COVID-19 and Sickle Cell Disease–Related Deaths Reported in the United States

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Abstract
Sickle cell disease (SCD) is associated with increased risk of poor health outcomes from respiratory infections, including COVID-19 illness. We used US death data to investigate changes in SCD-related mortality before and during the COVID-19 pandemic. We estimated annual age- and quarter-adjusted SCD-related mortality rates for 2014-2020. We estimated the number of excess deaths in 2020 compared with 2019 using the standardized mortality ratio (SMR). We found 1023 SCD-related deaths reported in the United States during 2020, of which 86 (8.4%) were associated with COVID-19. SCD-related deaths, both associated and not associated with COVID-19, occurred most frequently among adults aged 25-59 years. The SCD-related mortality rate changed <5% year to year from 2014 to 2019 but increased 12% in 2020; the sharpest increase was among adults aged ≥60 years. The SMR comparing 2020 with 2019 was 1.12 (95% CI, 1.06-1.19). Overall, 113 (95% CI, 54-166) excess SCD-related deaths occurred in 2020.

Keywords
sickle cell disease, COVID-19, mortality
(ie, 3-month quarters), overall and according to whether the death was associated with COVID-19. We also tested the significance of differences using the Pearson $\chi^2$ test, with $P < .05$ considered significant.

We calculated annual SCD-related death rates per 100,000 US population from 2014 through 2020 and examined trends over time. Denominator data were obtained from the 2014-2020 national population projections provided by the US Census Bureau. Annual rates were initially adjusted for both age at death and quarter of death. We further examined age-specific rates adjusted for quarter of death. For all rates, we estimated the corresponding 95% CIs using Poisson regression. We assessed the year-to-year variation (percentage difference) in rates. Significant differences in death rates were based on nonoverlapping 95% CIs.

We calculated the expected numbers of deaths in 2020 by applying 2019 age- and quarter-specific SCD-related death rates to 2020 population estimates. We calculated standardized mortality ratios (SMRs) as the number of observed deaths divided by the number of expected deaths. We also estimated the proportion of excess deaths attributable to COVID-19. This activity was reviewed by the Centers for Disease Control and Prevention (CDC), determined to be public health surveillance not requiring institutional review board review, and conducted consistent with applicable federal law and CDC policy (see eg, 45 CFR part 46, 21 CFR part 56; 42 USC §241(d); 5 USC §552a; 44 USC §3501 et seq).

### Results

In 2020, a total of 1023 SCD-related deaths occurred in the United States, of which 86 (8.4%) had COVID-19 as the underlying or contributing cause of death (Table 1). Overall, SCD-related deaths occurred most frequently among non-Hispanic Black/African American people and young adults aged 25-59 years. The distribution of deaths by COVID-19 status differed significantly by quarter; COVID-19–associated deaths occurred more frequently in quarters 2 and 4 than in quarters 1 and 3. We found no significant differences in the distributions of race and ethnicity or age group by COVID-19 status.

### Table 1. Characteristics of overall sickle cell disease (SCD)–related deaths and SCD-related deaths with and without COVID-19 listed among causes of death reported to occur from January 1 through December 31, 2020, in the provisional US multiple cause of death data set

| Characteristic | SCD-related deaths (n = 1023) | SCD-related deaths with COVID-19 ICD-10 codeb (n = 86) | SCD-related deaths without COVID-19 ICD-10 codeb (n = 937) | $P$ valuec |
|---------------|-----------------------------|-------------------------------------------------|-------------------------------------------------|----------|
| Quarter, no. (%) |                             |                                                 |                                                 |          |
| Quarter 1 (January–March) | 255 (24.9) | 6 (7.0) | 249 (26.6) | <.001 |
| Quarter 2 (April–June) | 263 (25.7) | 30 (34.9) | 233 (24.9) |
| Quarter 3 (July–September) | 268 (26.2) | 20 (23.3) | 248 (26.5) |
| Quarter 4 (October–December) | 237 (23.2) | 30 (34.9) | 207 (22.1) |
| Race, no. (%) |                             |                                                 |                                                 | .46      |
| Non-Hispanic Black/African American | 837 (81.8) | 73 (84.9) | 764 (81.5) |
| Non-Hispanic White | 25 (2.4) | 3 (3.5) | 22 (2.3) |
| Non-Hispanic Other | 161 (15.7) | 10 (11.6) | 151 (16.1) |
| Age, no. (%), ye |                             |                                                 |                                                 | .07      |
| 0-24 | 87 (8.5) | 5 (5.8) | 82 (8.8) |
| 25-59 | 703 (68.7) | 53 (61.6) | 650 (69.4) |
| ≥60 | 233 (22.8) | 28 (32.6) | 205 (21.9) |

