Excess deaths among adults with sickle cell disease in 2020 compared to prior years

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Abstract
In 2020, there was a 20% increase in excess deaths in the USA due to COVID infections but also to changes in the healthcare system due to the pandemic. We hypothesized that people living with sickle cell disease (SCD) may be vulnerable to these changes as SCD can lead to rapid decompensation. We examined all deaths of people with SCD at our center in 2020. Cause of death was determined, clinical variables, and healthcare utilization, and the presence of COVID infection, sepsis, and acute organ failure during the death event was obtained from the electronic medical record. Deaths in 2020 were compared to deaths in 2017–2019. In 2020, deaths increased 244% (22 vs 9), but acute or previous COVID infections were identified in only 36% of 2020 deaths. People who died in 2020 were more likely to have developed acute organ failure during the death event (70.6% vs 21.1%, \( p = 0.003 \)) compared to prior years. They were also more likely to have a history of stroke and more frequent hematology clinic visits. Deaths in 2020 doubled compared to prior years and COVID infection could not account for all of this excess mortality. People who died in 2020 may have had more severe disease as suggested by having more clinic visits and higher rates of stroke and were more likely to develop organ failure during the death event. This demonstrates that people with SCD may be especially vulnerable to delays in care. Larger multicenter studies should be conducted to examine this further.

Keywords Hematology · Sickle cell disease · COVID-19 · Mortality · Cause of death

Background
In 2020, there was an over 20% increase in excess deaths in the USA with the largest impact seen in the non-Hispanic Black population and in people age \( \geq 65 \) [1]. COVID-19 infection could not account for the entire increase, and deaths were also attributed to the strain on the healthcare system and delays in patients seeking care due to the pandemic [1]. SCD is the most common inherited red blood cell disorder affecting \( \sim 100,000 \) Americans and the majority identify as non-Hispanic Black [2]. COVID-19 infection caused increased rates of hospitalization and death in people with SCD compared to the general population [3–5]. A study using US vital statistics showed a 12% increase in deaths in 2020 compared to 2019 in people living with SCD, but only 8.4% were associated with COVID-19 [6]. We sought to expand upon these data. We examined individuals with SCD who received their care at our Sickle Cell Center in Bronx New York and died in 2020 comparing their clinical characteristics to patients who died in the previous 3 years. We hoped this would allow us to identify patient characteristics that predispose to poor outcomes to possibly prevent future deaths.

Methods
This study was approved by the Albert Einstein College of Medicine IRB; informed consent was waived. Death date was collected from our electronic medical records (EMR) and death certificates. Clinical variables collected from EMR included age at time of death, gender, race, genotype, sickle cell related comorbidities including end stage renal disease (ESRD), venous thromboembolism (VTE), stroke,
acute chest, hydroxyurea use, use of chronic scheduled blood transfusions (simple or exchange), and healthcare utilization in the 12 months prior to death date. Healthcare utilization included emergency room visits not resulting in an admission, hospital admissions, and hematology clinic visits including in-person and televisits at our center.

To attribute cause of death, two hematologists performed manual review of the EMR blinded from each other and deaths were categorized as due to sudden death, cardiovascular, sepsis (including COVID-19), stroke, acute organ failure (including multi organ failure syndrome), chronic organ failure, hemorrhage (not including hemorrhagic stroke), and unknown when records of the death event were not available. A third hematologist served as a tie breaker. Patients were also categorized as having sepsis (yes or no) and acute organ failure (yes or no) (liver or renal) during the death event. For example, if a patient developed acute liver failure then suffered a brain bleed from hepatic coagulopathy cause of death would be stroke, but the presence of acute organ failure (liver) would be noted.

Decedents in 2020 were divided in four categories: Acute COVID-19 was diagnosed if there was a positive PCR swab during the hospitalization leading to death or in the prior 2 weeks. Past COVID-19 was defined by a negative PCR swab during the death event but a positive PCR swab and/or antibody test more than 2 weeks before the death event with documented resolution of symptoms. No evidence of COVID-19 infection was defined by a negative PCR swab and/or antibody test documented in the EMR and no positive tests present or noted per prior patient report. Unknown COVID-19 status was unknown if no testing was present in the EMR.

To examine how 2020 decedents differed from decedents in the prior 3 years, we compared all available clinical and hematological variables using the Kruskal Wallis test for continuous variables and chi² tests for dichotomous variables. To examine the impact of COVID-19 infection on deaths, 2020 decedents with known COVID-19 (acute or past) were compared to those with no COVID-19. Unknown COVID-19 status patients were excluded.

Results

Our center serves approximately 1000 adult patients, and this number has been relatively stable from 2017 to 2020. In the years 2017, 2018, and 2019, the number of death were 9, 10, and 8, respectively. In 2020, there were 22 patient deaths, a surge of 244%. This increase was most evident in the first three quarters of the year (Fig. 1). When baseline clinical characteristics were compared with decedents in the prior 3 years, patients who died in 2020 were more likely to have history of stroke and had more hematology clinic visits (Table 1). Otherwise, there was no difference in age, gender, genotype, hydroxyurea use, use of chronic transfusions, history of sickle cell related comorbidity, or ED visits or admissions in the prior 12 months (Table 1). The two patients on chronic transfusions who died in 2020 did not have a change in transfusion rate prior to death.

