






Association between trauma triage and time-to-vaso-occlusive events in patients with sickle cell disease after traumatic injury: a retrospective study

Ektha Parchuri ^{1,2}, Maria Pacella-LaBarbara,³ Julia O'Brien,¹ Danielle S Gruen ², Frances Guyette ³, Joshua B Brown ², Laura De Castro,⁴ Charles R Jonassaint ^{1,4}

¹Center for Research on Health Care, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

²Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

³Emergency Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

⁴Section of Benign Hematology, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence to

Dr Charles R Jonassaint;
cjonassaint@pitt.edu

Received 24 June 2023

Accepted 9 October 2023

ABSTRACT

Introduction Sickle cell disease (SCD) is associated with vaso-occlusive events (VOEs) that can lead to disease complications, including early mortality. Given that similar inflammatory responses characterize VOE and traumatic injury, injured patients with SCD may be vulnerable to acute complications. This study is the first to examine whether traumatic injury is associated with increased severity of future VOEs.

Methods This cohort study was conducted using electronic health record data from an SCD clinic in Western Pennsylvania; 356 patients with SCD from January 2000 to July 2021 were identified via retrospective chart review. 55 patients were eligible based on continuous medical record data spanning 1 year preinjury and postinjury. Patients were sorted into three treatment groups based on injury management: (1) Neither triage to trauma team activation (TTA) nor inpatient admission (*Early Discharge*), (2) Triage but no inpatient admission (*Triage Only*), and (3) *Triage and In-patient*. Outcomes included time from injury to first VOE, annual VOE counts requiring an emergency department (ED) visit, and ED length of stay (LOS) for the first VOE after injury.

Results *Early Discharge* individuals experienced a VOE event within 2.93 days of injury, significantly shorter time to event than *Triage and In-patient* individuals at 52.375 days and *Triage Only* individuals at 100.16 days ($p=0.0058$). No difference in annual VOE counts was noted postinjury across all groups. However, a significant increase in VOE LOS preinjury (16.1 hours) to postinjury (77.4 hours) was noted only for the *Triage Only* group ($p=0.038$). Cox regression model showed that shortened time to VOE events was marginally associated with TTA status ($p=0.06$).

Conclusion Despite minimal changes in long-term VOE outcomes after injury, traumatic injuries may accelerate the time-to-VOE among the *Early Discharge* group. Therefore, future research is warranted to analyze whether the absence of postinjury triage assessment and intervention may cause unforeseen physiologic stressors contributing to VOE outcomes.

Level of evidence Level IV: retrospective case-control study with three negative criteria.

INTRODUCTION

Traumatic injury¹ is the leading cause of death for children and younger adults² and is associated with increased risk of chronic pain syndromes that are prevalent for years postinjury³ and health complications.⁴ Several factors link traumatic injury to

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ The temporal relationship between traumatic injury and adverse patient outcomes is currently unknown in the sickle cell disease (SCD) population.
- ⇒ Prior case studies suggest that exposure to injury causes rigorous sickling of red blood cells, providing high evidence of future pulmonary embolism and deep venous thrombosis risk; this is however only applicable to patients with SCT.
- ⇒ This dearth of knowledge has been known to lead to poor pain management, communication barriers, and decreased quality of care for injured patients with SCD.

WHAT THIS STUDY ADDS

- ⇒ This study is the first to quantify whether exposure to traumatic injury accelerates episodic vaso-occlusive pain events in patients with SCD.
- ⇒ Specifically, those with a trauma triage for any injury severity benefit from this additional assessment and/or inpatient admission for their injuries.
- ⇒ These results can be used to inform guidelines and interventions for injured patients with SCD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study reveals a critical need for future research to explore the physiological response to trauma which can explain current findings.
- ⇒ Additionally, as patients with SCD continue to be excluded in trauma registries across the nation, intentional efforts for inclusion and representation within clinical research is greatly needed.

increased risk for later morbidity and mortality. Traumatic injury initiates a systemic reaction that triggers an inflammatory response and activates the coagulation cascade.⁵ Though this process is necessary for healing,⁶ prolonged and imbalanced systemic inflammation from tissue damage can cause an overproduction of proinflammatory cytokines⁷ and causes endothelial dysfunction at unrelated sites.⁸ The resulting tissue edema and tissue hypoxia incites further damage, which may lead to increased mortality.^{5,6}

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Parchuri E, Pacella-LaBarbara M, O'Brien J, et al. *Trauma Surg Acute Care Open* 2023;**8**:e001200.

