Triage Status is a Predictor of Higher Emergency Department Utilization Among Traumatically Injured Patients with Sickle Cell Disease

by

Ektha Parchuri

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This essay is submitted

by

Ektha Parchuri

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and approved by

Essay Advisor: Nancy W. Glynn, PhD, Associate Professor, Director, Master's Degree Programs, Department of Epidemiology, School of Public Health, University of Pittsburgh

Essay Reader: Charles Jonassaint, PhD, MHS, Assistant Professor of Medicine, Department of Medicine, University of Pittsburgh School of Medicine

Essay Reader: Maria L. Pacella-LaBarbara, PhD, Research Assistant Professor of Emergency Medicine, University of Pittsburgh School of Medicine

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Abstract

Introduction: Sickle cell disease (SCD) impacts one in 500 African Americans and is associated with vaso-occlusive events (VOE), leading to severe complications if unmanaged. Effective pain management in emergency settings is often delayed due to stigma and limited resources. Given similar inflammatory responses characterizing both VOE and traumatic injury, this study is the first to examine whether traumatic injury aggravates VOE-related outcomes and pain management needs.

Methods: A retrospective chart review was conducted from an SCD clinic in Western Pennsylvania from 2000-2021. SCD and injury status was determined using ICD-9/10 data. Patients were sorted into three treatment groups based on injury hospital management: 1) neither trauma triage nor ICU admission ("early discharge"), 2) triage but no ICU ("triage only"), and 3) "triage-ICU". Primary outcomes included pre/post-injury annual frequency of VOE events and ED length of stay (LOS) for VOE; secondary outcomes included time from injury to first VOE.

Results: A total of 356 patients with SCD from 2000-2021 were identified; 55 patients with prior traumatic injury were included. No significant increase in annual frequency of VOE or ED LOS for VOE post-injury. Triage only individuals experienced a significant increase in ED LOS for first VOE (MD= 61.3 hours, p=0.038). All triaged-injured SCD patients experienced a significant post-injury increase in LOS for VOE (MD=34.06 hours, t=2.205, p=0.023), compared to non- triaged (MD = 0.01, t=2.006, p=0.997). Kaplan-Meier log-rank test revealed early

discharge individuals experienced a VOE event within 2.93 days of injury, followed by triage-ICU individuals at 52.375 days and triage-only individuals at 100.16 days (p=0.0058). No-ICU patients experienced a VOE event in less than 1 day, compared to those ICU patients at 52.16 days (K2 log rank = 0.9, p=0.33). Hazard rate of VOE events was affected by trauma triage (p=0.06).

Conclusions: Triage status was a significant predictor in poor VOE outcomes, resulting in increased annual VOE events and longer ED length of stay for VOE. It is in the best interest of public health experts and of public health significance to develop specific triage protocols for ED management of the injury in SCD patients.

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Preface

I would like to thank Dr. Charles Jonassaint, Dr. Joshua Brown, Dr. Francis Guyette, Dr. Maria Pacella, and Dr. Laura De Castro for their continued mentorship, support, and willingness to move mountains for me to achieve my goals. Charles has been the backbone of this project, introducing me to mentors, peers, and lifelong friends who would not have made this project possible. I am forever thankful to Dr. Brown and Dr. Guyette who introduced me to their field of Emergency surgery and Trauma services and helped seed the pathway for my future career. Dr. Pacella has been invaluable in helping shape this project to where it is today with her insight. Dr. De Castro introduced me to a new family at the American Society of Hematology who continue to cheer me on for all my future endeavors within Hematology and Emergency Medicine. I could not have done it with all these individuals who shared my passion and visions for this field, encouraging me to push boundaries and continue advocating for better emergency care for patients with Sickle Cell Disease. I am indebted to my patients, whom I shared many laughs, tears, and hopes for our future; I have learned so much from each encounter and will strive to always do so as a future physician.

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1.0 Introduction

1.1 Sickle Cell Disease

According to The Center for Disease Control and Prevention, it is estimated that in the United States, more than 100,000 individuals suffer from Sickle Cell Disease (SCD); with recent improvements in prenatal genetic screening measures, this number is expected to rise (Dumovich & Singh, 2023). Prevalence of this disease globally is high among people of Sub-Saharan African, South Asia, the Middle East, and the Mediterranean. This disease impacts 1 in 500 African Americans and is therefore overwhelmingly represented amongst racial minorities. SCD is a multisystem disorder and the most common genetic disease in the United States. The disease is caused by a mutation in the hemoglobin beta chain, specifically the Glu6Val substitution in chromosome 11. This mutation results in the polymerization of hemoglobin S (HbS), transforming normal, circular red blood cells into a sickled "(" shape; such a transformation results in early destruction of erythrocytes, releasing free hemoglobin and heme iron into the plasma (Sedrak & Kondamudi, 2023). The degree of this hemolytic disorder is largely dependent on various genotypes associated with SCD, with the highest degree of HbS polymerization noted in patients with HbSS and HbS β^0 genotypes. Other rather less severe forms of SCD are HbSC and HbSβ^+ genotypes (Dumovich & Singh, 2023).

