STIMULUS REPORT

blood advances

Impact of sickle cell trait on morbidity and mortality from SARS-CoV-2 infection

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Key Points

- There is no impact of SCT on respiratory, renal, or circulatory complications or mortality in patients with SARS-CoV-2 infection.
- The prevalence of SCT in the hospitalized cohort was significantly higher than the prevalence in the community (12% vs 7.31%).

The COVID-19 pandemic has highlighted racial health disparities within the United States. Although social determinants of health are the most likely drivers of this disparity, it is possible that genetic traits enriched in the black population like sickle cell trait (SCT) could worsen the morbidity and mortality of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients admitted for SARS-CoV-2 infection who identified as black or African American were included in the study (n = 166). Blood remnants were tested for SCT, and clinical data were abstracted from the chart. There was no difference in mortality between those with SCT and those without. There was no difference in respiratory complications between groups, but those without SCT had a much higher burden of chronic lung disease (P = .004). Those with SCT had higher creatinine on admission (P = .004), but no difference in in-hospital renal complications (P = .532). Notably, 12% of the cohort had SCT, which is higher than the expected 7.31% (P = .025). Our study did not show any evidence of increased end organ damage, morbidity, or mortality from SARS-CoV-2 infection among patients with SCT but did show differences in admission creatinine and preexisting lung disease.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has highlighted racial health disparities within the United States. For example, during the first surge in April 2020, predominantly black counties suffered an infection rate 3 times higher and a death rate 6 times higher than predominantly white counties.[1,2] The mechanisms underlying this alarming disparity remain to be fully elucidated, although it has been hypothesized that structural racism directly resulting in higher rates of chronic disease and lower socioeconomic status in the black population may be the driver of some of the observed differences in morbidity and mortality.[2]

In addition to social determinants of health, it is also possible that genetic traits enriched in black populations, such as sickle cell trait (SCT), may worsen the course of SARS-CoV-2 infection. Individuals with SCT often have the same quality of life and mortality as the general population.[3] However, sickle hemoglobin (HbAS)-containing red blood cells can be induced to sickle under conditions of stress (for example, exertion in low oxygen environments), which is believed to account for sudden deaths observed in some individuals with SCT.[3-5] Given that HbAS-containing red blood cells can sickle in low oxygen environments and severe SARS-CoV-2 infection is characterized by hypoxia, we hypothesized that individuals with SCT would have a lower tolerance for this hypoxic state, leading to higher rates of hospital admission as well as a higher mortality rate. This study

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The data that support the findings of this study are available from the corresponding author, L.E.M., upon reasonable request.

Table 1. Patient demographic information, comorbidities, laboratory data on admission, and complications from SARS-CoV-2 infection

Demographics	AA/AC (N = 146)	SCT (N = 20)	P*
Age, y, median (range)	64 (22-103)	66 (22-81)	.550
Male sex	75 (52%)	11 (55%)	.815
HbS, %, mean (range)	–	27.8 (17.8-34)	–
Body mass index (BMI), median (range), kg/m^2	27.87 (16.61-69)	28.85 (19.49-50.52)	.725
Smoking history†			.091
Current	11	4	
Former	33	4	
Never	99	9	
Comorbidities Patients, no.			
Hypertension†	110	14	.779
Obesity (BMI > 30)	52	8	.805
Diabetes mellitus†‡	69	11	.793
Chronic lung disease†	38	0	**.004**
Coronary artery disease†	19	3	1.00
Admission Laboratory tests Median (range)			
Creatinine, mg/dL	1.15 (0.39-32.6)	2.06 (0.56-14.3)	**.004**
EGFR,§ mL/min/1.73 m^2	57.84 (1.25-138.81)	32.64 (3.20-105.01)	**.014**
Lactate dehydrogenase, u/L†	386 (148-966)	330 (202-580)	.267
Hemoglobin, g/dL	12.35 (6.4-16.5)	11.95 (5.8-17.4)	.650
Platelets, cells/uL	218.5 (6-620)	222.5 (128-464)	.509
Lymphocyte, %†	15.4% (0-95%)	12.1% (1-30.1%)	.203
Absolute lymphocyte count, K/uL†	1.05 (0-5.24)	1.07 (0.39-4.97)	.605
Prothrombin time, s†	14.1 (11.9-35.8)	14.2 (12.8-36.5)	.969
Prothrombin time–international normalized ratio†	1.1 (0.9-3.6)	1.1 (1-3.7)	.922
Partial thromboplastin time, s†	32.4 (20.6-150)	35.6 (30.1-150)	.111
D-dimer, ng/mL†	1681.5 (172-10 000)	2480.5 (438-5000)	.232
Fibrinogen, mg/dL†	570.5 (303-936)	651 (233-838)	.648
C-reactive protein, mg/dL†	78.5 (0.4-479.1)	83.7 (0.7-300)	.517
Complications Patients, no.			
Respiratory compromise			.450
None	41	9	
1 to 6 L	55	3	
7 to 15 L	10	1	
Intubation	55	7	
Renal complications			.532
None	83	10	
Renal injury|	46	6	
Renal failure|	17	4	
Cardiomyopathy	14	1	.502
Venous thromboembolism	17	3	.732
Circulatory failure	55	8	1.00

