Association of Sickle Cell Trait with Risk and Mortality of COVID-19: Results from the United Kingdom Biobank

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Abstract. Sickle cell trait (SCT) carriers inherit one copy of the Glu6Val mutation in the hemoglobin gene and is particularly common in Black individuals (5–10%). Considering the roles of hemoglobin in immune responses and the higher risk for coronavirus disease (COVID-19) among Black individuals, we tested whether Black SCT carriers were at increased risk for COVID-19 infection and mortality according to the United Kingdom Biobank. Among Black individuals who were tested for COVID-19, we found similar infection rates among SCT carriers (14/72; 19.7%) and noncarriers (167/791; 21.1%), but higher COVID-19 mortality rates among SCT carriers (4/14; 28.6%) than among noncarriers (21/167; 12.6%) (odds ratio [OR], 3.04; 95% confidence interval [CI], 0.69–11.82; P = 0.12). Notably, SCT carriers with preexisting diabetes had significantly higher COVID-19 mortality (4/4; 100%) than those without diabetes (0/10; 0%; OR, 90.71; 95% CI, 5.66–∞; P = 0.0005). These findings suggest that Black SCT carriers with preexisting diabetes are at disproportionally higher risk for COVID-19 mortality. Confirmation by larger studies is warranted.

INTRODUCTION

The coronavirus (COVID-19) pandemic has impacted communities worldwide, but its effects are disproportionately expressed in certain groups. The Center for Disease Control reported that non-Hispanic Black individuals are approximately 1.4-times and 2.8-times more likely to test positive for and die of COVID-19, respectively, compared with White individuals.¹ This finding is supported by United Kingdom Biobank (UKB) studies, which found significantly higher positive rates among Black individuals even after adjusting for biological, behavioral, and socioeconomic factors.²,³ Additionally, evidence shows that individuals with chronic conditions such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and sickle cell disease (SCD) are particularly vulnerable to more severe COVID-19 disease.¹,⁴

The intersection of race and SCD makes it important to consider their impact on COVID-19. SCD is a genetic disorder whereby patients inherit two pathogenic mutations of the gene that codes for hemoglobin (Hgb). It mostly affects people of sub-Saharan African descent; therefore, it is common in many Black communities worldwide.⁵,⁶ Although SCD patients are relatively rare, individuals with only one pathogenic mutation, called sickle cell trait (SCD) carriers, are more common. Compared with SCD, which is associated with serious health conditions,⁶–⁹ most SCT carriers are considered asymptomatic. However, approximately 40% of the Hgb in carriers can induce sickling under certain conditions.⁶,⁷ Additionally, recent evidence suggests that Hgb may also have a modulatory role in the immune response against RNA viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹⁰,¹¹

Because of the novelty of the COVID-19 pandemic, it is still unknown how SCT carriers are uniquely affected by the virus because of defective Hgb. The larger number of carriers compared with SCD patients makes studying this condition more relevant to a larger population and more feasible (increased statistical power from larger sample sizes). Therefore, the goal of this study was to examine the association of COVID-19 and SCT carriers. Based on the role of Hgb in immune responses and higher risk for COVID-19 among Black individuals, we hypothesized that SCT was associated with an increased risk for COVID-19 and mortality, especially for Black individuals. Furthermore, we hypothesized that other candidate genetic and lifestyle risk factors as well as comorbidities may modify the risk of COVID-19 for SCT carriers.

METHODS

This study was performed using the UKB, a population-based study with extensive genetic and phenotypic data for approximately 500,000 individuals cross the United Kingdom 40 to 69 years of age at recruitment.¹² Extensive phenotypic and health-related information was available for each participant, including questionnaire answers, biological measurements, lifestyle indicators, and biomarkers in blood and urine. Follow-up information was provided by linking health and medical records. Candidate comorbidities and risk factors [body mass index (BMI), diabetes, chronic obstructive pulmonary disease, hypertension, cancer, stroke, and smoking status] were obtained through the International Classification of Diseases-10 (ICD-10) codes and self-report.

The UKB Axiom SNP array data were available for all subjects, whereas whole-exome sequencing (WES) data were available for approximately 40% of subjects. For subjects without WES data, SCT carriers were identified based on ICD codes alone (i.e., D57.3). Codes for SCD (D57.0, D57.1, D57.2, and D57.8) and β-thalassemia (D56.1) were excluded.