This inflammation and coagulation response to injury could be particularly concerning for patients with sickle cell disease (SCD), as SCD is characterized by a pathologic inflammatory cascade—even in the absence of polytrauma.⁹ SCD is an inherited hemolytic disorder caused by the polymerization of hemoglobin S (HbS) that affects nearly one in 500 African Americans, many of whom are from disadvantaged backgrounds. Polymerization of HbS results in early destruction of erythrocytes, which releases hemoglobin and heme iron into the plasma; this process causes endothelial dysfunction, ultimately instigating vaso-occlusion, a blockage of blood vessels.¹⁰ The degree of hemolysis can differ by SCD genotype, resulting in phenotypic variability of the disease.^{11,12} Recurrent and episodic vaso-occlusive events (VOEs) cause tissue damage as a result of oxidative stress, activation of leukocytes and platelets, and the release of inflammatory cytokines.¹³ Thus, in SCD, the physiological response to traumatic injury and resulting inflammatory cascade may trigger or increase likelihood of VOE. Patients with VOE experience acute and chronic pain, resulting in emergency department (ED) visits, hospitalization, and/or evolving pain management needs.¹⁴ It is therefore likely that SCD may be a risk factor that needs to be accounted for in trauma triage to trauma team activation (TTA).

Trauma disproportionately impacts racial and ethnic minority groups, with African Americans living in high poverty neighborhoods having the highest risk of mortality and prevalence of chronic pain after injury.^{3,15} Consequently, patients with SCD, most of whom are of African descent, represent a vulnerable population that may respond to and recover differently from traumatic injury compared with those without SCD. Yet, there is a dearth of research on the prevalence and clinical impact of traumatic injury among patients with SCD;¹⁶ the extant literature is limited to case reports of such potential association among specific populations (eg, infants and victims of homicide).^{17,18}

TTA based on trauma triage protocol and inpatient admission drastically improve both in-hospital and 1-year mortality and minimize future risk of secondary complications or disability among injured patients.^{19,20} Despite these data, no specific prehospital guidelines or protocols exist for evaluating injured patients with SCD requiring emergency interventions, as prior research is limited and protocols tend to cover pain management and resuscitation for trauma patients more broadly. Therefore, it is of critical public health importance to analyze whether traumatic injury has an impact on SCD, to not only analyze whether the SCD population is an emerging subset of trauma patients at greater risk for poor outcomes, but also to develop guidelines for clinicians and emergency services providers to appropriately care for patients with SCD who are acutely injured.

Given the benefits of trauma triage and inpatient care in non-SCD populations,^{19,20} the *primary objective of this study* was to analyze whether ED management of the traumatic injury (eg, TTA and intensive care unit/inpatient admission status) mediates the link between injury and VOE outcomes and time-to-first VOE postinjury. The *secondary objective* was to analyze whether traumatic injury is associated with VOE outcomes, including (1) Annual frequency of VOEs and (2) ED length of stay (LOS) for the first VOE after an injury among patients with SCD. We also assessed whether the type of injury (blunt vs penetrating) has an effect on VOE outcomes.

METHODS

Study design and population

This study uses retrospective EMR data from the UPMC Adult Comprehensive Sickle Cell Clinic Patient registry, which includes

patients with a confirmed SCD diagnosis who have received care at the clinic from January 2000 to July 2022. Our study population consisted of all patients with SCD included in the registry aged ≥ 18 years with at least one diagnosed traumatic injury event during an acute care encounter at 1 of 11 urban levels 1 and 2 trauma centers in Western Pennsylvania. Records of ED visits, Trauma History and Physical documentation, and ambulance records from 2000 to 2021 were reviewed to identify prior history of traumatic injury.

Consistent with WHO reporting, we identified records as traumatic injury-related if they had any of the following International Classification of Diseases (ICD), Ninth Revision codes (ICD 9) as a primary or secondary diagnosis, between 800–839, 850–904, 910–918, 925–929, 940–959 representing fractures of extremities; open wounds; superficial, internal, or crushing injuries; and spinal or nerve-related injuries.²¹ We defined the index date as the date of the most recent traumatic injury for each patient. Patients were excluded if EHR did not have at least one other clinical encounter for 1 year preindex and postindex date, or if the injury occurred more than 6 hours prior to documentation, was an isolated fall, or if the patient was incarcerated at the time of injury.

Measures

The following data were recorded via medical record review: age, gender, lab-confirmed SCD genotype, date of traumatic injury (index date), ED site, mechanism of injury, triage status after TTA (both SCD and trauma triages), and inpatient admission status.

ED treatment groups based on trauma triage and inpatient admission status

Study participants were categorized into three ED management groups based on their trauma triage and inpatient admission status. It has been found that TTA/trauma triage and inpatient admission improve both in-hospital and 1-year mortality and minimize future risk of secondary complications or disability among injured patients^{19,20} and therefore may be predictive of outcomes post injury in the SCD population. We defined our study cohorts as follows: (1) Patients with neither trauma triage nor inpatient admission were categorized as ‘*Early Discharge*’; their care included vital sign monitoring and initial examination by ED providers, followed by discharge to home. (2) Patients with only trauma triage to TTA but not inpatient admission are categorized as ‘*Triage Only*’; care included initial labs and monitoring by ED providers, and patients were discharged home after evaluation. (3) Patients with both trauma triage to TTA and inpatient admission are categorized as ‘*Triage and In-patient*’, sometimes necessitating acute care surgical management after evaluation.

