Individuals with sickle cell disease and sickle cell trait demonstrate no increase in mortality or critical illness from COVID-19 - a fifteen hospital observational study in the Bronx, New York

Individuals with sickle cell disease (SCD) or sickle cell trait (SCT) could confer different susceptibility to critical illness and mortality associated with COVID-19 compared to the general population. Most COVID-19 SCD and SCT publications to date are case series with small sample sizes, registry studies with limited clinical variables, and without case-matched controls. In this study, we investigated whether patients with SCD or SCT confer different risk profiles of COVID-19 disease compared to the general population and matched controls in one of the largest healthcare systems in New York City. We found that SCD patients with COVID-19 were more likely to visit the emergency department (ED) and to be admitted to the hospital compared to the general population with COVID-19. However, mortality rate, critical illness and other outcomes were not different compared to matched or unmatched controls. Similarly, SCT patients showed no differences in laboratory values and had no increased risk of worse COVID-19 related outcomes compared to the general population or their matched controls.

SCD is an inherited red blood cell disorder that cause red blood cells to "sickle" resulting in vaso-occlusive crisis (VOC) and multisystem disease.[1] Individuals with SCD have immune-compromised status, chronic anemia, endothelial dysfunction, chronic inflammation, hypercoagulability, and related comorbidities that could increase susceptibility to worse COVID-19 outcomes. SCT is the heterozygous inheritance for sickle hemoglobin that was generally thought to be a benign carrier state, but has been linked to adverse health effects.[2] The effects of COVID-19 on SCT individuals are not well documented.

The aim of the current study was to examine the clinical outcomes in SCD and SCT associated with COVID-19 disease. We used electronic health record data from the Montefiore Health System – a private, non-profit primary and specialty healthcare network of more than 180 locations across Westchester County, the lower Hudson Valley and the Bronx, New York, serving a large low-income and racially diverse population. Our catchment area was severely impacted by COVID-19 and has a large population of SCD and SCT patients. Data were standardized to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (*www.ohdsi.org*)[3] and searched for the period January 1, 2020 to January 21, 2021, imported into an SQLite database (*www.sqlite.org*), and queried using the DB Browser (version 3.12.0). The primary outcome was mortality. Secondary outcomes were ED visits, hospitalization, length of stay (LOS), intensive care unit (ICU) admission, invasive mechanical ventilation (IMV), acute kidney injury (AKI), and acute liver injury (ALI). SCD status, SCT status and major comorbidities were based on ICD-10 codes and OMOP concept ID (*Online Supplementary Figure S1*). SARS-CoV-2 infection was confirmed by a positive real-time polymerase chain reaction test via a nasopharyngeal swab. All ED visits and hospitalizations were primarily due to COVID-19. For comparison, three cohorts with SARS-CoV-2 infection from the same hospital system and same time frame were included as controls: i) general population, ii) SCD-matched controls without SCD, and iii) SCT-matched controls without SCT. Using a nearest neighbor matching algorithm, each SCD or SCT patient was matched with up to four controls from the general population based on age (within 3 years), sex, race, ethnicity, and major comorbidities. This retrospective, observational cohort study was approved by the Einstein-Montefiore Institutional Review Board with an exemption for informed consent and a HIPAA waiver. The study was conducted according to the ethical principles of the Declaration of Helsinki.

Among 12,659 COVID-19 patients, 53 had SCD (74% Hb-SS, 21% Hb-SC, and 6% Hb-S/β-thalassemia) and 62 had SCT (Table 1; *Online Supplementary Table S1*). Chart review was performed to confirm SCD or SCT diagnosis. Compared to the general population (median age 57 years; 30% Black; 42% Hispanic), both SCD (median age 30 years) and SCT cohorts (median age 47 years) were younger, had greater proportion of Black patients (76% and 61%, respectively) and fewer Hispanic patients (25% and 23%, respectively). There were more females with SCT which could be explained by more women knowing their trait status from recommended testing during pregnancy and men being less likely to seek medical care. Essential hypertension (21-40%) was the main comorbidity observed in all groups, but comorbidity burden was greater for SCD and SCT compared to the general population. SCD had lower BMI possibly due to increased metabolic demands and delayed physical and sexual maturation known to occur in SCD patients.[4]

After adjusting for age, sex, race, ethnicity and comorbidities as covariates in Logistic Regression, patients with SCD were more likely to visit the emergency department (adjusted odds ratio [adj. OR]=3.54, 95% confidence interval [CI]: 1.62-7.73, *P*=0.001) and to be hospitalized (adj. OR=7.26, 95% CI=3.75 to 14.08, *P*<0.001) as compared to the general population, but mortality and all other secondary outcomes were not significantly differ-

Table 1. Sample characteristics of COVID-19 patients with sickle cell disease, sickle cell trait, and the general population in this study.

