

## Sickle cell trait and multisystem trauma: an unaddressed urgent knowledge gap

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**ABSTRACT**

Sickle cell trait (SCT) has historically been considered a benign condition, but SCT-positive patients have increased baseline risk of venous thromboembolism and chronic kidney disease, as well as increased risk of sickled erythrocytes in settings of hypoxia, acidosis, and hypovolemia. Multisystem traumatic injuries are a common clinical scenario, in which hypoxia, acidosis, and hypovolemia occur; however, little is known about how SCT-positive status impacts outcomes in multisystem trauma. We conducted a scoping literature review to investigate what was known about SCT in the setting of multisystem trauma. In the 110+ years that sickle cell hemoglobinopathies have been known, only three studies have ever examined the relationship between SCT and multisystem traumas. All three articles were case reports. None of the articles intentionally measured the association between SCT and multisystem trauma outcomes; they only incidentally captured information on SCT. Our article then examines historical reasons why so little research has studied the pathophysiology of the multisystem trauma in patients with SCT. Among the reasons is that historical and logistical factors have long prevented patients from knowing their SCT-status: historical discriminations against SCT-positive patients in the 1960s and 1970s delayed federal mandating of SCT newborn screening until 2006, whereas difficulties communicating known SCT-status to afflicted children also contributed to lack of patient knowledge. In light of our findings, we offer specific calls to action for the trauma surgery research community: (1) consider testing for SCT in trauma patients that have unexpected complications, particularly venous thromboembolism, rhabdomyolysis, or renal failure and (2) support research to understand how SCT impacts multisystem trauma outcomes. We also offer specific guidelines about how to 'proceed with caution' in implementation of these goals in light of the troubled history of SCT testing and policy in the USA.

There are 1 to 3 million people in the USA with sickle cell trait (SCT) and over 800 000 trauma injuries annually.<sup>1,2</sup> Despite the likely high intersecting numbers of trauma patients in the USA with underlying SCT, research into the clinical impact of the confluence of both remains understudied. SCT has historically been considered 'benign' by many clinicians—however, there is reason to assess its potential impact in patients with multisystem trauma, which has never been done previously.<sup>3,4</sup>

There is strong biological plausibility to support worse outcomes in trauma patients with SCT.