SCD-related outcomes

We assessed three different outcomes. (1) *Time-to-first VOE* after the index date was defined as the time from injury to the first VOE requiring an ED or inpatient visit. If patients in the *Triage and In-patient* cohort experienced a VOE during their index hospitalization, this was still counted as a first VOE from time of injury. (2) *Annual frequency of VOE events* was measured by number of ED visits 365 days before and after the index date. (3) *ED LOS* of the most recent VOE event (reported in hours) immediately before and after the index date; LOS was assessed as the time between the date of admission for a VOE event to date of discharge. Two VOE events occurring within 280.8 hours

of each other were deemed as one event.²² Based on prior literature, VOE events were identified using ICD-9 codes 282.62, 282.64, 282.69, and 282.42 from ED visit documentation, representing vaso-occlusion both with and without crisis.²³

Statistical methods

Descriptive statistics were done to assess demographics and clinical characteristics. We represent means (m), and frequencies. For the primary objective, log-rank test was used to analyze time-to-VOE differences between the three treatment groups. We obtained survival curves using Kaplan-Meier stratified by trauma triage or inpatient admission status. Trauma triage/TTA status, inpatient admission, age, and sex were included as potential confounders, as age and sex may have an impact on SCD pathophysiology. For the secondary objective, preinjury and postinjury differences in annual frequency of VOEs and ED LOS were assessed using paired t-tests. Next, we assessed the impact of injury type (blunt vs penetrating) using two-sample t-tests. We tested ED management group differences (comparing *Early Discharge*, *Triage Only*, and *Triage and In-patient* cohorts) in preinjury and postinjury VOE outcomes using analysis of variance. All analyses were conducted using R V.4.1.3.

RESULTS

The patient registry included 356 adult patients with an SCD diagnosis who had a patient encounter from January 2000 to July 2021; 95 African American patients with SCD had a documented traumatic injury in that same timeframe. Patients were excluded if traumatic injury did not occur within 6 hours of documentation (n=10), had missing health record information 1 year before and after injury date (n=9), or incarceration at time of injury (n=3). Patients with isolated falls (n=18) were also excluded from this analysis. A total of 55 African American patients (male 48%, average age=37.6 years, SD=11.0) were used for our analysis, corresponding to genotypes Hb SS (n=26), Hb SC (n=16), HbSβ⁺ thalassemia (n=7), HbSβ⁰-thalassemia (n=3), and other (n=3) (table 1).

Of all patients with SCD, 49.1% had trauma triage to TTA after an injury, and 30.1% were admitted to an inpatient unit after the index injury. In this review of 55 patients, there were no SCD individuals with an inpatient admission for their injuries without a TTA; therefore, individuals with an isolated admission postinjury were not addressed in our analysis. Table 1 shows the number of patients in each of the ED management groups. Blunt injuries represented the most common mechanism of injury across all groups (82.9%). The proportion of penetrating injuries

Table 1 Cohort demographics and mechanism of injury characteristics

Characteristics	Total group (n=55)	Early discharge (n=28)	Triage only (n=10)	Triage and inpatient (n=17)
Age, mean (SD)	37.6 (11)	34.8 (10)	36.1 (10.2)	40.9 (12)
Gender, n (%)				
Female	42 (51.2)	16 (57.1)	8 (80)	5 (29.4)
Male	26 (48.8)	12 (42.9)	2 (20)	12 (70.6)
Mechanism of injury, n (%)				
Blunt	47 (82.9)	26 (92.9)	8 (80)	13 (76.5)
Penetrating	8 (17.1)	2 (7.1)	2 (20)	4 (23.5)

Demographic and mechanism of injury characteristics for the total sample and cohorts are defined above. No significant differences in characteristics were noted between cohorts.

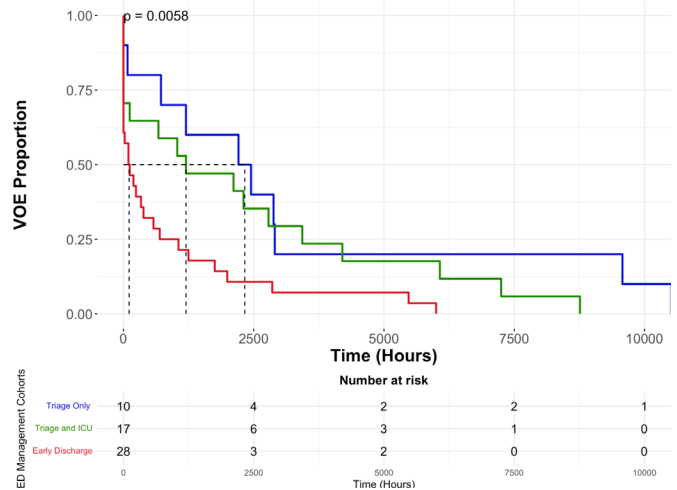


Figure 1 Kaplan-Meier curves showing effect of ED management on time-to-VOE after an injury. Time-to-VOE after an injury is further stratified by ED management groups. For *Early Discharge* patients, time-to-VOE is less than 100 hours or 3 days. This is to be compared with *Triage Only* and *Triage and In-patient* patients, with time-to-VOE of 2404 hours (or 100 days) and 1257 hours (52 days), respectively. ED, emergency department; VOE, vaso-occlusive event.