	(a) SCD n = 53	(b) SCT n = 62	(c) General population n = 12,544	*P* (a *vs.* c)	*P* (b *vs.* c)
Age in years, median (IQR)	30 (20-47)	47 (32-62)	57 (39-70)	<0.0001	0.008
Female sex, n (%)	25 (47%)	49 (79%)	6525 (52%)	0.49	<0.001
Black, n (%)	40 (76%)	38 (61%)	3815 (30%)	<0.0001	0.0002
Hispanic, n (%)	13 (25%)	14 (23%)	5201 (42%)	<0.001	0.001
2+ comorbidities, n (%)	13 (25%)	24 (39%)	2534 (20%)	0.02	<0.0001

Note: Between-group comparison of continuous variables were performed using Wilcoxon rank-sum tests, and categorical variables were analyzed with Fisher's exact test. For additional sample characteristics, including comorbidities, vitals and laboratory values, please see *Online Supplementary Table S1*. IQR: interquartile range; SCD: sickle cell disease; SCT: sickle cell trait.

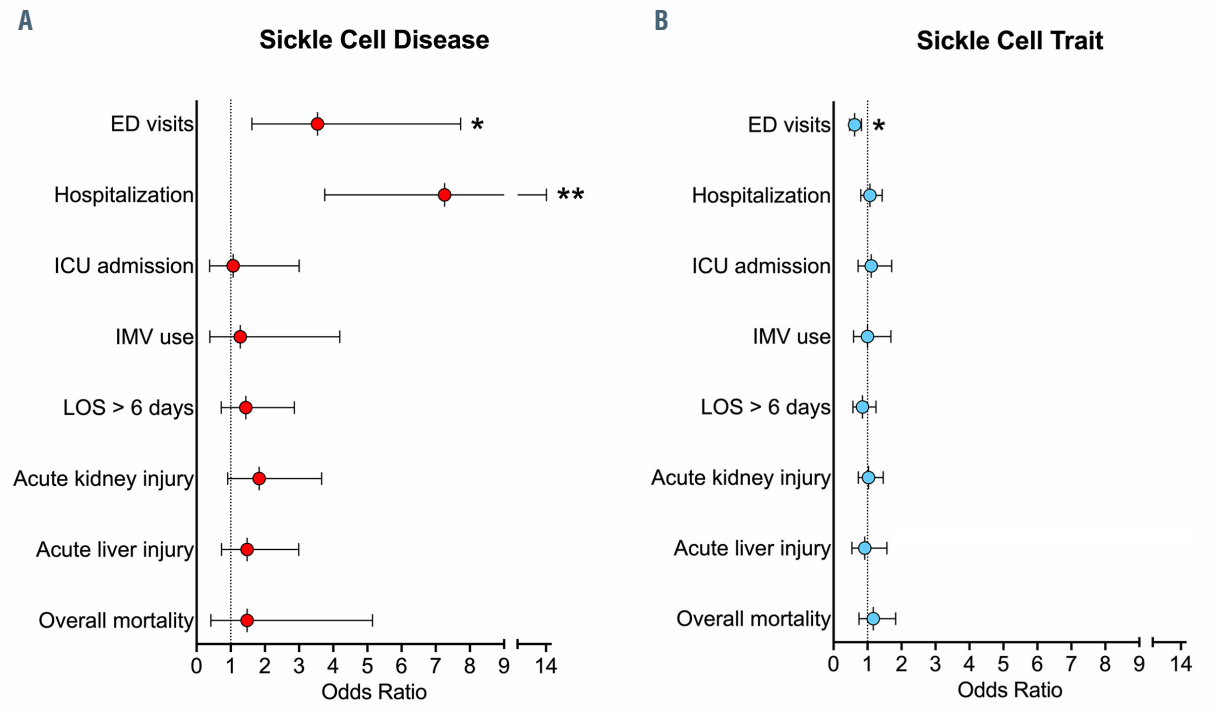

Figure 1. Covariate-adjusted Logistic Regression with odds ratios for clinical outcomes among COVID-19 patients with sickle cell disease or sickle cell trait relative to the general population with COVID-19. (A) Compared to the general population, sickle cell disease (SCD) patients with COVID-19 were more likely to visit the emergency department (adjusted odds ratio [adj. OR]=3.54, 95% confidence interval [CI]: 1.62-7.73, *P*=0.001) and to be hospitalized (adj. OR=7.26, 95% CI: 3.75-14.08, adj. *P*<0.001), but all other outcomes were not significantly different (*P*>0.05) in Logistic Regression adjusted for age, gender, race, ethnicity, and comorbidities as covariates. (B) COVID-19 patients with sickle cell trait had no increased risk of COVID-19 related clinical outcomes compared to the general population, except they were less likely to visit the emergency department (adj. OR=0.62, 95% CI: 0.47-0.82, *P*=0.001). The general population is the reference (vertical dotted line, OR=1). Error bars represent 95% CI. **P*<0.01, ***P*<0.001. ED: emergency department; ICU: intensive care unit; IMV: invasive mechanical ventilation; LOS: length of stay.

ent (Figure 1 and *Online Supplementary Table S2*). There were no differences in clinical outcomes between SCT patients and the general population, except ED visits were lower in SCT (adj. OR=0.62, 95% CI: 0.47-0.82, *P*=0.001).

