Adverse clinical outcomes associated with sickle cell trait at high altitude

Sickle cell trait (SCT) is a prevalent condition affecting more than 300 million individuals worldwide. Although formerly regarded as a benign carrier state, with complications rarely occurring outside of high-altitude or extreme physiologic conditions, recent population-level data has revealed an increased risk for chronic kidney disease (CKD) and pulmonary embolism (PE) in general populations.[1] In this study, we sought to evaluate whether chronic, moderately high altitude exposure can increase the breadth and severity of SCT complications compared to sea-level cohorts. We used data from Colorado, which has the highest mean elevation of any state in the USA (2,070 m). We found that the risk for known SCT complications such as CKD and PE, as well as other clinical outcomes in which prior evidence was either weak or mixed, were significantly increased. In the latter category, adverse pregnancy outcomes including pre-eclampsia and intra-uterine death were particularly notable. The strength of the associations observed in this study generally exceeds prior reports and suggests that SCT patients living at high-altitude are at greater risk for morbidity than their sea-level counterparts.

Compared with sickle cell disease (SCD), the lower HbS concentration in SCT means that red blood cell (RBC) sickling rarely occurs during regular vascular transit but can be induced by added insults such as hypoxia or acidosis. These conditions can occur either systemically (e.g., with high-altitude exposure, sepsis) or locally (e.g., within the inner renal medulla or splenic pulp).[2,3] Sickling of RBC in SCD is associated with membrane changes, including decreased deformability, loss of phospholipid asymmetry, and microvesiculation, that result in chronic activation of coagulation and inflammatory pathways.[4,5] Evidence to support SCT as an intermediate phenotype in these respects includes data showing moderately increased coagulation activation,[6,7] circulating cell-free mitochondrial DNA (a driver of chronic inflammation in SCD),[8] and markers of metabolic dysfunction and oxidative stress[9] in SCT patients at a level above healthy controls, but below those seen in SCD.

This retrospective cohort study used de-identified electronic health record data from UCHealth, a large regional healthcare system in Colorado that includes an academic medical center, 13 community-based hospitals, and more than 200 outpatient clinics. This study is classified as not human subjects research and did not require specific consent or institutional review board approval. Data from the 12 largest primary statistical areas of Colorado, which includes approximately 95% of Colorado's population, estimates the weighted average elevation for a Colorado resident to be at around 1,600 meters, which results in an approximately 20% decrease in the inspired partial pressure of oxygen compared to sea level.[10-12]

Diagnostic codes were used to define case and control cohorts and outcomes of interest (*Online Supplementary Table S1*). Individuals aged ≥18 years with a diagnosis of SCT were analyzed for known and possible associated outcomes, and were compared to a 1:5 randomized matched sample of controls without SCT (matched on age within 2 years, race, ethnicity, sex, and entry into the database within 2 years). Data from 2004-2023 were included in this analysis. Individuals with diagnostic codes for sickle cell anemia (HbSS), sickle/HbC disease (HbSC), sickle-β thalassemia (HbS-β^{thal}), other sickle cell disorders, and hemolytic anemias were excluded from both case and control groups.

Outcomes of interest included CKD, PE, deep vein thrombosis (DVT), hematuria, rhabdomyolysis, splenic infarction, pre-eclampsia, and intra-uterine death. Odds Ratios (OR) with 95% Confidence Intervals (CI) were estimated using multivariate logistic regression adjusted for age and Black or African American race, as well as sex when applicable. De-identified subject data were analyzed using Python version 3.11.4. Logistic regression models were built using StatsModel version 0.14.0.

We included 1,460 SCT patients with complete demographic data, along with 7,300 matched controls (N=8,760). There were 1,060 (72.6%) women and 400 (27.4%) men in the case cohort, and matching proportions in the control group. A majority (76.0%) were black or African American. The median age of the cohort was 38 years (interquartile range [IQR]: 31-50).

We found significant associations for CKD (OR: 3.2, 95% CI: 2.5-4.1), DVT (OR: 2.5, 95% CI: 1.7-3.5), PE (OR: 4.3, 95% CI: 3.1-6.0), hematuria (OR: 2.5, 95% CI: 2.0-3.2), rhabdomyolysis (OR: 3.1, 95% CI: 1.6-6.1), splenic infarction (OR: 55.9, 95% CI: 19.9-156.8), pre-eclampsia (OR: 3.7, 95% CI: 2.6-5.2), and intra-uterine death (OR: 4.6, 95% CI: 2.0-10.5) (Table 1). Male sex was strongly associated with rhabdomyolysis (OR: 14.3, 95% CI: 5.9-34.6) and splenic infarction (OR: 8.8, 95% CI: 4.4-17.6), and was moderately associated with CKD (OR: 1.5, 95% CI: 1.2-1.9).

To confirm the validity of our SCT cohort, we analyzed laboratory data to confirm that hemoglobin concentration was normal, and that HbS and HbA percentages were within the expected ranges in SCT (<50% and >50%, respectively). We included the highest hemoglobin for each patient to avoid capturing acute blood loss events. Lab values were consistent with SCT and showed a median hemoglobin of 14.3 g/dL (IQR: 13.2-15.3, N=1270), a median HbS of 38.4% (IQR: 34.4-40.2%, N=193), and a median HbA of 58.4% (IQR: 56.4-63.2%, N=291).