tended to be higher in the *Triage Only* (23.1%) and *Triage and In-patient* (20%) ED management groups, compared with *Early Discharge* (7.1%) ($\chi^2=2.577$, $p=0.276$).

Primary objective analysis

Time-to-VOE after injury stratified by ED management

Time-to-VOE after an injury was shortest for *Early Discharge* patients. Kaplan-Meier log-rank test showed that for all study patients with SCD, the time-to-first VOE was 26.25 days after an injury. Patients with *Early Discharge* experienced a VOE event within 2.93 days of their injury, followed by *Triage and In-patient* at 52.375 days and *Triage Only* at 100.16 days (K2 log rank=10.3, $p=0.0058$) (figure 1).

Independent effects of TTA and inpatient admission were also assessed separately. Controlling for SCD genotype, age, and gender, the Cox regression model showed a marginal effect of TTA status on VOE events (K2 log rank=12.09, $p=0.06$). Patients with a TTA experienced a VOE event at 79.65 days (K2 log rank=9.5, $p=0.002$) post injury; similarly, patients with an in-patient admission experienced a VOE event at 52.16 days (K2 log rank=0.9, $p=0.33$) (figure 2).

Secondary objectives analysis

Changes in annual VOE count and ED LOS postinjury

There were no significant preinjury postinjury differences in the annual VOE count (m=5.9 vs m=6.03, $t=1.982$, $p=0.716$) or average ED LOS of VOE (m=41.87 hours vs m=25.14 hours, $t=1.984$, $p=0.185$). Stratifying by mechanism of injury (ie, blunt or penetrating), there were no significant pre-post differences or between-group differences in annual VOE count for blunt (m=5.78 vs m=6.57, $t=1.982$, $p=0.512$) or penetrating (m=1.75 vs m=3.75, $t=1.986$, $p=0.323$) injuries. No within-group differences in average VOE ED LOS post injury for blunt (m=29.2 hours vs 41.9 hours, $t=1.984$, $p=0.326$) or penetrating (m=1.44 hours vs m=14.4 hours, $t=1.998$, $p=0.229$) injuries was noted. No between-group effects were noted (table 2).

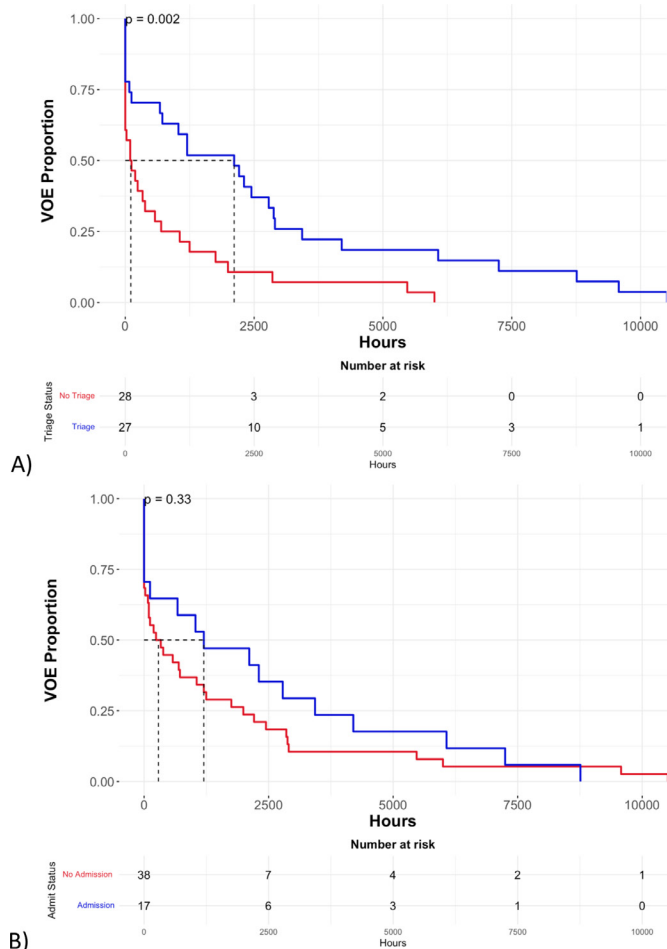


Figure 2 Kaplan-Meier curves showing effect of triage and in-patient admission status on time-to-VOE after an injury. (A) Time-to-VOE stratified by triage status confirms earlier findings; for patients who are triaged by TTA after injury, time-to-VOE is 1912 hours (79.67 days). Patients without triage had a time-to-VOE of 18.3 hours ($p=0.002$). (B) Time-to-VOE stratified by in-patient admission status yields similar trends; for patients who are ultimately admitted to an in-patient unit after injury, time-to-VOE is 1252 hours (52 days). Patients without admission had a time-to-VOE of 21.4 hours ($p=0.33$). TTA, trauma team activation; VOE, vaso-occlusive event.