Abbreviation: ICD-10, International Classification of Diseases, Tenth Revision.

aData source: Centers for Disease Control and Prevention.16

bData source: Centers for Disease Control and Prevention.18

$\chi^2$ test of significance of difference in distribution of characteristic between SCD-related deaths with a COVID-19 ICD-10 code and SCD-related deaths without a COVID-19 ICD-10 code. $P < .05$ was considered significant.

dDeaths grouped by race and ethnicity reported on death certificate. Non-Hispanic Other includes American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islander, >1 race, race unknown, and Hispanic origin.

eDeaths grouped by age at death reported on death certificate.
Table 2. Sickle cell disease (SCD)–related age-standardized mortality ratio estimates for 2020 compared with 2019 in the United States, by quartera

| Quarter                        | Age-standardized mortality ratio (95% CI) | % Change 2020 vs 2019 (95% CI) | No. of excess deaths (95% CI) |
|--------------------------------|------------------------------------------|--------------------------------|------------------------------|
| Total                          | 1.12 (1.06-1.19)                         | 12 (6 to 19)                   | 113 (54 to 166)              |
| Quarter 1 (January–March)      | 1.09 (0.96-1.23)                         | 9 (–4 to 23)                  | 21 (–11 to 47)               |
| Quarter 2 (April–June)         | 1.23 (1.08-1.37)                         | 23 (8 to 37)                  | 48 (19 to 71)                |
| Quarter 3 (July–September)     | 1.30 (1.14-1.45)                         | 30 (14 to 45)                 | 62 (33 to 84)                |
| Quarter 4 (October–December)   | 0.93 (0.81-1.05)                         | –7 (–19 to 5)                 | –18 (–55 to 11)              |

aData source: Centers for Disease Control and Prevention.16

The SMR comparing total 2020 SCD-related deaths with the number of deaths expected based on 2019 data was 1.12 (95% CI, 1.06-1.19), with an estimated 113 (95% CI, 54-166) excess deaths (Table 2). Quarter-specific SMRs for SCD-related deaths were 1.09, 1.23, 1.30, and 0.93 for quarters 1 through 4, respectively. In each of the first 3 quarters of 2020, excess SCD-related death estimates exceeded the number of reported SCD-related deaths associated with COVID-19; COVID-19 was estimated to explain 6 of 21 (28%), 30 of 48 (62%), and 20 of 62 (32%) excess deaths in quarters 1, 2, and 3, respectively. In contrast, in quarter 4, the number of reported SCD-related deaths associated with COVID-19 exceeded the excess death estimate.

Discussion

This investigation of SCD-related mortality during the COVID-19 pandemic in comparison with previous years identified an increase in SCD-related mortality during the pandemic. SCD-related deaths occurred most frequently among young adults aged 25-59 years, regardless of association with COVID-19. Conversely, during the study period, COVID-19 deaths in the US general population were most commonly reported among adults aged ≥65 years.21