When the death events were examined, patients who died in 2020 were more likely to have experienced acute organ failure, especially liver failure, during the death event than prior years (Table 1). When COVID-19 status among the decedents in 2020 was examined, 3 had an acute COVID-19 infection, five had past COVID-19, 8 had no COVID-19, and 6 had unknown COVID-19 status. Compared to 2020 patients without COVID, 2020 patients with acute or past COVID infection used less hydroxyurea ($p=0.02$) and had
Table 1 Decedents by year of death

|                          | 2017–2019 | 2020 | p    |
|--------------------------|-----------|------|------|
| n                        | 24        | 22   |      |
| **Baseline clinical characteristics** |           |      |      |
| Age 50% (25%/75%)        | 44 (31/54) | 52 (39/61) | 0.1 |
| Gender (% female)        | 55.6      | 54.6 | 0.9  |
| Genotype (% SS/SB0)      | 81.5      | 95.5 | 0.1  |
| Hydroxyurea (% taking)   | 38.5      | 40.1 | 0.9  |
| Chronic transfusions (%) | 12.5      | 9.1  | 0.7  |
| Hx of ESRD (%)           | 22.2      | 23.8 | 0.9  |
| Hx of VTE (%)            | 40.1      | 31.8 | 0.5  |
| Hx of stroke (%)         | 31.8      | 63.6 | 0.04 |
| Hx of acute chest (%)    | 62.5      | 77.3 | 0.3  |
| ED visits 50% (25%/75%) | 0 (0/2)   | 0 (0/3) | 0.8 |
| Admissions 50% (25%/75%) | 2 (1/7)  | 4 (2/7) | 0.09 |
| Heme clinic visits 50% (25%/75%) | 3 (0/8) | 7.5 (3/10) | 0.05 |
| **During death event**   |           |      |      |
| Sepsis (%)               | 42.0      | 47.0 | 0.8  |
| Acute organ failure, either (%) | 21.1    | 70.6 | 0.003 |
| Acute liver failure (%)  | 15.8      | 52.9 | 0.02 |
| Acute renal failure (%)  | 21.1      | 47.1 | 0.1  |
| **Cause of death**       |           |      |      |
| Sudden death n (%)       | 11.1      | 4.6  | 0.4  |
| Cardiovascular n (%)     | 14.8      | 13.6 | 0.9  |
| Sepsis (%)               | 11.1      | 13.6 | 0.8  |
| Stroke (%)               | 7.4       | 9.1  | 0.8  |
| Acute organ failure (%)  | 7.4       | 22.7 | 0.1  |
| Chronic organ failure (%)| 14.8      | 18.2 | 0.7  |
| Hemorrhage (%)           | 3.7       | 4.6  | 0.8  |
| Unknown (%)              | 39.6      | 13.6 | 0.2  |

Conclusions

SCD deaths at our center more than doubled in 2020 and rate of organ failure during the death event more than tripled compared to prior years, yet many patients had no confirmed history of COVID-19. Compared with prior years, 2020 decedents were more likely to have a history of stroke and more hematology clinic visits and were more likely to experience acute organ failure during the death event.

In 2017–2019, we had an average of 9 deaths/year at our center, but in 2020, 22 patients died, but only 3 had acute and 5 had past COVID-19. Therefore, acute or past COVID-19 infections did not account for all of excess deaths. In 2020, COVID related deaths in NY state in the general population peaked in April and May [1, 7]. However, when we examined our death rates by quarter rates were stable in previous years but in 2020 peaked during the first three quarters. This suggests the cause of the excess deaths in 2020 was something that occurred during the first three quarters of the year, not only when COVID-19 deaths were peaking in NY state. We suspect excess deaths in adults with sickle cell disease in 2020 were contributed to by delays in care caused by both patient reluctance to present to the hospital and changes in healthcare delivery due to the pandemic. Over 70% of patients who died in 2020 developed acute organ failure compared to just 21% in the prior 3 years. Further, patients who died in 2020 may have had more severe disease as evidenced by 64% having a history of stroke compared to 32% in prior years and by higher rates of annual clinic visits prior to death. We hypothesize that patients with more severe disease took longer to receive appropriate treatment resulting in higher rates of organ failure and death.

Our study has limitations: it is small and took place at a single center. While we examined all death events for which we had data, a few took place outside of our center so cause of death was listed as unknown.

This study emphasizes the need for further studies on the impact the pandemic had on the health of adults with SCD. Patients with SCD are a medical complex population and quick access to quality care is vital for their health. Strategies are needed to mitigate the negative impact that reductions in access to health care have on this vulnerable population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-022-04994-6.

Author contribution SAC contributed to study design, protocol writing and development, data acquisition, data interpretation, and manuscript writing. HB contributed to data acquisition, data interpretation, and manuscript writing. JS contributed to data interpretation and manuscript writing. JB contributed to data acquisition and data interpretation. MT contributed to data acquisition and data interpretation. LV contributed to data acquisition and data interpretation. AC contributed to data acquisition and data interpretation. CM contributed to study design, protocol writing and development, data acquisition, data interpretation, and manuscript writing.

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Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Waiver of informed consent was granted by the institutional IRB as all data obtained was retrospective and all identifying information was removed.

Conflict of interest Dr. Susanna Curtis declares participating in consultancy boards with Global Blood Therapeutics and Novartis. Dr.
Caterina Minniti declares consultancy with Global Blood Therapeutics, Novartis, Forma, Novo Nordisk, Chiesi, F. Hoffmann-La-Roche, Bluebird Bio, CSL Behring.

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