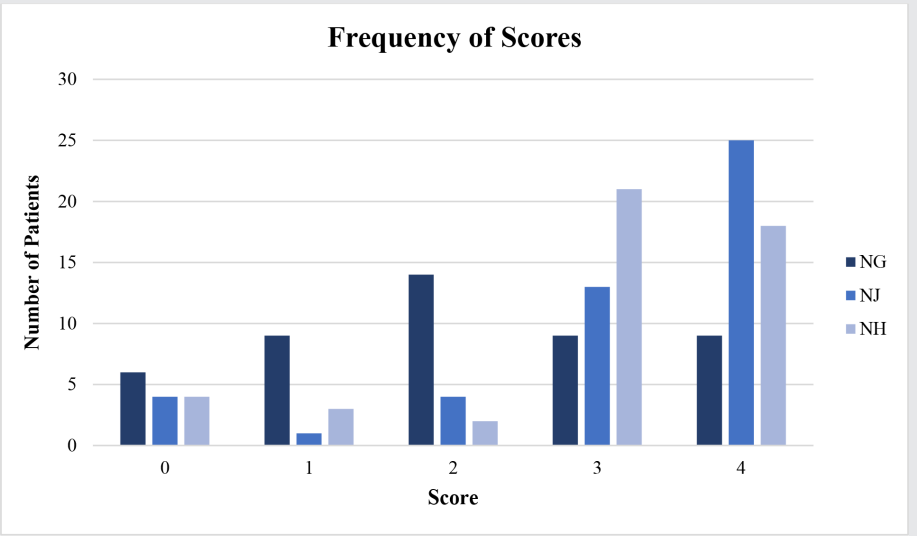

Figure 1. Frequency of Scores for Each Reviewer. Bars correlate to the respective reviewer (G, J, or H).

Results

Patient ages ranged from 33 to 94 years. The mean age ± SD was 65.6 ± 15.7 years; the median age was 67 years. Thirty-six patients were male and 11 patients were female. The majority of patients were Hispanic (n = 23), followed by non-Hispanic White (n = 8), non-Hispanic black (n = 3), and Asian (n = 1); race and ethnicity for 12 patients could not be identified from the record. Obesity is considered a risk factor for COVID-19 severity. Body mass indices ranged from 17.81 to 58.36 kg/m^2 with a mean BMI ± SD of 30.83 ± 8.6 kg/m^2 and a median of 29.51 kg/m^2.

The mean scores were 2.13 for reviewer G, 3.15 for reviewer J, and 2.98 for reviewer H. Adjusted COVID-19 deaths were 25.0/47 (53%) for reviewer G, 37.0/47 (79%) for reviewer J, and 35.5/47 (76%) for reviewer H. The adjusted deaths were calculated as score 0 was 0%, score 1 was 25%, score 2 was 50%,

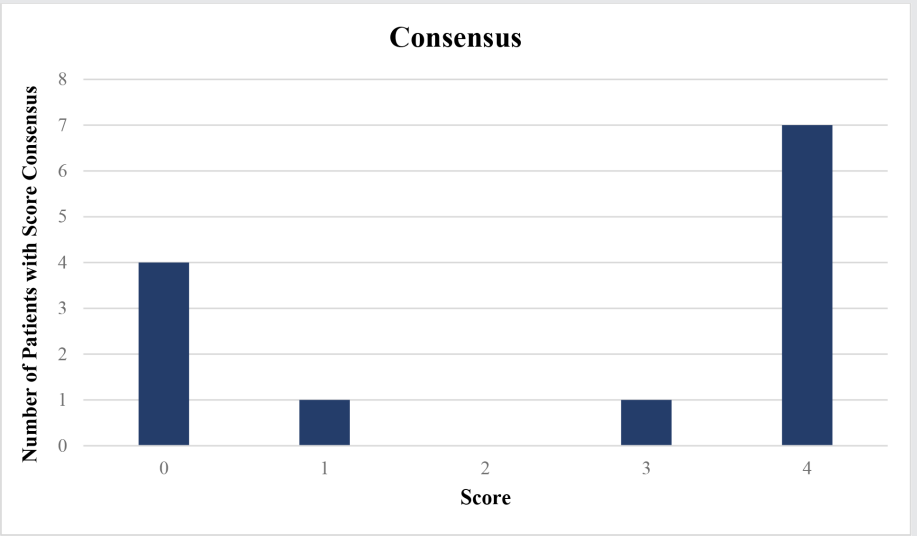

Figure 2. Consensus of Score Among Reviewers. Number of patients with consensus where all three reviewers agreed on the score for the patient.

score 3 was 75%, and score 4 was 100% likely to be a COVID-19 death.