For 33/41 of the splenic infarction cases, SCT was diagnosed at the same encounter, suggesting that many SCT patients are unaware of their HbS carrier status. In support of previous reports,[3] we found an association between race and splenic infarction (χ^2 test $P<0.001$), with univariate logistic regression suggesting that Black or African American race is protective (OR: 0.3, 95% CI: 0.1-0.5) and White race is a risk factor (OR: 5.5, 95% CI: 2.8-10.9). Of note, all 4 cases of splenic infarction in the control group occurred in individuals who self-identified as Black, suggesting that undiagnosed SCT could be contributing to these outcomes.

We speculate that chronic exposure to hypoxia as experienced in Colorado augments the underlying pathophysiology of SCT by promoting polymerization of deoxyHbS. However, it is possible that this high-altitude "stress test" has implications for sea-level patients, who may be experiencing the same pathophysiologic processes at a sub-clinical or more sporadic rate. It is unclear how much of this effect was due to chronic exposure to high altitude *versus* acute and/or repeated exposure to very high altitudes, which is common for Colorado residents spending their leisure time in the mountains. Future studies incorporating geolocation data, potentially via wearable devices, could help address this question. The predominance of child-bearing age women in our cohort suggests that the diagnosis of SCT was established (or confirmed) through antepartum screening, but also makes the substantial rates of venous thromboembolism and CKD in our young cohort especially alarming.

A potential limitation in our study is the use of diagnostic codes rather than globin genotyping to define SCT status. However, by evaluating the hematologic profiles of enrolled subjects with SCT, we were able to rule out other forms of SCD or other anemias and confirm that the range of total Hb concentration and percentage of HbS were as expected in SCT. For instance, this enabled us to verify that compound sickle cell syndromes such as sickle-β thalassemia, which are occasionally misclassified as SCT but can be identified by their unique hematologic profiles (Hb S>50%, Hb A<50%), did not have a substantial impact on our results. In this analysis, we did not include subjects under 18 years of age, an age group in which the majority of chronic complications associated with SCT (such as CKD) are presumably very rare. While we were unable to directly measure socioeconomic status in this data set, our experimental design has helped control for this potential confounder by exactly matching cases and controls based on age, sex, race, and ethnicity. Lastly, because many adults are unaware of their SCT status, it is possible that a significant proportion of our control cohort may also have SCT, which biases towards a null effect. This null bias should be considered when comparing the magnitude of our results to genotyping-based studies (*Online Supplementary Tables S2, S3*).

The association between SCT and adverse outcomes of pregnancy is controversial. Complications that previously received attention in SCT include pregnancy-related hypertensive disorders, intra-uterine death, pre-term delivery, low birth weight, and bacteriuria.[13] The strong associations we found for pre-eclampsia and intra-uterine death are clinically concerning and higher than most prior reports (*Online Supplementary Table S3*). Independently, high altitude has been associated with low birth weight and pre-eclampsia in a general maternity population.[14,15] In combination with our data, this suggests that pregnant women with SCT may be particularly vulnerable to adverse perinatal outcomes in high altitude environments.

Advancing recognition and management of SCT-associated health outcomes is an important health disparity issue, as SCT disproportionately affects underserved populations. Future prospective research should address whether improved identification and prevention of SCT-related morbidity could help reduce ongoing disparities in cardiovascular disease, kidney disease, and maternal health.

In summary, our findings suggest that chronic hypoxia in a high-altitude environment may exacerbate known SCT-associated outcomes such as CKD, and may escalate lower-strength associations such as morbidity in pregnancy toward clinical significance. Improving knowledge of the potential morbidities associated with SCT may assist clinicians in providing personalized, preventive care.

Table 1. Association between sickle cell trait and clinical outcomes.

	SCT patients Total 1,460 N (%)	Matched controls Total 7,300 N (%)	OR (95% CI)
Chronic kidney disease	136 (9.3)	273 (3.7)	3.2 (2.5-4.1)*
Deep vein thrombosis	46 (3.2)	97 (1.3)	2.5 (1.7-3.5)*
Pulmonary embolism	70 (4.8)	87 (1.2)	4.3 (3.1-6.0)*
Hematuria	117 (8.0)	246 (3.4)	2.5 (2.0-3.2)*
Rhabdomyolysis	14 (1.0)	23 (0.3)	3.1 (1.6-6.1)*
Splenic infarction	41 (2.8)	4 (0.1)	55.9 (19.9-156.8)*
Pre-eclampsia	58 (4.0)	82 (1.1)	3.7 (2.6-5.2)*
Intra-uterine death	11 (0.8)	12 (0.2)	4.6 (2.0-10.5)*

Odds Ratios (OR) with 95% Confidence Intervals (CI) were estimated using multivariate logistic regression adjusted for age and Black or African American race, as well as sex when applicable. SCT: sickle cell trait; N: number. *Associations significant at $\alpha<0.05$.

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Contributions

KAS conceptualized the study and performed data analysis. KAS and NSK contributed to data interpretation. All authors contributed to manuscript preparation.

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Data-sharing statement

The data that support the findings of this study are available from Health Data Compass. Restrictions apply to the availability of these data, which were used under license for this study. Data are available with the permission of https://www.healthdatacompass.org/.

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