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Socioeconomic status and time to provider for patients with sickle cell disease

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SOCIOECONOMIC STATUS AND TIME TO PROVIDER FOR PATIENTS WITH SICKLE CELL DISEASE

by

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ABSTRACT

Disparities in healthcare access and quality for patients with sickle cell disease (SCD) continue to pose significant challenges. This study aims to examine the relationship between socioeconomic factors and the time patients with SCD wait to see a provider in the emergency department (ED). Using a retrospective, comparative analysis of data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) ED sample between 2008-2018, this study includes ED visits of patients with SCD aged 18 and older who present with a pain crisis. The outcome variable is time to provider (TTP), defined as the length of time between patient arrival to the ED and the first interaction with a medical provider. Socioeconomic factors of interest include sex, employment, and education level. Covariates such as age, race, acuity, and time of presentation are considered. Statistical analyses include t-tests, one-way ANOVA, and multiple linear regression, along with evaluation of interaction effects. The study's timeline is three to four months, and resources include a computer with statistical software and personnel assistance. While limitations exist, including the reliance on NHAMCS data and the subjective nature of some measurements, the study aims to provide insights into the impact of socioeconomic factors on wait times in the ED for patients with SCD. The results have clinical and public health significance, highlighting implicit biases, care delays, and potential detrimental effects on patient well-being. The findings can inform interventions such as provider education, pain management protocols, individualized pain plans,

support groups, and improved access to primary care and social services. Overall, this study contributes to the understanding of disparities in care for patients with SCD and aims to improve the quality of healthcare for this population.

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LIST OF ABBREVIATIONS

ACS... Acute Chest Syndrome

CDC ....Centers for Disease Control and Prevention

CF... Cystic Fibrosis

ED .... Emergency Department

EDR... Emergency Department Reliance

ESI..Emergency Severity Index

HCP...Health Care Providers

Hgb..Hemoglobin

HRQL..Health-related Quality of Life

ICS ....Inhaled Corticosteroids

LBF .... Long Bone Fracture

MCV ....Mean Corpuscular Volume

NHAMCS ....National Hospital Ambulatory Medical Care Survey

NHLBI ....National Heart, Lung, and Blood Institute

OPR..Opioid Pain Reliever

PASS......................................Positive Prover Attitudes towards Sickle Cell Patients Scale

PCA..Patient-controlled Analgesia

PRaCY ....Perception of Racism in Children and Youth measure

SCD……………………………………………………….……………Sickle Cell Disease

TTP .... Time to Provider

INTRODUCTION

Background

Sickle cell disease (SCD) is a genetic condition that occurs due to a mutation of the beta-globin gene. This results in abnormal hemoglobin forming strands that cause red blood cells to adapt a sickled shape. When deoxygenated, the surface of these erythrocytes become stiff and sticky, resulting in clustering and occlusion of vessels, hemolytic anemia, and hypoxemia to tissues[1]. SCD affects people of many races and ethnicities worldwide, but is most prevalent in populations of sub-Saharan African origins, likely due to the selective advantage in protecting against malaria in heterozygous individuals[2]. SCD affects approximately 100,000 Americans, making it the most common inherited blood disorder in the United States[3], with the incidence being 1 in 500 live black births[4].

One important clinical manifestation of SCD is recurrent, unpredictable, and intense pain episodes due to vaso-occlusion[1]. Though pain crises often occur without an obvious cause, they may be triggered by stress, cold climates, dehydration, and infections[5]. As the pain level in acute vaso-occlusive crises is high, opioids are the standard of care in many institutions to treat these painful episodes[6].

Statement of the Problem

In general, Black patients are less likely to receive pain medications than White patients, and are given lower quantities when administered[7]. Several studies have found that patients seeking care for pain related to SCD are often associated with opioid abuse and addiction, and one study revealed that resident physicians estimated the rate of opioid addiction to be highest in patients with SCD than with chronic pancreatitis and back pain[8]. However, research shows that addiction rates in patients with SCD are no more prevalent than that of other painful chronic illnesses[9]. The opioid remains a public health crisis for Americans. In 2013, 16,225 people in the general population died from opioid pain reliever overdose, while only ten patients with SCD died due to the same cause[10].