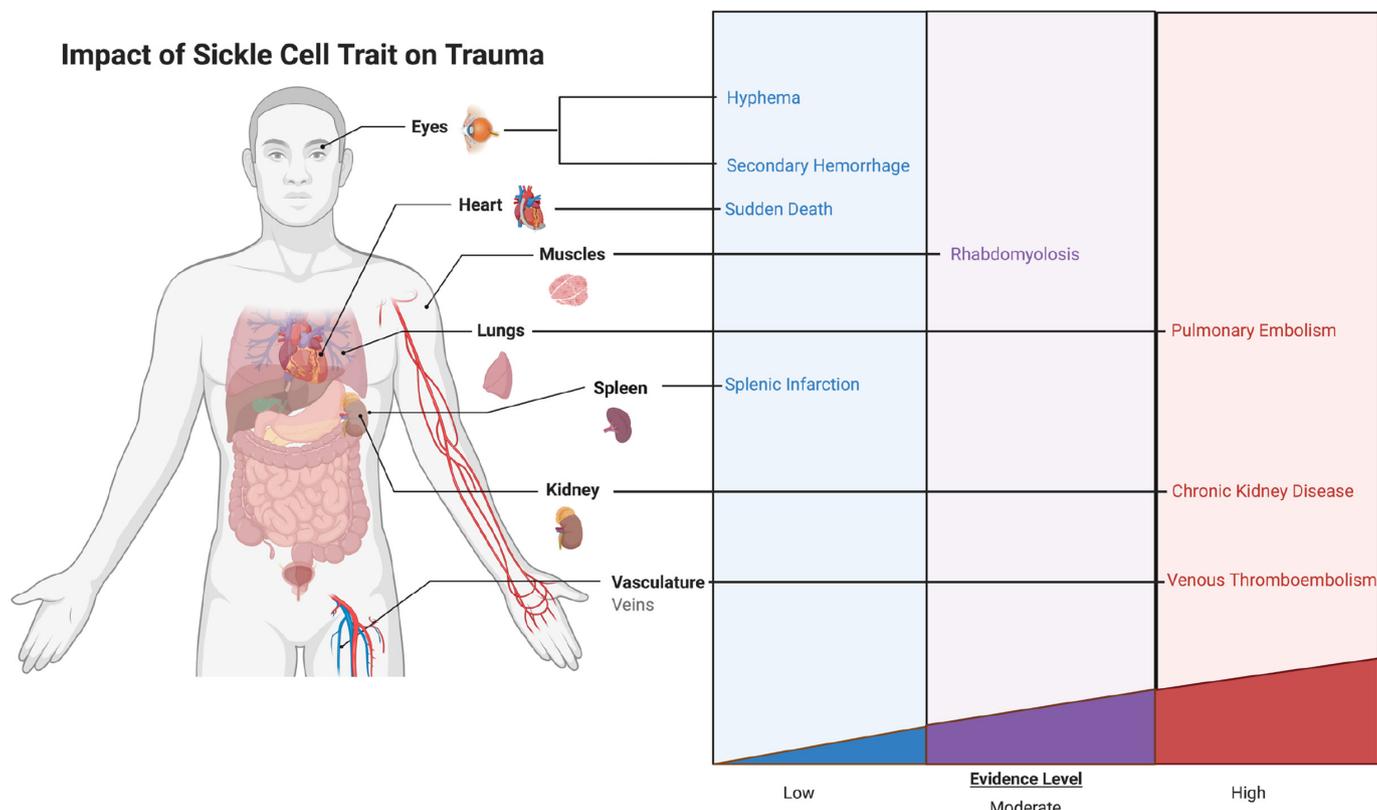
Patients with SCT do not have the frequent pain crises associated with sickle cell disease (SCD); however, they do have the potential for sickled erythrocytes.<sup>5,6</sup> Compared with SCD, however, the sickling of SCT only occurs in anatomic sites with low tissue oxygen (ie, the medulla of the kidney) or during physiologic extremes that cause systemic hypoxia or acidosis.<sup>5,6</sup> Patients with SCT have a close to twofold increased risk of venous thromboembolism (VTE) and chronic kidney disease without any other stressors.<sup>4,7-9</sup> Evidence also exists for associations between SCT with sudden death during exertion, splenic infarcts, and rhabdomyolysis (figure 1),<sup>3,4,10</sup> again in absence of severe physiologic stressors. Sickling in patients with SCT would thus be expected to follow multisystem trauma given that hypoxia, acidosis, and hypovolemia are all common stressors in this clinical scenario.<sup>11</sup>

In considering how SCT status affects trauma patients, it is worth considering that communities disproportionately impacted with SCT are also disproportionately impacted by violence. SCT is most commonly found, due to SCT's antimalarial advantages, in people with ancestry from malaria-endemic regions of the world. In the USA, this means SCT affects 8% to 10% of Black Americans,<sup>1,12</sup> 1% of non-African Latinx individuals, and 0.5% of White Americans. South Asians, Southern Europeans, and Middle Eastern individuals are also disproportionately affected.<sup>13-15</sup> Given US demographics, Black Americans make up the large majority of the nation's patient population with SCT. Accordingly, in understanding how best to consider and incorporate SCT-positive status into efforts to improve trauma outcomes, it is necessary to also reflect on how the high prevalence of SCT-positive status within Black communities may compound other known drivers of substandard trauma outcomes for Black patients—such as disparities in access to quality care at a structural, institutional, and interpersonal level.<sup>16</sup>

Further complicating efforts to better understand SCT's clinical impact on trauma outcomes, up to 84% of adult SCT carriers are unaware of their status.<sup>17,18</sup> This may be due, in part, to the recency of US mandates for newborn SCT screening—which was not federally required until 2006—as well as to difficulties in relaying the results of newborn screenings from parent to child.<sup>19</sup> As a result, many SCT-positive patients are not coded for the trait in their medical records, making retrospective analysis of associated outcomes impossible. The lack of patient knowledge about SCT status has led groups

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**Figure 1** ‘Evidence Level’ refers to the relationship between sickle cell trait status and the clinical outcomes outlined above. This figure is adapted from systematic review findings in Naik RP, Smith-Whitley K, Hassell KL, Umeh NI, de Montalembert M, Sahota P, Haywood C, Jr., Jenkins J, Lloyd-Puryear MA, Joiner CH, *et al.* Clinical outcomes associated with sickle cell trait: a systematic review. *Ann Intern Med* 2018;169(9):619–27.

like the National Institutes of Health to highlight SCT as an important, understudied gap in the literature requiring urgent examination.<sup>20,21</sup> Among the understudied gaps is a lack of clarity as to whether SCT has an impact on outcomes after trauma.