*P values are presented only for those features assessed at admission for at least 130 of the 166 patients.
†Variable with 1 or more patients with data missing. Individuals with missing data are excluded from the table and from the statistical assessment for that variable.
‡Includes asthma, chronic obstructive pulmonary disease, or ILD.
§EGFR calculated with the CKD-Epi equation.
|Renal injury defined as Cr > 1.5 mg/dL or Cr > 50% from baseline (if known). Renal failure defined as new dialysis need.

Table 2. Association of demographic information, comorbidities, and admission laboratory data with mortality

N = 166	P*
Age	.027
Male sex	.822
SCT	.732
BMI	.538
Smoking history†	.573
Hypertension†	.774
Diabetes mellitus†	**.016**
Chronic lung disease†	**.056**
Baseline O_2 requirement†	**.017**
Coronary artery disease†	.149
Admission laboratory tests	
Creatinine	.187
EGFR	.126
Lactate dehydrogenase†	**.036**
Hemoglobin	**.019**
Platelets	.066
Absolute lymphocyte count†	**.005**
D-dimer†	.082

*P values are presented only for those features assessed at admission for at least 130 of the 166 patients.

†Variable with 1 or more patients with data missing. Individuals with missing data are excluded from the table and from the statistical assessment for that variable.

aims to assess whether SCT conveys excess risk of morbidity or mortality from SARS-CoV-2 infection in black patients.

Methods

A multicenter, retrospective analysis of patients who identified as black or African American and who were admitted at Brigham and Women's Faulkner Hospital, Brigham and Women's Hospital, or Massachusetts General Hospital for management of SARS-CoV-2 infection from March 24, 2020 to June 2, 2020 was performed. Patients were identified using an electronic medical record report that selected for race as "black or African American" and a positive SARS-CoV-2 polymerase chain reaction test during that admission. Patient demographics, comorbidities, admission laboratory values, complications of SARS-CoV-2 infection, and status on discharge were abstracted by manual chart review. High-performance liquid chromatography was performed on discarded patient blood samples to test for SCT. Patients with sickle cell disease were excluded from the study. Categorical data were tested using the Fisher exact test. Continuous data were tested using the Wilcoxon rank sum test. A 1-sample test was used to compare a binomial proportion compared with fixed reference proportion. Testing was done at the nominal 0.05 2-sided significance level. This study was approved by the Institutional Review Board of Brigham and Women's Hospital and was conducted according to the Declaration of Helsinki.

Results and discussion

One hundred sixty-six patients who identified as black or African American admitted for SARS-CoV-2 infection are included in the analysis. Twenty patients had SCT (HbAS), 143 had normal hemoglobin (AA), and 3 had hemoglobin C trait (AC). The 146 patients with AA and AC hemoglobin were pooled for analysis. Patient demographics, comorbidities, and laboratory values on admission as well as complications of SARS-CoV-2 infection were assessed by SCT status and are shown in Table 1. The prevalence of SCT is 7.31% among African Americans,[6] and 12% (n = 20) of this cohort had SCT ($P = .025$). In-hospital mortality was also assessed. Among patients without SCT, 13% died in the hospital (n = 19/146) compared with 15% of patients with SCT (n = 3/20) ($P = .732$). The association between mortality and patient characteristics is shown in Table 2.