The polymerization of HbS and consequent erythrocyte destruction contribute to worsening pathophysiology of the disease over time, resulting in endothelial destruction. This process causes increased oxidative stress coupled with poor oxygen perfusion, causing subsequent damage to the endothelium and tissue damage. Oxidative stress ultimately instigates what is known

as vaso-occlusion, a blockade of blood vessels. Recurrent and episodic vaso-occlusive events (VOE) cause tissue damage stemming from the release of excess leucocytes, platelets, and pro-inflammatory cytokines. The downstream effect of this process causes increased adhesion of sickled cells, further reiterating this cycle of inflammation (Torres et al., 2016). Therefore, with every episodic vaso-occlusive event (VOE), the circulatory vasculature is dramatically deteriorated, leading to worsened outcomes and rise of secondary complications, such as acute chest syndrome (ACS), cerebrovascular accidents (CVA) or stroke, pulmonary embolism (PE), renal complications, eye complications, splenic sequestration, priapism, cholelithiasis, and osteonecrosis (Sedrak 2023). VOE therefore is associated with chronic pain, requiring extensive pain management protocols in emergency settings. With the exception of VOE, the phenotypic expression of SCD is limited. It is known that environmental factors, such as stress or anxiety, cold weather, air quality, comorbidities, port infections, and fetal hemoglobin level can cause a VOE (Sedrak 2023). Persistently high levels of pain associated with VOE requires immediate emergency intervention and pain management techniques (Sedrak 2023); however, since the clinical presentations of VOE can be highly variable, research remains limited. Nonetheless, persistent chronic pain results in frequent emergency department utilization (EDU), hospitalizations, evolving pain management needs, and high hospital-associated costs (Brumm 2020).

This synergy with persistent social and institutional barriers, SCD patients continue to face discrimination and mistrust amongst providers, further preventing access to proper care. It has been described that a variety of social factors tend to add to the burden of SCD; these include stigma associated with SCD, implicit bias, and racism (Boulet, Yanni, Creary, & Olney, 2010). Stigma bias intensify existing psychological symptoms and impose a burden that decrease quality

of life in SCD individuals, likely stemming from racism, socioeconomic status, and pain episodes that require treatment with opioids. Health care providers may ascribe negative characteristics to those living with SCD, often labelling individuals as "drug seeking" due to complicated pain management needs (Burgess, van Ryn, Crowley-Matoka, & Malat, 2006). These factors contribute to barriers in employment, schooling, and equality in healthcare. Furthermore, individual factors patients with SCD face include health literacy issues, demographic variables, cognitive deficits, and mental health challenges. An observational study of adolescents with SCD found lower health literacy levels compared to expected average grades; this impact may contribute to increased risk of poor medication and treatment adherence, worsening outcomes (Creary et al., 2017). Anemia associated with SCD has also been known to worsen cognitive deficits, and these neurocognitive deficits may also have a positive feedback loop for VOE development (Prussien, Jordan, DeBaun, & Compas, 2019).

Although the survival of patients with SCD has steadily improved over time, these physiological and social processes contribute to low life expectancies. The average projected life expectancy for patients with SCD is 54 years, decades shorter than those without SCD (Ojodu 2014); it has been shown that life expectancy is also interlinked with an individual's income. The predicted mean income for patients with SCD experiencing 0 and ≥4 VOCs in the past year was $47,488 and $34,569, respectively a seemingly linear relationship (Thom et al., 2019). Therefore, there remains a critical need to integrate social determinants of health when developing continuum of care protocols for SCD patients.

1.2 Treatment and Pain Management in SCD

Current evaluation plans for SCD have dramatically evolved over the past century. Improvements in newborn and prenatal screening have contributed to early interventions and consistent care. Diagnosis for SCD is based on hemoglobin electrophoresis to detect hemoglobin quantity and genotypes. Usual lab evaluation consists of a CBC with differential, reticulocyte count, complete metabolic panel, LDH level, bilirubin level, and blood type (Boulet et al., 2010). Imaging techniques have been employed to diagnose secondary complications, such as ACS. Chest x-rays, transcranial sonograms, and other imaging studies are used consistently to monitor disease progression. SCD management is prioritized by managing general health and reducing complications (Boulet et al., 2010). Health maintenance is utilized to continually screen for risk factors as described prior and complications as the disease progresses by age. For example, in young children, the risk of stroke is assessed through routine screening with transcranial doppler (TCD) to visualize large intracranial blood vessels (Crow, 2020).

VOE pain management is critical in reducing mortality (Beaudoin et al., 2018). Rapid assessment of centralized or generalized pain is needed for early administration of analgesic therapy appropriate according to predefined care plan, created by their Hematologists and prior encounters in the Emergency Department (ED). It is important to note that this care plan—which includes information on dosing, frequency, and type of analgesic—is rarely modified without consult from their Hematologist. For patients with rare VOE events, NSAIDs or acetaminophen may suffice (Sedrak & Kondamudi, 2023). A CBC complete panel, renal test, or urine test is required for patients presenting with fever. In the event of suspicion for ACS, stroke, or splenic sequestration, transfusion therapy is often recommended. Treatment plans include hydroxyurea, antihistamines, opiates, and antibiotics. The only known cure for SCD is a hematopoietic stem cell

transplantation (bone marrow transplantation); however, only 8% of the SCD population can find a proper donor match, and even a smaller subpopulation of matched donors can afford high costs associated with this procedure which is only covered by Medicaid if an individual participates in an approved prospective clinical study (Grady, Fiori, Patel, & Nysenbaum, 2021). Alternatively, simple or exchange transfusion is commonly used as a self-management recommendation for SCD although this procedure requires numerous follow-up visits and raises the risk for localized port infection (Druye, Robinson, & Nelson, 2018)

Despite these national recommendations outlined by the American Society of Hematology—an organization committed to promoting and supporting clinical hematology research and advocacy—there remains to be persistent barriers in treatment for SCD pain (Boulet et al., 2010). Medical students, residents, and attendings are prone to stereotyping pain tolerance between black and white patients as a result of structural and systemic inequity, rooting back to the early 19th century. As a result, African Americans generally receive lower quality of pain management than white patients and are likely to be labelled as "drug-seeking", despite reporting the same level of pain as white patients (Burgess et al., 2006). This inherent bias results in further mistrust of providers among individuals and families impacted by SCD, which worsens health outcomes and translates to EDU only when symptoms worsen. A qualitative study conducted in 2007 questions 10 women affected by SCD about their experiences of perceived racism, stress, and general healthcare system (Portia, 2007). These women reported that experiences in the ED triggered feelings of stress, a known factor for exacerbating or worsening VOE pathophysiology (Portia, 2007).