Consensus where all three reviewers agreed on the score for a patient was achieved in 13 patients. Consensus was more likely at the extremes of 0 and 4 with 4 being most likely for consensus. The reviewers had more difficulty reaching consensus for the middle scores where both COVID-19 and alternative diagnoses were plausible. No patient received a consensus score of 2.

The intraclass correlation among the three reviewers is 0.56, with a 95% confidence interval of (0.29, 0.74). Among them, the intraclass correlations between reviewers G and J, G and H, and J and H are 0.45 (0.01, 0.71), 0.52 (0.10, 0.75), and 0.77 (0.62, 0.86), respectively. Therefore, the agreement between reviewer G and J/H is considered to be poor, while the agreement between J and H is considered moderate. Interestingly, scores from reviewer G show a more uniform distribution across the categories, while those from reviewers J and H are skewed to higher values. The differences among the reviewers might be partially attributed to which degree a reviewer believes, *a priori*, that a death is likely to be associated with COVID-19, in parallel with the understanding of the definition of the categories.

Discussion

Determining the cause of death in COVID-19 cases has been an area of significant discussion. Current WHO guidelines allow for clinical acumen when determining the cause due to COVID-19, as well as the inclusion of "suspected" deaths. Early in the course of the pandemic, prior to the availability of PCR testing for SARS-CoV-2, there were legitimate concerns about missing cases due to the absence of any test that could confirm COVID-19. After PCR tests were widely available, however, the concerns have shifted to over-diagnosis of COVID-19 due to excessive cycle counts in the PCR test and the absence of any test that could confirm disease was due to SARS-CoV-2 rather than other etiologies producing lung injury as well as illness due to the immune response rather than the infectious agent. While these concerns are understandable given limitations in testing, the confounding comorbidities, and an urgent need for fatality statistics, this also allows for a spectrum of interpretations.

In this study the greatest consensus on COVID scores occurred with the highest or lowest likelihood of COVID-19 involvement, with far less consensus for middle or "gray area" scores. This suggests that classification is straightforward when COVID-19 is the only plausible explanation for death, or when the nature of the death, such as trauma or other cause unrelated to acute lung injury, makes exclusion of COVID-19 obvious. Although the current Internal Classification of Diseases (ICD) does allow for differentiation between "virus identified" (U07.1) and "virus not identified" (U07.2) diagnoses, these distinctions may have been important in March of 2020, but are no longer relevant with easy availability of PCR tests. Furthermore, while the "viruses not identified" category includes "suspected" and "probable" COVID-19 fatalities, the classification "suspected" or "probable" is limited and relies heavily on physician decision making.[11] Autopsies have also been employed to confirm COVID-19 deaths, although this is not feasible on a large scale.[12] The current problems of classification involve more difficult distinctions such as whether COVID-19 was the primary cause with serious comorbidities, or COVID-19 was the precipitating event in a chronic disease caused by serious comorbidities, or COVID-19 was an incidental bystander in a cascade of organ failure caused by serious chronic comorbidities. Therefore, we submit that more rigorous yet practical criteria could be used for certifying COVID-19 fatalities. While it may not be feasible for multiple physicians to determine the cause of death for the same patient, other methods could be useful. For example, using a standardized scale that accounts for comorbidities, key clinical signs, viral load, etc. could provide a quantifiable metric for the level of certainty for COVID-19 deaths. Other rating scales, such as the Hamburg scoring system, indicate the likelihood of death due to COVID-19 based on clinical judgment, similar to the one used here.[13] While this adds a layer of complexity to COVID-19 statistics, it could provide a more accurate fatality rate for a SARS-CoV-2 infection. Standardized training in

assessing COVID-19 fatalities or death certification may also be beneficial.[10] Although scoring systems as used in this study can improve consensus among reviewers as to cause of death in patients with positive PCR tests for SARS-CoV-2 who also have significant comorbid conditions, in the absence of an objective measure of COVID-19 disease, determination of cause of death in these patients will remain a subjective process.