Furthermore, parents of children with SCD believed that White patients are receiving better treatment than Black patients[11]. Since sickle cell disease is historically conceptualized as a predominantly "Black disease[12]," this has warranted further investigation of negative attitudes and racial bias against Black patients with SCD. Various disparities may be rooted in implicit bias and compounded by providers' apprehension about prescribing opioids and the recent opioid epidemic[13]. Studies found that patients presenting with acute vaso-occlusive crises experienced significant delays and wait times when compared to patients without SCD[14,15]. Though health-related racial stigma has been documented in patients with sickle cell disease, there is a gap in the literature to elucidate whether other socioeconomic factors influence patient care. The extent to which patients with SCD have been affected by sex disparities, employment, and education attainment renders further investigation.

Hypothesis

Hypothesis: Patients with SCD who are female, unemployed, and/or with lower educational attainment who present to the Emergency Department with a pain crisis will experience significantly greater times to be seen by a provider relative to other populations.

Objectives and specific aims

This retrospective study will be a cross-sectional, comparative analysis of data from public-use datasets of the National Hospital Ambulatory Medical Care Survey (NHAMCS) ED sample between the years 2008-2018 aimed to determine whether patients with SCD seeking care in the ED experience SES discrimination during care, while accounting for a number of potentially confounding factors.

- 1 – Study the relationship between socioeconomic status and the amount of time patients wait to see a provider in the Emergency Department of a hospital, taking into account demographic and social factors such as sex, education, and employment
- 2 – Control for covariates such as age, race, acuity, and time of presentation
- 3 – Evaluate interaction effects that may change under different conditions

REVIEW OF THE LITERATURE

Overview

History of Sickle Cell Disease

Sickle cell disease (SCD) was first described in a 1910 case report by James B Herrick as "peculiar elongated and sickle-shaped red blood corpuscles"[16]. The thin, elongated, sickle- and crescent-shaped erythrocytes in this blood smear were from a young, anemic Black man from the Caribbean island of Grenada, who originally presented with lower extremity sores, palpitations, and shortness of breath. At the time, Herrick was unable to definitively diagnose this acute-on-chronic condition with multi-system involvement and generalized pain. He suggested that there must be some intracellular change in the composition of the erythrocyte that determines its abnormal shape, what we now know to be a genetic disorder caused by a single protein mutation.

Pathophysiology

As a result of gene mutations producing structurally abnormal globin proteins, there are several types of hemoglobin (Hgb) that exist. Normal hemoglobin is termed Hgb A, and the most common and medically relevant variants include Hgb S and Hgb C. A point mutation at codon 6 of the beta-globin gene results in the substitution of the amino acid glutamic acid with valine, causing the abnormal formation of Hgb S[17]. When Hgb S releases oxygen to various tissues, the polymers stick to each other and change the shape of the cell, giving it its distinguished "sickled" shape. Sickled erythrocytes and damage to the cell membrane cause both vaso-occlusion and hemolytic anemia. The cycle of vaso-occlusion is due to inflammation and cell activation leading to multicellular adhesion and vaso-occlusion, ultimately causing tissue and organ damage[1]. Polymerization and sickling also leads to hemolysis and anemia, which appears clinically as lower hemoglobin levels.

Patients with sickle cell trait have only one abnormal hemoglobin beta-globin gene allele, inheriting Hgb S from one parent and Hgb A from another, resulting in the heterozygous state. Heterozygotes do not experience vaso-occlusive crises and are generally without any clinical symptoms or implications, typically only occurring when exposed to high-stress conditions (ex: hypoxia, high altitude, dehydration, excessive exercise)[18].

Epidemiology

Worldwide, there are around 300 million people with sickle cell trait, with an estimated 3 million African Americans with sickle cell trait in the United States[19]. SCD is most prevalent in sub-Saharan Africa, but also affects about 100,000 Americans, making it the most common inherited blood disorder in the United States[20]. The genetic mutation is most common in areas where malaria is endemic, due to the selective survival advantage in heterozygous individuals[2].