1.3 Traumatic Injury

Traumatic injury is defined as a tissue injury that occurs due to sudden violence or accident, primarily caused by falls, motor vehicle accidents, homicide, or self-inflicted injury (Krug, Sharma, & Lozano, 2000)). The sudden tissue death initiates a similar inflammatory cascade to that observed in SCD, disrupting immunologic and metabolic responses needed for homeostasis (Dumovich & Singh, 2023). Injury type is generally recognized as either blunt, penetrating, and deceleration in trauma; this hierarchy system can induce a spectrum of body responses to injury dependent on an individual's pre-existing health status. However, blunt force trauma is the most common mechanism of injury, and are further classified into four categories: contusion, abrasion, laceration, and fracture. These injuries arise from sudden encounter from a blunt object with the body, commonly seen after a fall or motor vehicle accidents (Mbanjumucyo et al., 2016).

In the United States, trauma is the leading cause of morbidity and mortality in children and adults under age 44 in 2022 (Rossiter, 2022). Globally, injury accounts for nearly 10% of the global mortality burden, disproportionately impacting individuals in low- and middle-income countries (Mbanjumucyo et al., 2016). Specifically, head trauma and exsanguination are the most common early causes of death due to blunt traumatic injuries. Traumatic brain injury (TBI), however, is often viewed as a separate category of injuries during initial field assessments due to their critical pathophysiology and immediate debilitating effects; examples of TBI include concussions (mild TBI), extra-axial hematoma, contusion, traumatic subarachnoid hemorrhage (SAH), and diffuse axonal injury (DAI) (Georges & J, 2023). Toxicokinetic principles are primarily used to assess biomarkers released secondary to neuronal injuries and are generally an indicator of outcomes. For blunt or penetrating injuries, prehospital parameters—such as lactate, base deficit, and field vitals—are used to quickly assess need for treatment and outcomes.

Trauma systems are organized approaches to patients who are acutely injured, occurring in defined geographic areas with outreach to local and regional emergency medical service (EMS) systems (Hoyt & Coimbra, 2007). Prehospital care, which will be outlined in greater detail later, is crucial for improving survival. It is dependent on rapid transport of patients to appropriate Trauma centers, coordination and effective communication systems, training, proper triage and transport, and early treatment interventions. Treatment and standard of care outlined in trauma triage protocols is equally important to determine need for immediate further testing to rule out life-threatening injuries and initiate necessary treatment. Annually, over 29 million people in the United States are treated for trauma in the ED (Carr et al., 2017). However, stark disparities and geographic variation in accessibility of trauma centers exist, especially for individuals living in rural areas (Hsia & Shen, 2011). Specifically, African American individuals are less likely to have access to trauma care, with trauma center closures disproportionately impacting African Americans, uninsured individuals, and individuals living in poverty (Tung et al., 2019), further exacerbating health outcomes.

The consequences of traumatic injury, in addition to high rates of morbidity and mortality (Sobrino & Shafi, 2013), may include persistent or chronic pain that is prevalent up to seven years post-injury (Rosenbloom, Khan, McCartney, & Katz, 2013). This process is likely due to the systemic reaction triggering an inflammatory response, which activates the coagulation cascade; while this process is necessary for healing (Darlington et al., 2015; Lord et al., 2014), prolonged and imbalanced systemic inflammation from tissue damage can cause an overproduction of proinflammatory cytokines (Hildebrand, Pape, & Krettek, 2005), causing endothelial dysfunction at unrelated sites (Shao et al., 2014). The resulting hypoxia leads to further permanent damage, contributing to poor survival rates (Darlington et al., 2015). Therefore, long-term pain

management is required for survivors of multisystem traumatic injuries, highlighting the critical importance of proper initial EMS assessment in-field.

1.4 Traumatic Injury in Sickle Cell Disease

Given critical overlap of physiological responses to traumatic injury and VOE that occur even in the absence of injury among SCD patients, there is a strong biological plausibility of worse outcomes in trauma patients with SCD. Further, similar to those affected by SCD, traumatic injury disproportionately impacts racial and ethnic minority groups, with African Americans overrepresenting individuals living in high poverty neighborhoods; this association places minority members at the highest risk of mortality and chronic pain following injury (Loberg, Hayward, Fessler, & Edhayan, 2018; Rosenbloom et al., 2013). Consequently, patients with SCD represent a vulnerable population that may respond to and recover differently from traumatic injury, compared to those without SCD.

Yet, there is a dearth of research on the prevalence and clinical impact of traumatic injury among SCD patients (Tessema et al., 2022); the extant literature is limited to case reports of such potential association among specific populations (e.g., infants and victims of homicide). Specifically, hypercalcemic crisis and subcutaneous fat necrosis, coupled with hypotension and tachycardia, were present in an infant with SCD following a traumatic birth; hospitalization was required at 7 weeks of age for acute kidney injury. However, it is unknown whether these complications were associated with traumatic birth injury or with improper prenatal care (Jabbour, Warrier, & Kretschmar, 2021). Similarly, a case series following trauma-induced homicides found intravascular red blood cell sickling at autopsy in 4 of 14 African American individuals with SCD

(29%), suggesting that trauma-induced changes may contribute to worsening sickling; however, some individuals had indications of phencyclidine (PCP) use and stress-related arrythmias. Given these and other confounders, combined with limited data from case studies, it remains unknown whether trauma may trigger worse SCD-related outcomes (Mercy, Heath, & Rosenberg, 1990). It is assumed, however, that since the secondary complications that arise from both traumatic injury and recurrent VOE are similar in nature, that there could be an undiscovered link between exposure to traumatic injury and earlier onset of secondary complications commonly seen in SCD pathophysiology. Given the stark differences in prehospital EMS interventions for traumatic injury and VOE, it is also likely that these differences may contribute to worse health outcomes for injured SCD patients.