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TABLE 1
Association of SCT with COVID-19 positivity and mortality in the UK Biobank

| Subjects | No. (%) tested for COVID-19 | Positive for COVID-19 | Died of COVID-19 |
|----------|-----------------------------|-----------------------|------------------|
| All      | 500,822                     | 44,724 (8.9%)         | 7,849 (17.5%)    | 495 (6.3%) |
| By race  |                             |                       |                  |
| White individuals | 471,180 | 41,660 (8.8%)         | 7,167 (17.2%)    | 445 (6.2%) |
| Black individuals | 8,017  | 882 (10.8%)           | 181 (21%)        | 25 (13.8%) |
| By SCT status |                   |                       |                  |
| No SCT   | 500,093                     | 44,631 (8.9%)         | 7,828 (17.5%)    | 491 (6.3%) |
| SCT      | 729                         | 93 (12.8%)            | 21 (22.6%)       | 4 (19%)    |
| Black individuals | 7,446  | 791 (10.6%)           | 167 (21.1%)      | 21 (12.6%) |

Cl = confidence interval; OR = odds ratio; SCT = sickle cell trait.
* Standard logistic regression analysis adjusted for age at COVID-19 test and sex.
† Standard logistic regression analysis adjusted for age at COVID-19 test, sex, and race.

For subjects with WES data, carriers were identified using a combination of ICD codes and heterozygous Glu6Val mutations in the HBB gene. Subjects with ICD codes for SCD, homozygous Glu6Val, or double heterozygous (heterozygous Glu6Val mutation plus any known mutations in HBB such as Glu121Lys, Glu121Gln, Asp73Asn, and Val23Ile) were considered to have SCD and removed from the remaining analyses. Blood types (ABO) were inferred from rs8176746 and rs8176719 genotypes, and APOE alleles were inferred from rs7412 and rs429358 genotypes (c2 = T/T, c3 = C/T, and c4 = C/C).

The COVID-19 test results for the UKB participants were provided by Public Health England (for participants residing in England). This information was updated weekly. Additional COVID-19 data are also collected through general practitioner (primary care) data, hospital inpatient data, death data, and critical care data (for COVID-19-positive patients); these data are updated monthly.

Logistic regression analysis with the maximum likelihood estimation method was used to test the associations of SCT and COVID-19 positivity/mortality and adjusted for other known demographic variables (race, age at testing, BMI, and sex). An exact logistic regression analysis was used when the sample size was small (total sample size < 40); we modeled the log odds of binary outcomes as a linear combination of the predictor variables. The estimates provided by exact logistic regression do not depend on asymptotic results caused by small cells. The model diagnosis and goodness of fit were examined using Hosmer and Lemeshow’s test. Specific models used for each test are described in each table.

RESULTS AND DISCUSSION

Based on the ICD codes and mutations in the HBB gene, 729 subjects recorded in the UKB were classified as SCT carriers. Consistent with previous reports, most of the carriers were Black (571/729; 78%). The estimated carrier rate by race was highest for Black individuals (571/8,017; 7.1%) and considerably lower for other races (Asian, 11/13,399 [0.1%]; White, 20/471,180 [0.004%]; mixed race, 40/2,928 [1.4%]; and other, 69/4,605 [1.5%]). It was noted that the carrier rate was significantly higher for females, especially those younger than 45 years at the time of recruitment. For Black individuals, for example, the carrier rate was 7.8% (360/4,633) for females and 6.2% (211/3,384) for males overall (P = 0.009); however, it was 8.9% (82/920) for females and 4.6% (36/783) for males among subjects younger than 45 years at the time of recruitment (P = 0.0007) (Supplemental Table 1). This novel observation warrants confirmation and may suggest higher mortality for men at younger ages.

By December 21, 2020, COVID-19 test results were available for 44,724 subjects (approximately 8.9% [44,724/500,822] of the UKB population). Among those tested for COVID-19, 17.5% (7,849/44,724) had positive results; of these, 6.3% (495/7,849) died of COVID-19 (Table 1). Black individuals had nonsignificantly higher COVID-19 positivity rates (21.0% [181/862] compared to 17.2% [7,167/41,660]; P = 0.94) but significantly higher COVID-19 mortality rates overall (12.6% [21/167] compared to 6.2% [445/7,167]; P < 0.0001). The mean age at the time of the COVID-19 diagnosis was significantly younger for Black individuals (64.5 years) than for White individuals (69.7 years) (P < 0.0001). Similarly, the mean age at the time of death attributable to COVID-19 was significantly younger for Black individuals (71.1 years) than for White individuals (75.1 years) (P < 0.0001). Most of these findings are consistent with those of other published studies.

Compared with individuals who were not SCT carriers, SCT carriers had similar COVID-19 positivity rates but higher COVID-19 mortality rates overall among Black individuals (Table 1). For Black individuals, the positivity rates were 19.7% (14/71) and 21.1% (167/791) for subjects with SCT and without SCT (P = 0.96). The death rate was higher, but not statistically significant, for Black SCT carriers (4/14; 28.6%) than for Black noncarriers of SCT (21/167; 12.6%) (odds ratio [OR], 3.04; 95% confidence interval [CI], 0.69–11.82; P = 0.12).