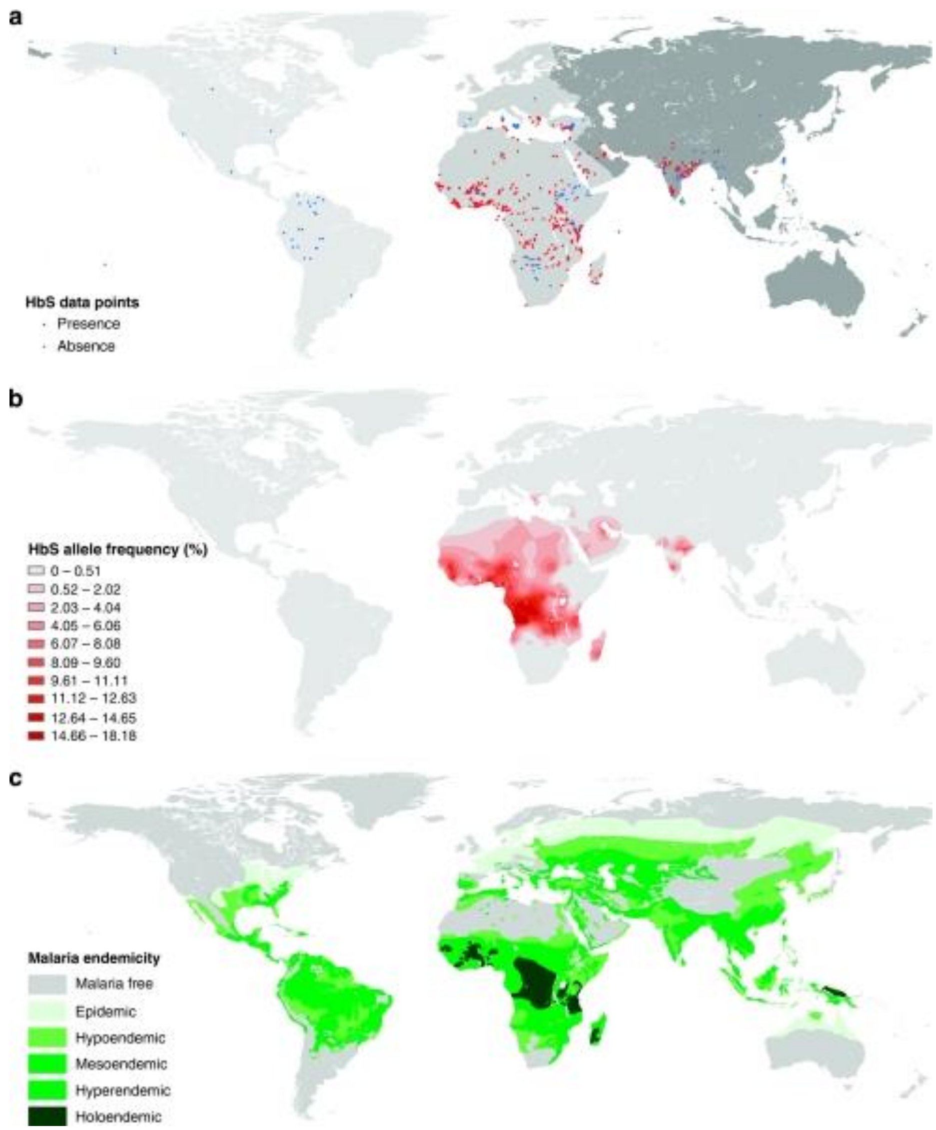

Figure 1: Global distribution of the sickle cell gene. Adapted from "Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis," by F.B. Piel, A.P. Patil, R.E. Rosalind, et al., 2010, *Nat Commun*, *1*(104). Copyright 2010 by Macmillan Publisher Limited.

In the United States, diagnosis of sickle cell disease is typically done with newborn or prenatal screening. The National Sickle Cell Anemia Control Act in 1972 was signed by President Nixon with the goal of ending the discriminatory genetic testing for SCD which had been required by several states and instead made screening voluntary. This law, which included not only screening, but also counseling programs and research, made SCD the first genetic disorder to receive federal recognition and funding[21]. During hemoglobinopathy screening, blood is placed on a slide and inspected under a microscope. If sickling is observed, hemoglobin electrophoresis is utilized to confirm the diagnosis and analyze the presence and quantity of various forms of hemoglobin. By the mid-1980's, several states began to include screening for SCD in the Newborn Screening Program for all infants born in hospitals[22]. During this time, the discovery that penicillin prophylaxis led to reduced deaths from sepsis among infants and young children with SCD resulted in increased awareness and universal screening for SCD. By 1999, all 50 states and the District of Columbia include SCD in the Newborn Screening Program. This is the way that most people with SCD are diagnosed in the United States. Additionally, many American families learn of their trait status via the Newborn Screening Program, which has led to increased awareness of the disorder.