1.5 Prehospital Interventions and Emergency Department Management for Vaso-occlusive Events in Sickle Cell Disease

Management of VOE and other SCD-related complications in the ED setting is dynamic, complex, and evolving. In 2014, the National Heart, Lung, and Blood Institute (NHLBI) established prehospital and in-hospital guidelines for the management of acute sickle cell pain in the ED. Patients with SCD should be rapidly prioritized for triage and assessment, assigned highest priority for evaluation by a physician. This initial assessment should highlight new complications, followed by rapid administration of opioid analgesic, reassessment, and repeat dosing every 15 to 30 minutes until pain has been controlled (Wells, Pasero, & McCaffery, 2008). It is crucial that individualized SCD-specific protocol created for each patient is adhered to prevent opiate tolerance. Elevated levels of serum phospholipase A2 levels are associated with ACS and require

immediate transfusion. Patients are also assessed for hypoxia and are given simple exchange transfusion if no other co-complications occur. These interventions are added to pain management medications prescribed by Hematologists as daily standard of care (such as Hydroxyurea, Oxycodone, etc). Recent emerging research suggests that patient-controlled analgesia (PCA) devices may be helpful for not only patient autonomy but more effective pain management and quality improvement (McNicol, Ferguson, & Hudcova, 2015).

However, negative provider attitudes towards individuals living with SCD is the main barrier for effective prehospital management of VOE, with many physicians believing that SCD patients may exaggerate their pain. However, the NHLBI's new recommended protocol provided elements of improving the ED experience for people with SCD pain, focusing on pillars such as provider and system improvement. Key facets this new model focuses on is to 1) reduce frustration on part of ED providers (management of opioid tolerance), 2) increase knowledge regarding SCD-pain (educational videos on stigma and bias), 3) SCD-specific quality improvement (PCA pumps or IV dosing alternatives), and 4) guidelines to improve overall ED care (reduce wait times) (Glassberg, 2017).

Other prehospital management for VOE includes the administration of intravenous fluid (IV) to reduce blood viscosity and dilute the inflammatory cytokines associated with VOE (Jang et al., 2021). However, there seems to be conflicting evidence suggests that administering IV fluids may result in poor pain control in SCD patients as a result of fluid overload (Ojo, Ojukwu, Asmare, Odipe, & Larbi, 2022). Overall, there are significant gaps in creating an impactful prehospital guideline which benefit SCD patients given the barriers.

1.6 Prehospital Interventions and Emergency Department Management for Traumatic Injury

In-field triage assessment is determined by a range of prehospital parameters predictive of outcomes and treatment need. Triage criteria is based on Glasgow coma scale score > 13, respiratory rates < 10/min or > 29/min, or ventilatory support determine triage to a trauma center. This is often coupled with systolic blood pressure, heart rate, and heart rate variability readings to determine need for hemorrhage control. Mortality from trauma is declining for those with faster access to trauma centers, improvement in resuscitation strategies, and adherence to evidence-based guidelines for treatment; surgical intervention or interventional radiology need is predicted based on these parameters as well (Candefjord, Asker, & Caragounis, 2022). Additionally, emerging evidence suggests that prehospital blood transfusion improves patients' physiology and maintains perfusion to key organs and tissues, often through freeze-dried plasma (FPs), packed red blood cells (PRBCs), or whole blood (WB) (Jackson, Sperry, & Yazer, 2021). Other analgesics given prehospital for injured patients include tranexamic acid (TXA), an antifibrinolytic agent shown to reduce overall mortality from hemorrhage by reducing trauma-induced coagulopathy when administered within three hours of injury; however, TXA is not yet a well-adopted intervention despite evidence of maximum survival benefits (Pabinger, Fries, Schochl, Streif, & Toller, 2017).

Upon arrival to a trauma center, the preferred method of evaluation is the "ABCDE rule" under advanced trauma life support (ATLS) guidelines; these include an assessment of airway, breathing, circulation and control of hemorrhage if applicable, disability, and exposure (Dumovich & Singh, 2023). Another common exam is the focused abdominal sonogram for trauma or FAST exam; this technique uses ultrasound to identify free fluid in the abdomen, indicative of internal bleeding. FAST is generally preferred over CT due to time constraints, with a CT used to confirm

findings if the FAST is positive. These tests occur simultaneously with blood transfusion as determined by prehospital lactate, base deficit, systolic blood pressure, and shock index values (Dumovich & Singh, 2023).

Specifically for individuals with TBI, key parameters include loss of consciousness (LOC), altered mental status (AMS), post-traumatic amnesia (PTA), Glasgow coma scale to determine TBI severity. A comprehensive evaluation includes clinical history and presentation, labs including glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase (UCH-L1), and neuroimaging. CT and MRI are used to measure TBI severity and other parameters, including an assessment of hemorrhage, edema, vascular injury, and intracranial pressure.

Prehospital assessment is vital in determining need for trauma triage, admission to an intensive care unit (ICU), and need for emergency surgery. Triage and ICU admission is a significant predictor of mortality and quality of life measures following trauma, with under triage heightening the risk of poor outcomes. Older adult patients following injury are more likely to be under triaged than younger patients, as calculations for Injury Severity Score is skewed based on injury characteristics and age (for example, falls) ??(Candefjord et al., 2022). There remains a critical need to develop applicable triage protocols for different subpopulations of injured patients.