We also examined whether other candidate demographic and genetic factors as well as comorbidities affected COVID-19 positivity and mortality of Black SCT carriers (N = 71). Most of these variables were not significantly associated with COVID-19 positivity and mortality (Table 2), partially because of the small sample size. However, comorbid diabetes (type 1 diabetes and type 2 diabetes) was more common in SCT carriers who were positive for COVID-19 (4/14; 28.6%) than in SCT carriers who were negative for COVID-19 (7/57; 12.3%) (OR, 2.81; 95% CI, 0.51–13.80; P = 0.21). In particular, diabetes was significantly more common in SCT carriers who died of COVID-19 (4/4; 100%) than in those who survived (0/10; 0%) (OR, 90.71; 95% CI, 5.66–infinite; P = 0.0005).
| Variables                  | COVID-19-positive (N = 14) | COVID-19-negative (N = 57) | OR (95% CI) | P value | Died of COVID-19 (N = 4) | Remained alive (N = 10) | OR (95% CI) | P value |
|----------------------------|-----------------------------|-----------------------------|-------------|---------|--------------------------|--------------------------|-------------|---------|
| Demographic factors       |                             |                             |             |         |                          |                          |             |         |
| Age, mean (SD)            | 64.37 (8.05)                | 64.26 (8.66)                | 1 (0.93–1.07) | 0.97    | 73.86 (4.66)             | 60.57 (5.5)             | 1.98 (1.11–11.62) | 0.009   |
| Sex, no. of females       | 8 (57.1%)                   | 46 (80.7%)                  | 0.32 (0.08–1.36) | 0.08    | 4 (100%)                 | 4 (40%)                  | 0.17 (0.01–1.86) | 0.08    |
| Smoking current/previous  | 2 (14.3%)                   | 18 (31.6%)                  | 0.36 (0.04–1.87) | 0.32    | 1 (25%)                  | 1 (10%)                  | 2.68 (0.00–238.74) | 0.50    |
| BMI, mean (SD)            | 30.09 (4.85)                | 29.99 (4.8)                 | 1 (0.88–1.14) | 0.94    | 32.4 (3.34)              | 29.06 (5.22)             | 1.15 (0.89–1.56) | 0.33    |
| Genetic factors           |                             |                             |             |         |                          |                          |             |         |
| APOE, e4-positive, n      | 3 (21.4%)                   | 19 (33.3%)                  | 0.62 (0.10–2.88) | 0.74    | 2 (50%)                  | 1 (10%)                  | 9.84 (0.35–770.19) | 0.12    |
| ABO, type O, n            | 7 (50%)                     | 28 (49.1%)                  | 1.04 (0.31–3.92) > 0.99 |         | 1 (25%)                  | 6 (60%)                  | 0.37 (0.00–9.28) | 0.57    |
| Comorbidity               |                             |                             |             |         |                          |                          |             |         |
| Diabetes, n               | 4 (28.6%)                   | 7 (12.3%)                   | 2.81 (0.51–13.80) | 0.21    | 4 (100%)                 | 0 (0%)                   | 90.71 (5.66–inf) | 4.70E-04 |
| Obesity (BMI ≥ 30), n     | 6 (42.9%)                   | 28 (49.1%)                  | 0.86 (0.26–2.87) > 0.99 |         | 3 (75%)                  | 3 (30%)                  | 4.94 (0.29–312.26) | 0.26    |
| Chronic obstructive       | 2 (14.3%)                   | 9 (15.8%)                   | 0.89 (0.08–5.19) > 0.99 |         | 0 (0%)                   | 2 (20%)                  | 1.04 (0.14–14.58) | 0.99    |
| Pulmonary disease, n      | 10 (71.4%)                  | 32 (56.1%)                  | 1.94 (0.48–9.48) | 0.37    | 4 (100%)                 | 6 (60%)                  | 2.95 (0.28–inf) | 0.24    |
| Cancer diagnosis, n       | 0 (0%)                      | 8 (14%)                     | 0 (0.00–2.36) | 0.34    | 0 (0%)                   | 0 (0%)                   | 0 (0%) |         |
| Stroke, n                 | 0 (0%)                      | 1 (18%)                     | 0 (0.00–158.0) > 0.99 |         | 0 (0%)                   | 0 (0%)                   | 0 (0%) |         |

**Note:** Supplemental table appears at www.ajtmh.org.

The analysis of variance test was used for continuous variables. Fisher's exact test was used when the expected number of subjects in any cell was < 5.
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