Clinical Course and Prognosis

During the first six months of life, infants with SCD are asymptomatic due to the presence of fetal hemoglobin (Hgb F), which gradually decreases as the disease manifestations become apparent in late infancy and childhood[23]. The disorder often increases in severity in adulthood as more end-organ damage accumulates over time. The history and physical examination of patients with SCD varies greatly between individuals. Common clinical manifestations of the disease include painful vaso-occlusive crisis, acute chest syndrome, stroke, infections, skin ulcers, jaundice, chronic renal insufficiency, splenic sequestration, avascular necrosis, pulmonary hypertension, eye complications, priapism, cholelithiasis, and aplastic crisis[24].

A study published in 2013 by Lanzkron et al. used the National Center for Health Statistics cohort of over 16,654 adults with SCD from 1979 to 2005 to examine age at death and calculate mortality rates[25]. They found that the median age at death in 2005 was 38 years for males and 42 years for females. Life expectancy in patients with SCD is estimated to be about 20-30 years reduced compared to the normal population, however, recent advances in therapy are prolonging survival[6,24].

Management

Management of SCD entails both health maintenance and treatment of acute symptoms/complications. Health maintenance includes prophylactic management and vaccination. After newborn screening, prophylactic penicillin twice a day is recommended to continue through age 5 and older, as well as receiving vaccinations against pneumococcal and other encapsulated organisms[26].

Hydroxyurea is a ribonucleotide reductase inhibitor that was discovered in the 1970s, originally used to treat myeloproliferative disorders[6]. It was approved for SCD in 1998 and is now widely used in SCD to reduce the frequency of pain and the incidence of acute chest syndrome (ACS) by increasing levels of fetal hemoglobin (Hgb F). It also works by decreasing leukocyte production and altering expression of adhesion molecules, increasing RBC volume and therefore mean corpuscular volume (MCV), and donating nitric oxide, ultimately increasing blood flow and local vasodilation, which improves pain from vaso-occlusive crises.

Another cornerstone in the management of SCD is the use of blood transfusions. Donor erythrocytes which contain normal hemoglobin (Hgb A) are transfused to reduce the percentage of circulating Hgb S to mitigate some of the effects of sickling and increased blood viscosity. This is used in both episodic (acute) and chronic settings. Episodic transfusions are commonly used prophylactically in preparation for surgical operations and in the setting of SCD complications such as stroke, multisystem organ failure, and ACS. Chronically, transfusions may be used to prevent strokes in children. Common side effects of blood transfusions include alloimmunization, autoimmunization, iron overload, hyperviscosity, and hemolysis[6].

Since 2017, three new medications have been approved in the management of SCD: L-glutamine, crizanlizumab, and voxelotor[27]. L-glutamine was the first of the three medications to be approved; its mechanism is not entirely known, however, it is predicted to decrease the oxidative damage of red blood cells and has been shown to reduce the frequency of VOCs. In 2019, crizanlizumab was approved to reduce the frequency of VOCs in adults with SCD. It is a monoclonal antibody that binds to P-selectin, an adhesion molecule contributing to inflammation, atherosclerosis, and coagulation. Voxelotor, an Hgb S polymerization inhibitor, was also approved in 2019 with the goal to inhibit erythrocyte sickling and decrease blood viscosity in patients with SCD. The approval of these three new medications comes after a twenty-year gap in the development of SCD therapies, representing a promising future to improve health outcomes in these patients.

Research is also investigating the possibility of repurposing existing medications based on knowledge of SCD pathophysiology. For example, a 2017 triple-blind, randomized trial by Glassberg et. al was conducted to study the efficacy and feasibility of using inhaled corticosteroids (ICS) in non-asthmatic individuals with SCD. They found that there was a small, but clinically significant, reduction in pain scores over time, and a decrease in the cytokine sVCAM, which served as a primary marker for vascular injury, as increased levels are closely correlated with increased SCD morbidity and mortality. These findings suggests that an ICS may be a useful adjuvant therapy for individuals with SCD[28].