1.7 Prehospital Interventions for Traumatically Injured Patients with Sickle Cell Disease

Currently, there are no guidelines for prehospital interventions and ED management for SCD patients following polytrauma. This is largely concerning because existing triage protocols and field assessments for injury severity is determined by clinical lab values, such as lactate and base deficit. Such measurements are non-generalizable to the SCD population since the resting

blood lactate value in individuals with HbSS and HbSC disease is 3-4 times higher than that of patients without SCD (65). IV fluid administration for injured patients is common practice to raise lower systolic blood pressure values (Kabil et al., 2022); however, recent evidence suggests that fluid overload is common in patients with SCD who receive IV fluids (Ojo et al., 2022). Furthermore, while blood transfusions are common to resuscitate patients with severe injuries and is used as standard practice, SCD patients who already receive routine blood transfusions may experience increased blood viscosity if transfusions are used again for resuscitation following injuries, possibly contributing to poor VOE outcomes (Adjepong, Otegbeye, & Adjepong, 2018). However, given limited research in understanding perioperative management of SCD patients, there are many gaps in knowledge to design appropriate triage and surgical protocols specific to the SCD population.

1.8 Gaps in Knowledge

To summarize, there are many limitations in current understanding of how injury impacts SCD patients and the development of VOE or secondary complications. The racism experienced by individuals with SCD pertaining to pain management have contributed to their unintentional underrepresentation in current clinical studies within the field of Emergency Medicine. Excessive wait times for pain relief, insufficient medication, and stigma associated with treatment for pain management has exacerbated SCD pain, furthering tethering the patient's relationship with healthcare. Consequently, known prehospital parameters to assess injury severity, triage need, and other interventions are not generalizable for the SCD population; as a result, trauma? triage protocols and emergency surgery recommendations are missing altogether. Lack of research on

the inflammatory reactions following injury in SCD populations further complicates the ability to create diagnostic screening criteria and design treatment. Furthermore, many SCD patients are not coded for their SCD trait in their medical records, making retrospective analysis of associated outcomes even more difficult (Tessema et al., 2022). Prior research in this field have only captured incidental information on injured SCD patients, limited to case reports; no reports have intentionally measured this association.

1.9 Public Health Importance

SCD testing in the United States has historically been problematic, although steadily improving over the last few decades; there continue to be persistent lack of public awareness for SCD. The burden of SCD is high, with individuals facing both the burden of the disease as well as high costs of treatment given socioeconomic disadvantage. It has been found that the lifetime cost per SCD patient with Medicaid is greater than $460,000; given that this data was extracted from the Florida Medicaid data, this projected cost value is likely underestimated as Medicaid covers patients for only a portion of their lives (Grady et al., 2021). Additionally, high emergency department utilization (EDU) costs associated with frequent VOE events results in high hospital-associated costs, physician burn out, continued cycle of stigma, and therefore poor outcomes. All these processes are possibly heightened when SCD patients experience multisystem traumatic injuries. It remains unknown as to whether exposure to traumatic injury increases the frequency and duration of subsequent VOE events following polytrauma; should this association be linear, it is likely that traumatic injury can exacerbate long-term EDU and pain management needs. Given the history of racism and poor treatment of SCD pain, it is also likely that a sudden increase EDU

can force providers to unintendedly reiterate their biases of SCD patients as “drug-seeking”; this can result in a dismissal of worsening symptoms following polytrauma and increase morbidity and mortality. In non-SCD populations, trauma triage following Trauma Triage Assessment (TTA) and ICU admission drastically improve both in-hospital and 1-year mortality and minimize future risk of secondary complications or disability amongst injured patients (Granstrom, Strommer, Schandl, & Ostlund, 2018; Ong et al., 2009). Therefore, under triage and lack of ICU admission in patients with SCD can contribute to worsening outcomes. It is of critical public health importance to determine whether traumatic injury has an impact on SCD pathology, to not only determine whether the SCD population is an emerging subset of trauma patients with poor outcomes, but also develop guidelines for clinicians and emergency services providers to appropriately care for acutely injured patients.

2.0 Objectives

The primary objective was to determine whether traumatic injury has an effect on VOE outcomes, including 1) annual frequency of VOEs and 2) ED LOS for the first VOE following an injury among SCD patients. Injury type (blunt vs penetrating) was assessed to determine its effect on VOE outcomes. Additionally, the secondary objective of the study was to determine whether the ED management of the traumatic injury (e.g., Trauma Team Activation [TTA] and intensive care unit [ICU] admission status) is associated with VOE outcomes and time-to-first VOE post-injury. We hypothesize that there is a linear relationship between lack of trauma triage and ICU admission and poor VOE outcomes.

3.0 Methods

3.1 Study Population

This study uses retrospective electronic medical record (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 Sickle Cell Clinic from January 2000-July 2022. Our study population consisted of all SCD patients included in the registry aged ≥ 18 years with at least one diagnosed traumatic injury event during an acute care encounter at one of 11 urban Level I and II Trauma Centers in Western Pennsylvania. Records of ED visits, Trauma History and Physical documentation (Trauma H&P), and ambulance records from 2000-2021 were reviewed to identify prior history of traumatic injury.

Consistent with World Health Organization (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.xx-839.xx, 850.xx-904.xx, 910.xx-918.xx, 925.xx-929.xx, 940.xx- 959.xx, representing fractures of extremities; open wounds; superficial, internal, or crushing injuries; and spinal or nerve-related injuries (Clark, Black, Skavdahl, & Hallagan, 2018). We defined the date of the most recent traumatic injury for each patient as the index date. Patients were excluded if EHR did not have at least one other clinical encounter for one-year pre- and post-index date, or if the injury occurred more than six hours prior to documentation, was an isolated fall, or if the patient was incarcerated at the time of injury.

3.2 Measures

The following data were abstracted via medical record review: age, gender, lab confirmed SCD genotype, date of traumatic injury (index date), ED site, mechanism of injury, triage status (both SCD triage for VOE and trauma triages), and ICU admission status.