Overall, we estimated a 12% excess in SCD-related deaths during 2020 compared with 2019, which aligns with reports of excess deaths for the general US population in 2020.22,23 Our estimates of quarter-specific excess deaths were not uniform. In quarter 1, we found a nonsignificant increase in observed SCD-related deaths compared with expected SCD-related deaths. In quarters 2 and 3, we found a significant increase in observed SCD-related deaths compared with expected SCD-related deaths. These findings aligned with our expectations, given the timing of the start of the COVID-19 pandemic and that the largest number of excess deaths for the general US population in 2020 was also observed during quarters 2 and 3.21 However, COVID-19 deaths did not explain all of the estimated excess SCD-related deaths during the first 3 quarters of 2020. Possible reasons for this discrepancy include undercounting of COVID-19 deaths and indirect COVID-19 pandemic effects related to reduced access to or use of health care, for example, because of fear of seeking care in emergency departments (EDs). Studies in the general US population reported that other causes of death, such as heart disease, also increased in 202022,23 and that in the 10 weeks after declaration of the COVID-19 national emergency, the number of ED visits in the United States for myocardial infarction and stroke declined 23% and 20%, respectively.24

In contrast to our findings for the first 3 quarters, we found that in the fourth quarter of 2020, the number of COVID-19 SCD-related deaths exceeded the estimated number of excess deaths. This finding may be partly explained by incomplete reporting of deaths in the provisional data set, whereby COVID-19 death reporting may have been prioritized. Alternatively, increased mortality from COVID-19 may have been offset by lower mortality from other causes that are historically higher in winter months; for example, the marked reduction in influenza activity during 2020.22 Given the established risks for influenza-related morbidity among people with SCD,3 the low level of influenza may have substantively affected SCD-related mortality in quarter 4.

Our findings had several limitations. First, the provisional counts for COVID-19 deaths were based on death certificates received and coded as of March 1, 2021, which may have been incomplete, especially for the final weeks of 2020. Second, reliance on ICD-10 coding may have led to misclassification of the cause of death. The ICD-10 code for COVID-19 was implemented in March 2020.19 Although NCHS staff members reviewed and recoded death certificates from the first quarter of 2020 to capture data on COVID-19 deaths that occurred before implementation of the COVID-19 ICD-10 code, some COVID-19 deaths were likely missed. A previous study indicated that despite the NCHS recodes, COVID-19 was underreported on death certificates in the early months of the pandemic.22 We defined SCD-related deaths as deaths with an ICD-10 code that indicated SCD was a contributing factor. However, because not all decedents with SCD are reported as having a death related to SCD,25 some deaths among people with SCD could not be identified and included in this analysis. Third, because we did not have population-based data on the total number of people with SCD who became infected with SARS-CoV-2,
we could not assess COVID-19 fatality rates. A study describing COVID-19 outcomes among people with SCD in New York from January 1, 2020, to January 21, 2021, noted that people with SCD were more likely to visit the ED and be hospitalized than matched controls without SCD; however, the mortality rate was similar among people with SCD compared with matched controls, suggesting that effective treatment may improve outcomes.26 It must be noted, however, that controls without SCD in this study were matched to people with SCD based on age, sex, race and ethnicity, and major comorbidities, indicating the control group may have had substantial comorbidities and may not be reflective of the general population.

People with SCD are at increased risk of poor outcomes with respiratory infections; roughly one-third of acute chest syndrome events among people with SCD are attributable to respiratory infections.3,4 Beyond their underlying disease, some people with SCD face socioeconomic and health care challenges that might further complicate efforts to prevent or access timely care for respiratory infections, including COVID-19 illness. These challenges include low educational attainment and employment related to stroke and other disabling SCD complications,27,28 lack of health care providers with expertise in treating SCD and the corresponding downstream effects of delayed health care and high rates of ED use,28 and both structural and interpersonal racism in the health care system.28

Our findings indicate that COVID-19 may have contributed to increases in SCD-related mortality in the United States in 2020. This finding, together with the findings of published case series and a registry-based study that documented elevated COVID-19 morbidity and mortality rates among relatively young SCD patients,6-13,15,26 provide empirical evidence of the risk of severe outcomes among people with SCD who contract COVID-19. It is critical for eligible people with SCD to receive the COVID-19 vaccine to prevent COVID-19 illness. Also, early recognition of COVID-19 symptoms and appropriate testing are particularly important for this patient population so that treatment can be initiated immediately.

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Supplemental Material
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