Differences in VOE outcomes by ED management

There were no ED management group differences for annual frequency of VOE preinjury or postinjury (table 2). For ED LOS, there were no between-group effects for ED management; however, within-group differences revealed that the *Triage Only* post injury ($m=77.4$ hours) was significantly higher than preinjury measures ($m=16.1$ hours, $t=2.201$, $p=0.038$) (table 2). When the triaged groups were combined, SCD individuals who had trauma triage to TTA experienced a significant postinjury increase in LOS for VOE (mean difference=34.06 hours, $t=2.21$, $p=0.023$), compared with LOS for VOE for those who were not triaged (*Early Discharge*), from 32.9 hours preinjury to 33 hours postinjury ($t=2.006$, $p=0.997$).

DISCUSSION

To our knowledge, this is the first study assessing trauma impact in SCD, and specifically VOE-related outcomes after traumatic injury among patients with SCD. In this study, individuals with penetrating injuries were overrepresented in *Triage Only* and

Table 2 SCD outcomes stratified by ED management group and mechanism of injury

Outcomes	Early Discharge			Triage Only			Triage and In-patient			Blunt			Penetrating			Comparison		
	Pre	Post	P value*	Pre	Post	P value*	Pre	Post	P value*	Pre	Post	P value	Pre	Post	P value*	Diff	P value	
Annual VOE count, mean (SD)	3.2 (6.3)	3.92 (5.8)	0.72	8.5 (18.7)	10.2 (17.8)	1.7	7.1 (15.6)	7.1 (15.6)	0.50	6.6 (15)	6.57 (12.8)	0.132	5.78 (13.1)	6.57 (12.8)	1.75 (2.87)	3.75 (7.91)	2.0	0.323
Average VOE duration, mean (SD)	32.9 (67.6)	33 (82.9)	0.1	16.1 (27.2)	77.4 (77.5)	61.3	17.6 (34.9)	35.6 (60.3)	18.0	17.6 (34.9)	41.9 (76.2)	0.297	29.2 (56.7)	41.9 (76.2)	1.44 (2.23)	14.4 (34.9)	12.96	0.229

The *Early Discharge* cohort had neither trauma triage to TTA nor inpatient admission on presentation to ED after an injury. The *Triage Only* cohort had trauma triage to TTA, but no inpatient admission. The *Triage and In-patient* cohort had trauma triage to TTA and subsequent inpatient admission. The annual number of VOE events was recorded 12 months before and after the trauma index date. Duration of VOE event was the length of VOE immediately before and subsequently after the trauma index date. *P value compares preinjury and postinjury changes within each group. P value compares between *Triage Only* and *Triage and In-patient* to *Early Discharge* (reference) or *Blunt* and *Penetrating* groups. ED, emergency department; SCD, sickle cell disease; TTA, trauma team activation; VOE, vaso-occlusive event.

Triage and In-patient groups, as opposed to the *Early Discharge* ED management group; this factor validates existing protocols that preferentially triage penetrating injuries which require immediate medical intervention. The annual frequency of VOE events experienced by individuals in our review at baseline (preinjury) was 5.9, and the average ED LOS of a preinjury VOE event was 22.5 hours; however, since a large proportion of VOE episodes can be managed at home, the actual rate of VOE may be underestimated.²⁴

After injury, there is no significant increase in either annual VOE count or ED LOS for postinjury VOE. However, significant increases in ED LOS for VOE were noted in those who were ultimately trauma triaged to TTA, irrespective of inpatient admission status. Since LOS for VOE was used to analyze severity of VOE,²⁵ we assume that those with a trauma triage experienced an increase in severity of VOE. This is likely due to the severity of injury that requires a trauma triage to begin with.

Our results suggest that although there seems to be no independent effect of injury on long-term impact on VOE outcomes, time-to-VOE may be impacted by injury management. Exposure to an injury may result in early onset of vaso-occlusion. Half of all patients with SCD experienced a VOE event within 26.25 days after injury. Specifically, those without TTA and are therefore discharged early, experience faster time-to-VOE.

Results need to be replicated in a prospective cohort, however, increased incidence of VOEs post injury could be explained by the inflammatory response and coagulation cascade; plasma levels of proinflammatory cytokines (ie, IL-1 β) are generally increased in patients with SCD, specifically in the Hb SS genotype which is overrepresented of our sample.^{13,26} These markers are responsible for complement activation and leukocyte adhesion, impacting coagulation and causing vaso-occlusion—this cycle is nearly identical for the inflammatory response after an injury. Therefore, it is likely that increased inflammatory response after an unresolved injury (perhaps caused by early discharge) is linked directly to early onset VOE, but translational studies are critically needed to quantify the link between acute and chronic physical stress and early erythrocyte sickling in the context of SCD.