3.3 ED Treatment Groups Based on Triage and ICU Admission Status

Study participants were categorized into three ED management groups based on their trauma triage and ICU admission status. We defined our study cohorts as follows: 1) Patients with neither trauma triage nor ICU admission were categorized as "*Early Discharge*" and their care included vital sign monitoring and initial examination by ED providers, followed by discharge to home. 2) Patients with only trauma triage are denoted as "*Triage Only*"; care included initial labs and monitoring by ED providers, but not ICU admission, and patients were discharged home after evaluation; 3) Cohorts with both trauma triage and ICU admission are denoted as "*Triage and ICU,*" sometimes necessitating acute care surgical management following evaluation.

3.4 Outcomes

We assessed three different outcomes. **1) Annual frequency of VOE events** was measured by number of ED visits 365 days before and after the index date. **2) ED length of stay (LOS)** of the most recent VOE event (reported in hours) immediately before and after the index date; this

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 (12 days) of each other were deemed as one event (Zaidi et al., 2021). **3) Time-to-first VOE** following the index date-—defined as the time from ED or hospital discharge for the traumatic injury to the first VOE requiring an ED visit. 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 (Kang et al., 2020).

3.5 Statistical Analysis

Descriptive statistics were generated to assess demographics and clinical characteristics. For the primary objective, pre- post-injury differences in annual frequency of VOEs and ED LOS was examined using two-sample t-tests. Next, we assessed the impact of injury type (blunt vs penetrating) using two-sample t-tests. For the secondary objective, we tested ED management group differences (compare early discharge, triage-only, and triage-ICU) in pre- post-injury VOE outcomes using one-way analysis of variance (ANOVA). Log-rank test was used to determine time-to-VOE differences between the three treatment groups, furthermore, obtaining survival curves using Kaplan-Meier stratified by trauma triage or ICU admission status. Trauma triage status, ICU admission, age, and sex were included as potential confounders. All analyses were conducted using R-4.1.3.

4.0 Results

Patient registry included 356 adult patients with an SCD diagnosis who had a patient encounter from 2000-2021; 95 of these SCD patients 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 one-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 for this analysis, as isolated falls can be due to syncope or other neurological preconditions. A total of 55 qualifying patients (male 48%, average age=37.6, SD=11.0) were used for our analysis, corresponding to genotypes Hb SS (n=26), Hb SC (n=16), $HbS\beta^{+}$ thalassemia (n=7), $HbS\beta^{0}$-thalassemia (n=3), and other (n=3). (Table 1).

Table 1 Patient Demographics and Injury Characteristics

	All	Early Discharge	Triage Only	Triage and ICU
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)

There were 49.1% of all SCD patients that were trauma triaged following an injury, and 30.1% were admitted to an ICU following the index injury. Table 2 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 tended to be higher in

the triage only (23.1%) and triage-ICU (20%) ED management groups, compared to early-discharge (7.1%) (X^2= 2.577, p=0.276). Only one SCD patient had a VOE triage, which was to the 5 level.

Table 2 Annual Frequency of Vaso-occlusive Events and Duration of Vaso-occlusive Event, 12-months Pre- and Post-injury for SCD Patients

VOE Measures	ED Treatment Groups	Pre-Injury	Post-injury	P-Value
Annual Frequency of VOE, mean (SD)				
	Total (n=55)	5.19 (13.6)	6.03 (13.6)	0.716
	***Early Discharge* (n=28)**	3.2 (6.3)	3.92 (5.8)	0.634
	***Triage Only* (n=10)**	8.5 (18.7)	10.2 (17.8)	0.837
	***Triage and ICU* (n=17)**	6.6 (15)	7.1 (15.6)	0.929
	Blunt (n=47)	5.78 (13.1)	6.57 (12.8)	0.512
	Penetrating (n=8)	1.75 (2.87)	3.75 (7.91)	0.808
Annual Duration of VOE, mean (SD)				
	Total (n=55)	25.14 (47.3)	41.87 (73.5)	0.185
	***Early Discharge* (n=28)**	32.9 (67.6)	33 (82.9)	0.997
	***Triage Only* (n=10)**	16.1 (27.7)	77.4 (77.5)	0.038*
	***Triage and ICU* (n=17)**	17.6 (34.9)	35.6 (60.3)	0.297
	Blunt (n=47)	29.2 (56.7)	41.9 (76.2)	0.326
	Penetrating (n=8)	1.44 (2.23)	14.4 (34.9)	0.229

There were no significant pre - post-injury differences in the annual frequency of VOE (M = 5.9 vs 6.03, t = 1.982, p=0.716) or average ED LOS of VOE (M = 41.87 vs. 25.14 hours, t=1.984, p=0.185). When analysis controlled by injury type (either blunt or penetrating injuries), there were no significant pre /post-injury differences in the annual frequency of VOE (M=5.43 vs 5.98, t=1.982, p=0.875) or average ED LOS of VOE (M=33.76 vs 51.23 hours, t=1.983, p=0.673).

There were no ED management group differences for annual frequency of VOE pre / post-injury (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 (mean= 77.4 hours) was significantly higher than pre-injury measures (mean=16.1 hours), p=0.038). Overall, SCD individuals who were triaged following an injury experienced a significant increase in ED length of stay for VOE, compared to those who were not triaged.