The higher morbidity and mortality from SARS-CoV-2 infection in African Americans are well documented. Overall, this study showed no difference in morbidity or mortality outcomes between individuals with and without SCT among patients admitted for SARS-CoV-2 infection, which mirrors the results from *International Classification of Diseases, Tenth Revision* code analysis by Singh et al.[7] However, there were a few notable differences between the 2 groups. At the time of admission, individuals with SCT had significantly higher creatinine (median: 2.06 vs 1.15; $P = .004$) and lower EGFR ($P = .014$) than those without SCT, consistent with the known higher rates of EGFR decline in patients with SCT.[8] However, there was no difference in rates of renal insufficiency or renal failure between groups ($P = .532$) as well as no association between EGFR and death ($P = .126$). In addition, we expect to see elevated D-dimer levels in patients with SCT,[9] but our cohort showed no difference in D-dimer levels ($P = .232$) perhaps because infection with SARS-CoV-2 is overwhelmingly proinflammatory attenuating any baseline differences between groups. Furthermore, patients with SCT were much less likely to have a history of chronic lung disease than those without SCT ($P = .004$) with no significant difference in smoking status ($P = .091$). Given the higher prevalence of lung disease among patients without SCT, we would expect this group to have more respiratory complications. However, there was no difference in respiratory complications between patients with SCT and those without ($P = .450$). The significance of this finding is unclear, but the impact of SCT on risk of hypoxia in patients infected with SARS-CoV-2 is an intriguing question.

In addition to the differences in admission laboratory tests and preexisting chronic lung disease, 12% of hospitalized patients with SARS-CoV-2 infection had SCT, which is significantly higher than the reported prevalence of SCT of 7.31% among African Americans[6] ($P = .025$). It is possible that elevated creatinine on presentation in the patients with SCT contributed to the decision to admit to the hospital, which may partially explain the higher rate of SCT seen in hospitalized patients than in the general population. Overall, these data suggest that the presence of SCT may be a risk factor for hospitalization for SARS-CoV-2 infection but does not appear to be a risk factor for increased morbidity or mortality from the infection.

Our study has some limitations. Although this is a multicenter study, it is limited by the restriction to 1 metropolitan area. The exact prevalence of SCT among the centers included in this study is unknown, so it is possible that the prevalence of patients with SCT in the hospital is actually reflective of the surrounding community. It is also a retrospective study and thus prone to unanticipated confounders. Most notably, this study is limited to those with SARS-CoV-2 infection who required hospital admission. A larger prospective study across multiple regions of the United States should be considered to further assess rates of hospitalization and symptomatic SARS-CoV-2

infection by presence or absence of SCT in the African American community.

The increased morbidity and mortality from SARS-CoV-2 infection that is seen in those who identify as black or African American in the United States are alarming and not well understood. It is likely that structural racism directly resulting in higher rates of comorbidities and lower socioeconomic status in the black population is the major contributor to this disparity. Although it is possible that there are genetic contributions to this disparity from variants like SCT, our study did not show any increased end organ damage, morbidity, or mortality from SARS-CoV-2 infection among patients with SCT. The high prevalence of SCT among this cohort of hospitalized patients with SARS-CoV-2 infection is concerning but may be partially attributed to higher baseline creatinine levels in patients with SCT. Nonetheless, this data further support that structural racism rather than genetic susceptibility is likely the primary driver for the disparate outcomes in SARS-CoV-2 infection seen in the United States and highlight the dire urgency to intentionally invest health care and governmental resources in black communities to ameliorate these disparities.

Authorship

Contribution: L.E.M. performed the research and wrote the paper; K.M. performed the research; D.N. analyzed the data; G.M. performed the research; D.M.D. designed the research; R.F. performed the research and edited the paper; H.-S.P. performed the research; K.J. performed the research; and M.O.A. designed the research and wrote the paper.

Conflict-of-interest disclosure: M.O.A. serves on the scientific advisory board of Fulcrum Therapeutics and Global Blood Therapeutics. The remaining authors declare no competing financial interests.

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