#### LITERATURE REVIEW: SCT’S IMPACT ON MULTISYSTEM TRAUMA

We conducted a scoping literature review to analyze what was known about SCT in the setting of multisystem trauma. This search aimed to find all articles related to SCT and trauma outcomes. We were particularly looking for evidence of SCT’s role in multisystem trauma, since these injuries would be most likely to induce the physiologic extremes that could potentiate sickling.<sup>4,5</sup> Using the Public Library of Medicine (PubMed) database and Cochrane Reviews, we searched for publications related to SCT and trauma outcomes in September 2021. Search queries included: [“sickle cell trait” AND trauma] and [“sickle cell trait” AND injury]. All publications were reviewed for relevance by study authors and included if results discussed the impact of SCT after traumatic injury. We identified 185 articles in total and 3 that were specific to multisystem trauma and SCT (table 1). These three articles were a case report of an infant with a traumatic birth history, a case series of four trauma-induced homicides from injury by police, and a retrospective review of the National Trauma Data Bank, with SCT as an incidental variable that was ultimately unremarkable.<sup>22–24</sup> Only 29% of articles were from prior to 2000. The majority of the articles were case reports (52%), of which 69% were related to ocular trauma. The remaining articles were opinion or editorial pieces. None advanced our understanding of the effects of SCT during the physiologic stress of multisystem trauma.

#### AN IMPORTANT KNOWLEDGE DEFICIT

We found only three articles regarding SCT’s impact on multi-system trauma, despite SCT’s presumed significant prevalence in US trauma patients and its potential impact on pathways that would be critical to trauma outcomes. Most striking was that no articles intentionally measured the association between SCT and trauma outcomes; they only incidentally captured information on SCT.

#### WHY THIS MATTERS: THE HISTORICAL CONTEXT OF SCT TESTING

The history of SCD and SCT testing in the USA has been problematic. In the 1960s and 1970s, following the victories of the US Civil Rights Movement, several US states began requiring SCT status testing for patients. Many community groups, perhaps most notably the Black Panther Party, began testing throughout local communities.<sup>25</sup> Ostensibly, this extra testing and awareness about the neglected conditions, SCD and SCT, was seen as beneficial. However, major problems emerged. First, community programs habitually mixed up SCD and trait, which led to thousands of parents receiving erroneous information about their children’s health and life expectancies.<sup>26,27</sup> Second, in institutions like state governments, insurance agencies, and the US Armed Forces, companies and educational psychologists often used SCT as an excuse to legally discriminate against those who tested positive—that is, primarily Black Americans.<sup>26,28</sup>

For example, in the 1970s, SCT-positive individuals were banned from enrolling at the US Air Force Academy, but not from enlisting in Air Force Reserve Officers’ Training Corps (ROTC) programs—a thinly veiled attempt to deny admissions

**Table 1** Available literature that discusses the impact of sickle cell trait and trauma

Literature results on SCT with trauma	Frequency (%) N=185
Publication date	
On or before 2000	54 (29%)
After 2000	131 (71%)
Publication type	
Case reports	96 (52%)
Original research	58 (31%)
Other (opinion, editorial)	31 (17%)
Publication content*	
Not directly related to SCT and Trauma (incidental mention of SCT or trauma, mental trauma, and so on)	150 (81%)
Unisystem trauma and SCT	32 (17%)
Multisystem trauma and SCT	3 (2%)
TOTAL directly related to SCT and trauma	35 (19%)
Anatomic setting of trauma (N=34)	
Ocular	24 (69%)
Rhabdomyolysis (muscle)	4 (11%)
Renal	2 (6%)
Splenic	0 (0%)
Other (cardiac, bone, thigh GSW, neck)	5 (14%)
Physiological characteristics (N=35)	
Acidosis	0 (0%)
Dehydration	1 (3%)
Exertion	1 (3%)
Hypertension	1 (3%)
Hypoxia	2 (6%)
Infarct/myonecrosis	0 (0%)
Procoagulant and endothelial damage (VTE)	0 (0%)
Vaso-occlusion and sickling	11 (31%)