Prehospitalization care for patients with SCD undergoing a VOE event includes the administration of intravenous fluid to reduce blood viscosity and dilute the inflammatory cytokines associated with VOE.²⁶ Patients who are injured commonly receive intravenous fluids depending on the level of trauma triage;²⁷ therefore, it is likely that early onset VOE noted in patients who were not triaged could be attributed to lack of appropriate and timely administration of intravenous fluids. Nonetheless, since lack of trauma triage was the most predictive factor of early onset VOE, there remains a need for prospective studies to fully analyze causal links between injury and VOE-related outcomes.

Traditionally, perioperative management of SCD has been understudied; patients with SCD are at a heightened risk for sepsis, infection, thrombotic events, and longer LOS.²⁸ Although routine preoperative blood transfusions may improve tissue oxygen delivery, transfusion may increase blood viscosity,²⁹ possibly contributing to poor VOE outcomes.

Patients with SCD also consistently report increased racial stigmatization and socioeconomic barriers in access to care in EDs.¹⁴ In the context of trauma, non-Hispanic white patients were more likely to receive an opioid analgesic in the ED than were African American patients, further exacerbating the severity of acute post-traumatic pain.³⁰ Therefore, poor VOE outcomes after an injury may pose additional challenges in terms of continuity of

care and pain management, resulting in increased hospitalizations and associated costs.³¹

A surprising finding of this study is that only one patient with SCD included in the study was triaged using the Emergency Severity Index (ESI) to level 5 for a VOE in the absence of injury. Standard of care supported by the 2014 Evidence-Based Management of Sickle Cell Disease Expert Panel Report highlights the need for the ESI triage of all patients with SCD presenting to the ED at a minimum level 2.²⁵ If VOE pain is more frequent and severe after an injury, this downplaying of ESI triage level may contribute to worsening complications associated with chronicity of SCD and injury pain or outcomes.

Clinical outcomes for patients with SCD with injuries are unknown due to a knowledge gap in the current literature;¹⁶ this is especially concerning, as SCD generally impacts quality of life in African American and Hispanic communities.³² Although our findings are preliminary, they highlight a substantial intersection between traumatic injury and heightened risk of poor VOE outcomes. Further research in the field is required to improve our understanding of changing psychosocial and biological interactions, as well as to develop guidelines to appropriately assess and address subsequent chronic pain after trauma.

Some limitations of this study should be noted, including the retrospective nature of the data and reliance on medical records and consistent provider coding of VOE. As a result, demographic and clinical data—such as insurance status, intubation, fluid, blood product, or analgesic management, and mortality—was not accounted for in this present review and should be explored as potential modifiers in future studies. Future studies should be designed prospectively to ensure comprehensive data collection given the present limitations. Additionally, we acknowledge that there may be VOEs self-managed by patients with SCD at home, or if patients presented to hospitals outside the 11 urban centers included in this study; therefore the true impact of injury on VOE incidence may be underestimated in our review. This is also applicable for any unplanned admissions for trauma-related complications that occurred outside these 11 urban centers. Our study did not provide insight on the monthly number of VOE events for 12 months after an injury; future studies should also aim to perform a subgroup analysis of different VOE time points. Further, ED treatment is not clearly defined, since there are no protocols defining standard of care for patients with SCD trauma, treatment provided during trauma triage and inpatient care can be highly variable between clinical teams; additional treatment given to injured patients with SCD was not recorded in this study. This can result in discrepancies in VOE-related outcomes. In addition, our review does not consider SCD individuals with an isolated inpatient admission after their injuries without a TTA, as they are not represented in our sample. Future studies should aim to expand their cohorts to include this subset should it be significant.

Lack of associations may be due to heterogeneity of trauma severity within the groups. Our study is limited by a lack of a national-level or institutional-level SCD registry, leading to inconsistent coding of VOE events and other complications. It has been reported in prior studies that SCD is not listed within the National Trauma Data Bank, which poses a barrier for further research in terms of representation of patients with SCD in clinical studies.³³ Our study further supports this claim: SCD was not listed as a ‘pre-existing condition’ within our institutional-level trauma registry, resulting in underrepresentation and a low sample size.

Future research can be directed towards greater inclusion of patients with SCD in trauma registries and studies to expand on measures such as demographic information, comorbidities, and prehospital treatment. Furthermore, there remains a critical need to understand mortality and long-term morbidity, quality of life outcomes, clinical and inflammatory biomarkers of injury severity, and the effect of critical surgical interventions on SCD-related outcomes.