With a median age of 30 years, our SCD cohort was relatively young consistent with other reports.[5,6] Despite being of young age, SCD patients had more comorbidities than the older general population, consistent with SCD-related complications[7] and end organ damage. SCD patients had lower hemoglobin and hematocrit, and higher monocyte count, reticulocytes, leukocytes, aspartate aminotransferase and bilirubin compared to the general population and SCT (*Online Supplementary Table S1*), consistent with red blood cell dysfunction and hepatobiliary manifestations of SCD.[1,8] SCD patients had higher lactate dehydrogenase (LDH) and D-dimer (*Online Supplementary Table S1*), which could be suggestive of more severe COVID-19 disease[9] but other explanations are possible. Elevated LDH, however could result from intravascular hemolysis, ischemia-reperfusion damage and tissue necrosis associated with SCD but could be further elevated in acute VOC.[10] More studies are needed to further evaluate the consequences of immunological dysregulation associated with COVID-19 in SCD and SCT patients.

Hospital visits were likely associated with SCD-related pain or acute chest syndrome (ACS) triggered by the COVID-19 disease[11] as 67% of admitted SCD patients had one or more SCD-related symptoms at admission, including ACS (n=11), pain crisis (n=11), anemia (n=5), and splenic infarct (n=1). Crisis manifestations of SCD might have contributed to favorable outcomes due to proactive seeking of medical care for SCD-related symptoms.

In order to limit the potential confounding effects of group differences in demographic variables and preexisting conditions on COVID-19 outcomes, we conducted additional comparisons with age-, sex-, race-, ethnicity- and comorbidity-matched controls (Table 2). We found neither significant differences (*P*>0.05, Wilcoxon rank-sum tests) in COVID-19 related outcomes between SCD patients and matched controls, nor between SCT patient and their matched controls. Our findings suggest that individuals with SCD or SCT in this cohort did not carry an added risk of worse COVID-19 outcomes compared to individuals with similar demographics and health status without SCD or SCT. However, SCD patients could have other severe outcomes not evaluated here (e.g., pain or pneumonia).[12]

The mortality rate in our SCD patients (6-8%) is comparable to those reported in the US[6] and UK registries[13] (7.3% and 8.4%, respectively). Singh *et al.*[12] found that Black individuals with SCD were more likely to be hospitalized and to develop pneumonia and pain, but no differences in mortality rate compared to matched Black individuals without SCD/SCT were observed, consistent with our findings. Similarly, Alkindi *et al.*[14] reported COVID-19 infection may have triggered the onset of VOC, but it did not significantly influence the morbidity or mortality of SCD patients. The Bronx was disproportionally impacted by the first wave of COVID-19 with more hospitalizations and deaths than any other NYC borough,[15] which may explain the high mortality (11%) in our non-SCD population.

Although we presented one of the largest single center

Table 2. **Comparisons of COVID-19 outcomes between hospitalized individuals with sickle cell disease (SCD) or sickle cell trait (SCT) and their respective age-, sex-, race-, ethnicity- and comorbidity-matched controls without SCD/SCT.**

Clinical outcomes, n (%)	SCD n = 39	Matched controls n = 91	*P*	SCT n = 31	Matched controls n = 109	*P*
Length of stay > 6 days	16 (47%)	37 (42%)	0.69	10 (33%)	38 (37%)	0.83
Intensive care	4 (10%)	17 (19%)	0.30	5 (16%)	11 (10%)	0.35
Invasive mechanical ventilation	3 (8%)	10 (11%)	0.75	4 (13%)	10 (9%)	0.51
Acute kidney injury	13 (33%)	32 (35%)	>0.99	16 (52%)	49 (45%)	0.55
Acute liver injury	12 (34%)	23 (32%)	0.83	4 (16%)	18 (20%)	0.78
In-hospital mortality	3 (8%)	5 (6%)	0.70	7 (23%)	20 (18%)	0.61

Note: Categorical variables were analyzed with two-sided Fisher's exact tests. Acute kidney injury was defined by KDIGO standards either a 0.3 mg/dL increase within 48 hours or 1.5 times the lowest reading during hospitalization due to lack of data prior to hospitalization. Acute liver injury was defined as serum levels of alanine aminotransferase and aspartate aminotransferase both exceeding 1x upper limit of normal, with the upper reference range as 40 U/L.

cohorts of SCD and SCT with COVID-19, additional multiple institutional data are needed to achieve greater generalizability. As with any retrospective study, there could be unintentional patient selection bias. Sickle cell trait status may be misclassified and, conversely, individuals may be unaware of their trait status. While we carefully reviewed patient charts to confirm trait status, patients were not tested for SCT due to the retrospective nature of the study. Finally, long-term outcomes of SCD and SCT COVID-19 patients should also be explored.

In conclusion, although more COVID-19 patients with SCD visited the emergency department and were hospitalized, SCD and SCT did not carry an added risk of COVID-19 related escalated care and death compared to COVID-19 patients in the general population or those with similar demographics and health history. Our study underscores the importance of matched controls in defining risks associated with COVID-19.

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