\* '+' designation defines articles that reference patients/subjects with sickle cell trait who had sustained trauma or injury to one or multiple body sites and systems (ie, eyes, chest, thigh, and so on). Publications that were directly related to trauma in patients with SCT and subjects include all ranges of publication dates and types except opinion and editorial pieces.  
SCT, sickle cell trait; VTE, venous thromboembolism.

to Black Americans at the Air Force Academy since those in ROTC were eligible for Air Force service, too.<sup>26</sup> Similarly, in the 1970s, The Job Corps—a workpower training program of the US Department of Defense—used SCT-positive status to prevent the entry of primarily Black Americans into the fields of carpentry or automobile repair, under the pretense that these fields were too ‘physically demanding’.<sup>26–28</sup> Companies, including a major US airline, fired employees solely because they possessed SCT.<sup>26</sup> Medical insurance was sometimes more expensive for patients with pre-existing SCT<sup>29</sup>—a practice which may have been actuarially prudent, but nonetheless contributed to exacerbating racial health disparities in insurance access.

Many physicians and prominent advocates of the era were disheartened by how SCT and SCD testing was treated. They resented how SCT was used as an excuse to bar people—primarily Black Americans—from opportunities. They also thought that serious medical harm resulted from community testing groups maliciously confusing SCT with SCD and presenting parents with harmful advice and prognoses for children. Physicians and advocates began a successful movement to remove SCT testing requirements for newborns.<sup>26–27</sup> Although this effort saved

patients and their families from unjust treatment, it contributed to today’s lack of patient knowledge about personal SCT status, or its impact on clinical outcomes, including in trauma.

### ‘PROCEED WITH CAUTION’: APPLYING SCT STATUS

Concerningly, out of the three articles discussing SCT’s impact on multisystem trauma outcomes, one was a case series of four law enforcement-related homicides. The authors attributed the deaths to SCT.<sup>23</sup> Notably lacking from the article was explicit acknowledgement of how traumatic injury, not SCT, was primarily responsible for the patients’ death, and how SCT alone cannot lead to the outcomes described. In May 2021, *The New York Times* documented how such practice is common and unjust: SCT has been used for the past 25 years to defend at least 45 police-related homicides of individuals with SCT, including as recently as the murder of Mr George Floyd.<sup>30</sup> The American Society of Hematology (ASH) wrote an official position statement in solidarity with *The New York Times* findings<sup>31</sup>—with ASH President Dr Martin Tallman adding, ‘The use of sickle cell trait to cover up’ the death of people while in police custody is ‘abhorrent [because] sickle cell trait is unlikely to supersede other inflicted traumas as the major cause of death’.<sup>32–34</sup>

In calling attention to the research gap that exists in studying the possible physiological link between SCT and trauma outcomes, it is important to be cognizant that if a link is found, SCT should not nefariously be used by clinicians or political officials as a rationale to justify preventable mortality. Rather, SCT status should justly be used by clinicians as a reason to treat SCT-positive trauma patients with an abundance of caution. The research agenda should be conducted with community input to reflect current social considerations and ramifications.

### CALLS TO ACTION

Our lack of understanding regarding the role SCT plays in multi-system trauma is concerning, given its impact on quality of care for those in Black and Latinx communities.<sup>12</sup> If SCT is found to be physiologically linked to multisystem trauma outcomes, then the high prevalence of SCT in communities of color in the USA may intersect with today’s concurrent epidemic of violent trauma, particularly in communities affected by legacies of structural racism, economic marginalization, and worsened by the recent COVID-19 pandemic.<sup>16</sup> In light of our scoping literature review’s results and its clinical contexts, we have developed the following calls to action for the trauma surgery community—(1) consider testing for SCT in trauma patients that have unexpected complications, particularly VTE, rhabdomyolysis, or renal failure; (2) support research to understand how SCT impacts multisystem trauma outcomes; and (3) maintain significant caution with causal attribution of SCT to death, especially in cases of grievous bodily injury, given the current lack of medical or surgical literature to support such assertions.

We hope that these proposals, if implemented, may contribute meaningfully to improving outcomes for SCT-positive trauma patients and also may help to advance much needed medical and surgical knowledge that should have been addressed long ago.

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