CONCLUSION

In conclusion, data from this retrospective cohort study suggest that patients with SCD who experience a traumatic injury develop early onset VEOs, and experience an increase in the frequency and duration of VEO events post trauma. This is especially true for patients with early discharge, or those who are not trauma-triaged to TTA or admitted to an inpatient service; more appropriate intervention may serve to prevent VEO. Given the likely intersection of inflammatory responses for both trauma and vaso-occlusion, further research is needed to inform care guidelines and adequately manage the exacerbation of chronic pain after injuries. Future research should be directed to address gaps in awareness and cultural competence when caring for patients with SCD after trauma, which disproportionately and negatively impact communities of color.

Acknowledgements Research reported in this publication has been presented at the 64th American Society of Hematology Annual Meeting and Exhibition in December 2022. Conference abstract has been accepted for publications in *Blood Advances* 2022. E. Parchuri, D. Gruen, F. Guyette, C. Jonassaint, J. Brown, L. Decastro; The Impact of Multi-System Trauma in Patients with Sickle Cell Disease. *Blood* 2022; 140 (Supplement 1): 10865–10866. doi: <https://doi.org/10.1182/blood-2022-159851>.

Contributors EP, CRJ, and JOB played crucial roles in writing the main article text, performing data analysis, and employing analytical methods. EP, FG, CRJ, and JOB contributed to the interpretation of the results and provided valuable insights into the implications of the findings. CRJ, as the principal investigator, oversaw the execution and design of the study, outlining the article and its coherence with research objectives, and actively contributed to data analysis. EP, ML-P, JOB, DSG, FG, JBB, LDC, CRJ all contributed to the design and conduct of the study, including collection of study-related data, and reviewed final versions of the article. CRJ is the author responsible for the overall content as the guarantor.

Funding Research reported in this publication was partially supported through a Patient-Centered Outcomes Research Institute (PCORI) Award (CER-2018C2-13320) and the National Institute of Mental Health under Award Number R34MH125152. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval All methods in this study performed in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) Committee of the University of Pittsburgh (STUDY18100025). Participation in the study was voluntary and written informed consent was obtained from the participants prior to enrolling in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Ektha Parchuri <http://orcid.org/0000-0003-3862-3919>
 Danielle S Gruen <http://orcid.org/0000-0003-1019-4390>
 Frances Guyette <http://orcid.org/0000-0002-9151-4896>
 Joshua B Brown <http://orcid.org/0000-0002-6936-035X>
 Charles R Jonassaint <http://orcid.org/0000-0002-5662-5806>