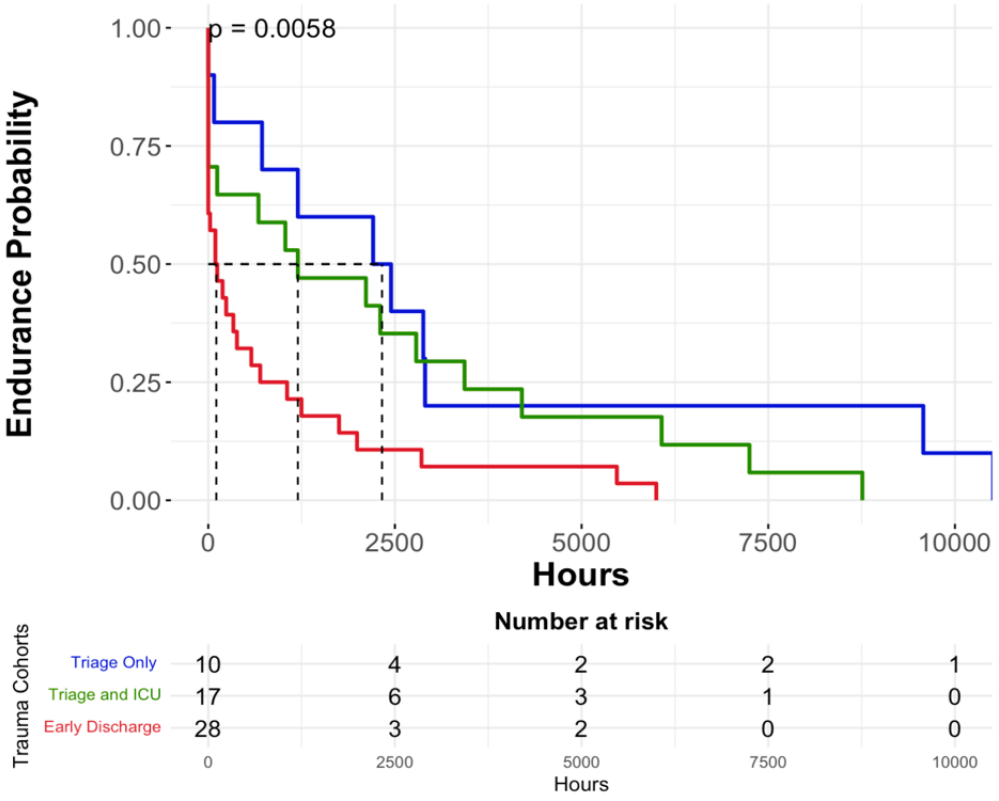

Figure 1 Overall Vaso-occlusive Events Stratified by Triage and ICU Combined Effects

Kaplan-Meier log-rank test showed that for all SCD individuals—the time-to-first VOE was 633 hours (or 26.3 days) following an injury. Patients with early-discharge experienced a VOE

event within 2.9 days of their injury, followed by "*Triage and ICU"* at 52.4 days and *"Triage only"* at 100.2 days (Figure 1).

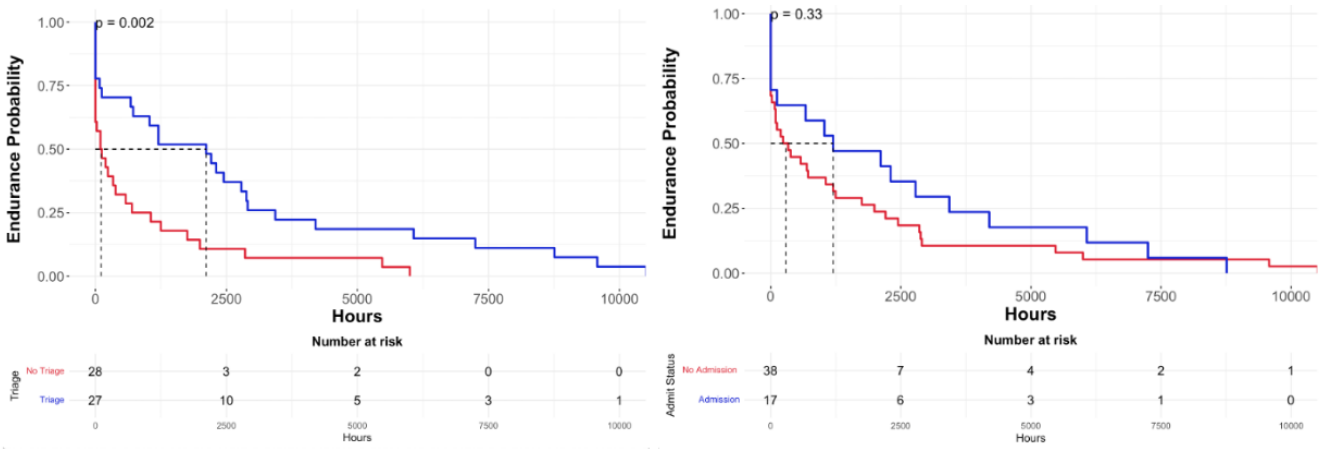

Figure 2 VOE Triage Status and ICU Admission Status

Separate triage and ICU admission status was further analyzed for the total study population to determine individual effects. Controlling for covariates, a Cox regression model showed a marginally significant effect of trauma triage status on VOE events, p=0.06. Specifically, patients who were not triaged experienced a VOE event in less than 1 day, compared to those who were triaged at 79.7 days, p=0.002). Similarly, patients without an ICU admission experienced a VOE event in less than 1 day compared to those who were admitted at 52.2 days, p=0.33 (Figure 2).

5.0 Discussion

To our knowledge, this is the first study assessing the impact of trauma including VOE-related outcomes following traumatic injury among SCD patients. In this study, individuals with penetrating injuries were overrepresented in *triage only* and *triage-ICU* groups, as opposed to the *early discharge ED* management group, validating existing protocols preferentially triaging penetrating injuries which require immediate medical intervention (Yancey & O'Rourke, 2023). The annual frequency of VOE events experienced by individuals in our review at baseline (pre-injury) was 5.9, and the average duration of a pre-injury 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 (Shah et al., 2019).