Finally, the need for more robust COVID-19 death certification is highlighted by controversies relating to COVID-19 case and fatality counts. Some have raised concerns that lack of rigor in diagnostic or death certification criteria makes COVID-19 statistics not only inaccurate but vulnerable to political or bureaucratic manipulation. While the evidence for this is limited at best, the possibility and perception of either manipulation or low rigor may nevertheless cause a decline in public trust in science and the ability for political organizations to cooperate on public health measures.[14] While science is not free from bias, it should nonetheless provide information that is as objective as possible to allow more effective public discourse. However, when the information itself fails to invoke confidence and is subject to significant skepticism, the quantitative basis for policy and public health discussions may become more tenuous. Where areas of uncertainty exist, acknowledgment of these uncertainties should be universally stated rather than adopting a false consensus.[15] Differences among political parties regarding COVID-19 data and policy can also hamper cooperativity and foster general mistrust in government or scientific institutions, which can affect implementation and adherence to public health policy.[16] Quantifying potential COVID-19 deaths using a rating scale could acknowledge levels of uncertainty in this process and provide a middle ground between polarized views regarding the severity of the COVID-19 pandemic. Although a global pandemic can provide many extenuating circumstances, we submit that institutions must balance rapid reporting and universal applicability of public health measures with quality and accuracy. Given the need for accurate fatality data as well as the potential for error in certifying COVID-19 fatalities, we submit that more rigorous criteria could be useful to both public health officials and the general public as well.

Article citation: Peterson CJ, Makram Fanous J, Mallah H, Yang S, Berdine G. Cause of death in fatal cases associated with positive COVID-19 PCR tests. The Southwest Respiratory and Critical Care Chronicles 2021;9(40):3–8
From: Department of Internal Medicine (CJP, JMF,HM, GB), Texas Tech University Health Sciences Center, Lubbock, Texas; Department of Biostatistics (SY), Pennington Biomedical Research Center, Baton Rogue, LA
Submitted: 7/6/2021
Accepted: 7/10/2021
Reviewer: Kenneth Nugent MD
Conflicts of interest: none

References

1. Amoretti MC, Lalumera E. COVID-19 as the underlying cause of death: disentangling facts and values. History Philosophy Life Sciences 2021;43(1):4.
2. Beaney T, Clarke JM, Jain V, et al. Excess mortality: the gold standard in measuring the impact of COVID-19 worldwide? J Royal Society Medicine 2020;113(9):329–334.
3. Viglione G. How many people has the coronavirus killed? Nature 2020;585(7823):22–24.
4. Sharma R, Kuohn Lindsey R, Weinberger DM, et al. Excess cerebrovascular mortality in the United States During the COVID-19 pandemic. Stroke 2021;52(2):563-572.
5. Fineberg HV. The toll of COVID-19. JAMA 2020;324(15): 1502–1503.
6. Kiang MV, Irizarry RA, Buckee CO, et al. Every body counts: measuring mortality from the COVID-19 Pandemic. Annals Internal Medicine 2020;173(12):1004–1007.
7. Excess deaths associated with COVID-19. Centers for Disease Control and Prevention. provisional death counts for coronavirus disease (COVID-19) Web site. https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm. Updated Mar 14, 2021. Accessed Mar 29, 2021.
8. Aburto JM, Kashyap R, Schöley J, et al. Estimating the burden of the COVID-19 pandemic on mortality, life expectancy and lifespan inequality in England and Wales: a population-level analysis. J Epidemiology Community Health 2021: jech-2020-215505.
9. Weekly updates by select demographic and geographic characteristics. centers for disease control and prevention. provisional death counts for coronavirus disease 2019

(COVID-19) Web site. https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#Comorbidities. Updated Mar 24, 2021. Accessed Mar 29, 2021.

10. Gill JR, DeJoseph ME. The importance of proper death certification during the COVID-19 pandemic. JAMA 2020; 324(1):27–28.

11. COVID-19 coding in ICD-10. World Health Organization. https://www.who.int/classifications/icd/COVID-19-coding-icd10.pdf?ua=1. Accessed Mar 31, 2021.

12. Elezkurtaj S, Greuel S, Ihlow J, et al. Causes of death and comorbidities in hospitalized patients with COVID-19. Scientific Reports 2021;11(1):4263.

13. Giorgetti A, Orazietti V, Busardò FP, et al. Died with or died of? Development and Testing of a SARS CoV-2 Significance score to assess the role of COVID-19 in the deaths of affected patients. Diagnostics (Basel) 2021;11(2):190.

14. Kreps SE, Kriner DL. Model uncertainty, political contestation, and public trust in science: Evidence from the COVID-19 pandemic. Science Advances 2020;6(43):eabd4563.

15. van der Bles AM, van der Linden S, Freeman ALJ, et al. The effects of communicating uncertainty on public trust in facts and numbers. Proceedings National Academy Sciences 2020;117(14):7672–7683.

16. Lazarus JV, Ratzan S, Palayew A, et al. COVID-SCORE: A global survey to assess public perceptions of government responses to COVID-19 (COVID-SCORE-10). PloS one 2020;15(10):e0240011–e0240011.