At the forefront of acute treatment of vaso-occlusive crises in patients with SCD is pain management. In 2014, the National Heart, Lung, and Blood Institute (NHLBI) published guidelines called "Evidence-Based Management of Sickle Cell Disease," composed by an expert panel of health care providers (HCPs) in family medicine, internal medicine, pediatric hematology, psychiatry, transfusion medicine, obstetrics and gynecology, emergency department nursing, and evidence-based medicine[6]. The guidelines were developed to assist healthcare professionals in managing common issues associated with caring for patients with SCD including routine health maintenance and recognition and treatment of common complications and comorbidities. Included in the recommendations are rapid triage, placement, and administration of analgesics. First dose of analgesic therapy is recommended to be initiated within 30 minutes of triage or within

60 minutes of registration. If there is severe pain in patients with SCD with a VOC, rapid initiation with parenteral opioids is strongly recommended with high-quality evidence. Intravenous opioids (such as morphine sulfate or hydromorphone) may be administered every 15-30 minutes until pain relief is obtained, and the dose may be escalated by 25 percent to achieve pain management. Around-the-clock opioid administration by patient-controlled analgesia (PCA) may also be initiated in the ED when and if possible. Finally, individualized prescribing and monitoring protocols may be utilized for more rapid, effective, and safe analgesic management.

Existing Literature

There are several disparities which exist as barriers to optimal healthcare for patients with sickle cell disease; these include, but are not limited to, access to care, provider knowledge, research funding, pharmaceutical investment, racial bias, and disease stigma. Altogether, these inequities result in disparate care and have adverse effects on patients' quality of healthcare.

Access to Care

One major barrier for patients with SCD is poor access to appropriate specialized health care[29]. Though specialized care centers with multidisciplinary teams designed to treat and improve outcomes in patients with SCD exist, they are scarce, particularly in low-income and rural communities that already lack in resources[30]. This barrier to access to comprehensive care is disproportionate for SCD compared to other orphan diseases (those affecting under 200,000 people nationwide). In fact, hemophilia and cystic fibrosis affect less than half the number of patients in the United States compared to SCD, but there is greater access to care centers for these populations[31]. Specialized health care providers with adequate knowledge of SCD pathology and treatment are an essential component of providing optimal care. Poor outcomes have been reported at non-specialized hospitals with few SCD patient populations, which is likely at least in part due to lack of hematologists with expertise in SCD[30].

A notably important time for patients to have adequate healthcare access is during the transition from child to adult care. While there are several comprehensive care programs for pediatric patients with SCD, accessible, trained providers for adults with SCD are limited[28]. A survey of 30 pediatric sickle cell centers revealed that only 60% routinely transfer their patients to an adult hematologist specializing in SCD[32]. As patients with SCD transition from pediatric to adult care, the mortality rates increase 2.3-fold, likely in part driven by limited access to specialized, adult healthcare[30]. Access to primary care providers specializing in adult care for patients with SCD may be an important aspect to improve disease outcomes. One retrospective study examined the Wisconsin Medicaid database over a 5-year period and found an increase in Emergency Department Reliance (EDR) in the group transitioning from child to adult care and young adults[33]. EDR was used to determine the difference between increased Emergency Department utilization due to increased need in chronic illness versus due to limited access to outpatient care. The higher EDR values suggest that the increase in ED utilization in the transition and young adult groups are due to lack of adequate access to care.

In addition to access to specialized care centers and providers, one study published in 2020 conducted a community-based needs assessment sampling patients with SCD, health care providers, and community stakeholders to identify barriers of care. Participants with SCD also identified lack of transportation, insurance challenges, and other financial barriers as influential factors when seeking healthcare services[34]. An analysis done in 2010 identified that about 60% of patients with SCD used Medicare or Medicaid as their primary payer, while from 2005 to 2009, only 32-38% of patients with hemophilia and 22-32% of patients with von Willebrand disease expected to use Medicare or Medicaid as their primary payer[30]. According to this article, Medicaid limits access to specialized healthcare and likely contributes to the difference in outcomes between people with SCD and those with other chronic conditions.

Provider Knowledge

To provide adequate care to patients with SCD, providers must be knowledgeable of current guidelines and treatment plan options. In a survey of 56 providers (32 of which reported to have expertise in caring for patients with SCD, 14 ED providers, 5 primary care providers, and 5 healthcare administrators/community-based organization), only 3 respondents indicated that they were aware of the NHLBI recommendations for the treatment of vaso-occlusive pain[34]. Though only a few reported knowing about the recommendations, many of the ED providers considered themselves knowledgeable and well-trained to manage patients with SCD. This discrepancy and lack of proper provider training and education may lead to inadequate pain management of patients with SCD in the ED setting.