REFERENCES

- Krug EG, Sharma GK, Lozano R. The global burden of injuries. *Am J Public Health* 2000;90:523–6.
- Rossiter ND. Trauma—the forgotten pandemic *Int Orthop* 2022;46:3–11.
- Rosenbloom BN, Khan S, McCartney C, Katz J. Systematic review of persistent pain and psychological outcomes following traumatic musculoskeletal injury. *J Pain Res* 2013;6:39–51.
- Sobrinho J, Shafi S. Timing and causes of death after injuries. *Proc (Bayl Univ Med Cent)* 2013;26:120–3.
- Pierce A, Pittet J-F. Inflammatory response to trauma. *Curr Opin Anaesthesiol* 2014;27:246–52.
- Lord JM, Midwinter MJ, Chen Y-F, Belli A, Brohi K, Kovacs EJ, Koenderman L, Kubek P, Lilford RJ. The systemic immune response to trauma: an overview of pathophysiology and treatment. *Lancet* 2014;384:1455–65.
- Hildebrand F, Pape H-C, Krettek C. Die Bedeutung der Zytokine in der Posttraumatischen Entzündungsreaktion. *Unfallchirurg* 2005;108:793–803.
- Shao Y, Cheng Z, Li X, Chernaya V, Wang H, Yang X. Immunosuppressive/anti-inflammatory cytokines directly and indirectly inhibit endothelial dysfunction—a novel mechanism for maintaining vascular function. *J Hematol Oncol* 2014;7:80.
- Conran N, Belcher JD. Inflammation in sickle cell disease. *Clin Hemorheol Microcirc* 2018;68:263–99.
- Uzunova VV, Pan W, Galkin O, Vekilov PG. Free Heme and the polymerization of sickle cell hemoglobin. *Biophys J* 2010;99:1976–85.
- Veluswamy S, Shah P, Denton CC, Chalacheva P, Khoo MCK, Coates TD. Vaso-occlusion in sickle cell disease: is autonomic dysregulation of the microvasculature the trigger? *J Clin Med* 2019;8:1690.
- Quinn CT. Minireview: clinical severity in sickle cell disease: the challenges of definition and prognostication. *Exp Biol Med (Maywood)* 2016;241:679–88.
- Torres LS, Okumura JV, Silva DGH, Mimura KKO, Belini-Júnior É, Oliveira RG, Lobo CLC, Oliani SM, Bonini-Domingos CR. Inflammation in sickle cell disease: differential and down-expressed plasma levels of annexin A1 protein. *PLoS One* 2016;11:e0165833.
- Sinha CB, Bakshi N, Ross D, Krishnamurti L. Management of chronic pain in adults living with sickle cell disease in the era of the opioid epidemic. *JAMA Netw Open* 2019;2:e194410.
- Loberg JA, Hayward RD, Fessler M, Edhayan E. Associations of race, mechanism of injury, and neighborhood poverty with in-hospital mortality from trauma: a population-based study in the Detroit metropolitan area. *Medicine (Baltimore)* 2018;97:e12606.
- Tessema FA, Lapping-Carr G, Affini MI, Selkridge IK, Oppong AY, Jones TA, Zakrisson T. Sickle cell trait and multisystem trauma: an unaddressed urgent knowledge gap. *Trauma Surg Acute Care Open* 2022;7:e000955.
- Jabour AJ, Warrier R, Kretschmar P. Multiple enlarging masses and failure to thrive in infant with sickle cell trait. *Clin Pediatr (Phila)* 2021;60:131–3.
- Mercy JA, Heath CW Jr, Rosenberg ML. Mortality associated with the use of upper-body control holds by police. *Violence Vict* 1990;5:215–22.
- Ong AW, Omert LA, Vido D, Goodman BM, Protetch J, Rodriguez A, Jeremitsky E. Characteristics and outcomes of trauma patients with IN-PATIENT lengths of stay 30 days and greater: a seven-year retrospective study. *Crit Care* 2009;13:R154.
- Granström A, Strömmer L, Schandl A, Östlund A. A criteria-directed protocol for in-hospital triage of trauma patients. *Eur J Emerg Med* 2018;25:25–31.
- WHO. Manual of the International statistical classification of diseases, injuries, and causes of death. Based on Recommendations of the Eight Revision Conference, 1965 and Adopted by the Nineteenth World Health Assembly; 1976.
- Zaidi AU, Glaros AK, Lee S, Wang T, Bhojwani R, Morris E, Donohue B, Paulose J, Iorga SR, Nellesen D. A systematic literature review of frequency of vaso-occlusive crises in sickle cell disease. *Orphanet J Rare Dis* 2021;16:460.
- Kang HA, Barner JC, Richards KM, Bhor M, Paulose J, Kutlar A. Association between vaso-occlusive crises and opioid prescriptions among patients with sickle cell disease: a retrospective claims-based study. *J Health Econ Outcomes Res* 2020;7:94–101.
- Shah N, Bhor M, Xie L, Halloway R, Arcona S, Paulose J, Yu H. Evaluation of vaso-occlusive crises in United States sickle cell disease patients: a retrospective claims-based study. *J Health Econ Outcomes Res* 2019;6:106–17.
- Evidence-based management of sickle cell disease: expert panel report. *Pediatrics* 2014;134:e1775.
- Jang T, Poplawski M, Cimpeanu E, Mo G, Dutta D, Lim SH. Vaso-occlusive crisis in sickle cell disease: a vicious cycle of secondary events. *J Transl Med* 2021;19:397.
- Kabil G, Frost SA, McNally S, Hatcher D, Saavedra A, Suster CJ, Moscovia M, Shetty A. Identifying factors associated with intravenous fluid administration in patients with sepsis presenting to the emergency department: a retrospective cohort study. *BMC Emerg Med* 2022;22:98.
- Brumm J, White RS, Arroyo NS, Gaber-Baylis LK, Gupta S, Turnbull ZA, Mehta N. Sickle cell disease is associated with increased morbidity, resource utilization, and Readmissions after common abdominal surgeries: a multistate analysis, 2007–2014. *J Natl Med Assoc* 2020;112:198–208.
- Adjepong KO, Otegbeye F, Adjepong YA. Perioperative management of sickle cell disease. *Mediterr J Hematol Infect Dis* 2018;10:e2018032.

- 30 Beaudoin FL, Gutman R, Zhai W, Merchant RC, Clark MA, Bollen KA, Hendry P, Kurz MC, Lewandowski C, Pearson C, *et al*. Racial differences in presentations and predictors of acute pain after motor vehicle collision. *Pain* 2018;159:1056–63.
- 31 Osborne JC, Osakwe Z, Odlum M. Opioid use in adults with sickle cell disease hospitalized during vaso-occlusive crisis: a systematic review. *J Hematol* 2021;10:46–52.
- 32 Ojodu J, Hulihan MM, Pope SN, Grant AM, Centers for Disease Control and Prevention (CDC). Incidence of sickle cell trait--United States, 2010. *MMWR Morb Mortal Wkly Rep* 2014;63:1155–8.
- 33 Grigorian A, Gabriel V, Nguyen NT, Smith BR, Schubl S, Borazjani B, Joe V, Nahmias J. Black race and body mass index are risk factors for rhabdomyolysis and acute kidney injury in trauma. *J Invest Surg* 2020;33:283–90.