There was no significant increase in either annual frequency of VOE or ED LOS for first VOE for individuals with multisystem traumatic injuries. However, significant increases in LOS for VOE was noted in those who were ultimately trauma triaged, irrespective of ICU admission status. Since LOS for VOE was used to determine severity of VOE (Jang et al., 2021), we assume that those who were triaged experienced an increase in severity of VOE. Our results suggest that while there seem to be no long-term VOE outcomes, exposure to an injury may result in faster time-to-VOE. Half of all SCD patients experienced a VOE event within 26.3 days following injury. Specifically, those without trauma triage experience faster time-to-VOE.

These trends are likely explained by the inflammatory response and coagulation cascade; plasma levels of pro-inflammatory cytokines (ie, IL-1β) are generally increased in SCD patients, specifically in the Hb SS genotype which comprises the majority of our sample (Jang et al., 2021; Torres et al., 2016). These markers are responsible for complement activation and leukocyte

adhesion, impacting coagulation and therefore causing vaso-occlusion —this cycle is nearly identical for the inflammatory response following an injury. Therefore, it is likely that increased inflammatory response following an unresolved injury (perhaps caused by early discharge) is linked directly to early-onset VOE, but further research is critically needed.

Prehospital care for SCD patients undergoing a VOE event includes the administration of intravenous fluid (IV) to reduce blood viscosity and dilute the inflammatory cytokines associated with VOE (Jang et al., 2021). Patients who are injured commonly receive IV fluids depending on the level of trauma triage (Kabil et al., 2022); 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 IV fluids. However, recent evidence suggests that administering IV fluids may result in poor pain control in SCD patients (Ojo et al., 2022), thereby explaining why those who were triaged experienced longer LOS for VOE following their injury. Nonetheless, since lack of trauma triage was the most predictive factor of early-onset VOE, there remains a need for prospective studies to fully determine causal links between injury and VOE-related outcomes.

Traditionally, perioperative management of SCD has been understudied; SCD patients are at a heightened risk for sepsis, infection, thrombotic events, and longer length of stay (Brumm et al., 2020). Although routine pre-operative blood transfusions may improve tissue oxygen delivery, transfusion may increase blood viscosity (Adjepong et al., 2018), possibly contributing to poor VOE outcomes. SCD patients also consistently report increased racial stigmatization and socioeconomic barriers for access to care in EDs (Sinha, Bakshi, Ross, & Krishnamurti, 2019). 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 (Beaudoin et al., 2018). Therefore, poor VOE outcomes following an injury pose

additional challenges in terms of continuity of care and pain management, resulting in increased hospitalizations and associated costs (Osborne, Osakwe, & Odlum, 2021).

An unexpected finding of this study is that only one SCD patient included in the study had a VOE triage and to the 5 level of the Emergency Severity Index (ESI). Standard of care supported by the 2014 Evidence-based management of sickle cell disease publication highlights the need for the triage of all SCD patient presenting to the ED and at least to Level 2 (66). This lack of SCD triage may serve to underscore the impact of an acute traumatic event on a person managing a chronic SCD diagnosis and its associated complications i.e. anemia and multiple end-organ damage.

Clinical outcomes for SCD patients with injuries are unknown due to a knowledge gap in the current literature (Tessema et al., 2022); this is especially concerning, as it specifically impacts quality of life in Black and Latinx communities (Ojodu, Hulihan, Pope, & Grant, 2014). While our findings are preliminary, they highlight a substantial intersection between traumatic injury and heightened risk of poor VOE outcomes; as such, it is likely that the high prevalence of SCD in communities of color also intersects with violent trauma caused by structural racism and economic marginalization (Tessema et al., 2022). Further research in the field is required to improve our understanding of the changing psycho-social and biological interactions, as well as to develop guidelines to appropriately assess and address subsequent chronic pain following trauma.

These results should be interpreted in the context of the following limitations: the lack of national or institutional level SCD registries contributes to inconsistent coding of VOE events and other complications, and the exclusion of SCD from the National Trauma Data Bankposes major barriers for further research in terms of patient recruitment and representation in clinical studies (Grigorian et al., 2020). Our study further supports this claim: SCD was not listed as a “pre-existing

condition" within our institutional level trauma registry, resulting in low sample size. Additionally, since there are no protocols defining standard of care for SCD-trauma patients, treatment provided during trauma triage and in-patient ICU care can be highly variable between clinical teams; additional treatment given to injured SCD patients due to their disease state was not recorded in this study. Such treatment may result in discrepancies in VOE-related outcomes and should be included in future work.

Despite these limitations, a major strength of our study is that it is the first review of injured SCD patients offering insight to potential worsened outcomes, and thereby drawing importance to the development of SCD-specific care. Additionally, this study highlights the historic exclusion of SCD patients in clinical studies in general. Moving forward, research on the intersection of traumatic injury and SCD should be directed towards greater inclusion of SCD individuals within trauma registries to expand on measures such as demographic information, comorbidities, and pre-hospital treatment. Furthermore, there remains a critical need to understand mortality and long-term morbidity, quality of life outcomes, clinical biomarkers of injury severity, and the effect of critical surgical interventions on SCD-related outcomes.

In conclusion, data from this retrospective study suggest that traumatic injury among patients with SCD may be associated with early-onset vaso-occlusion and increased post-injury frequency and duration of VOE events. This finding was especially evident for patients with early discharge, or those who are not trauma triaged or admitted to an ICU, potentially due to a lack of intervention that may serve to prevent VOE. Given the likely intersection of inflammatory responses for both trauma and vaso-occlusion, further research and critical care guidelines are needed to adequately manage the exacerbation of chronic pain following injuries. Future research should be directed to address gaps in guidelines literature for clinical management, all of which

disproportionately impact communities of color. Therefore, it is of critical public health importance to develop existing trauma registries across the nation to specifically include patients with SCD, which is crucial for understanding poor outcomes, developing protocols for emergency services providers, and reducing total hospital-associated costs for at-risk patients.

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