While hydroxyurea is approved by the US Food and Drug Administration for the treatment of SCD and has been shown to reduce painful episodes in both adults and children, the drug is still underprescribed by many physicians[30]. Current recommendations from the 2014 NHLBI guidelines include treating all adults with SCD and 3 or more moderate to severe pain crises within one year with hydroxyurea. In a national claims analysis that identified 677 adult patients with sickle cell anemia with at least 3 pain-related hospitalizations or ED visits within 12 months, 86 were treated with hydroxyurea within 3 months of their third encounter – making the proportion less than 15%[35]. This may be in part due to provider knowledge and comfort managing patients with SCD and their complications, and inadequate access to specialized providers that do have appropriate clinical training.

Research Funding and Pharmaceutical Investment

Sickle cell disease research is largely underfunded. A 2020 cross-sectional study compared disease-specific funding between SCD and cystic fibrosis (CF) and the associated between funding and research productivity[36]. Both SCD and CF are autosomal recessive genetic diseases associated with intermittent exacerbations requiring hospitalizations and premature mortality. In the study, which examined federal and foundation funding, publications, clinical trials, and new drug approvals spanning from

2008 to 2018, findings showed that federal funding, foundation expenditures, research articles, and US FDA drug approvals were all greater for CF compared with SCD. These results are especially striking when considering that at the time that the study was conducted, the estimated US population of those with SCD was 90,000 compared to approximately 30,000 with CF. Furthermore, the funding disparity was markedly increased after factoring in private foundation funding. Private charities rely on advocacy and donors. Though donors may come from any race, most of the SCD community is Black[3]. Although Black households donate a higher share of their wealth than White households[37], there are many competing demands for donations and complex societal factors. Throughout history, there has been distrust in the Black community regarding medical institutions, which contributes to decreased funding and research participation[36]. Between 2008-2018, four therapies for CF received FDA approval, while only one drug was approved for SCD[30]. The decrease in funding and research seen with SCD contributes to the impairment of novel drug therapy development, further perpetuating the healthcare disparities experienced within this community.

Racial Bias

Individuals with sickle cell disease face additional barriers due to racial bias and disease stigma. Patients with SCD in the United States are typically in the racial minority, adding on a layer of vulnerability. Disparities in pain treatment dependent on one's race, as a result of both unconscious bias and explicit racism, have been well-documented in literature. One retrospective study from an Emergency Department in Atlanta, Georgia reviewed records during a 40-month period to identify all patients discharged with isolated long bone fractures[38]. The study found that White patients were significantly more likely to receive ED analgesics than Black patients (74% versus 57%), despite their pain being recorded similarly in the medical records. Similarly, a 2015 cross-sectional study evaluated analgesia administration in patients aged 21 years or younger who received a diagnosis of appendicitis in the Emergency Department[39]. Findings revealed that Black patients with moderate pain were less likely to receive any analgesia than White patients, and Black patients with severe pain were less likely to receive opioids than White patients. This racial disparity with respect to analgesia administration exists across several disease states, suggesting a different threshold for treatment. Interestingly, data from a 1998 study shows that in general, health care providers do not view race as an influence on the quality of health care, pain medication decisions, and quality of interpersonal relations in patients with SCD[4]. However, certain groups of providers, such as African Americans and females, were more likely to perceive race as an influence on the delivery and quality of healthcare - perhaps due to their increased awareness of discrimination.

The racial biases experienced by people with SCD may be prevalent both in medical and community settings, adding to the list of daily stressors. In 2018, twenty Black American youth with SCD were interviewed and asked to recall any events they have encountered that were related to racial bias[40]. Their replies were documented on the PRaCY (Perception of Racism in Children and Youth measure), and results showed that all twenty participants reported racial bias in the community setting. Four racial bias events in medical settings were reported, including staff members that were repeatedly rude, feeling that their wait times were longer than others during clinical appointments, and that their pain was overlooked. The behavioral and emotional reactions that these children experienced varied from sadness and anxiousness to anger and inferiority. In another study, patients with SCD reported that being black was a large aspect of the negative experiences they have encountered with their disease[41]. During interviews, patients note that they felt they were treated differently due to their race and disease status in both public and medical settings. One participant noted, "My race does influence my experience with SCD because blacks are viewed in a negative light. Racism is an added burden to my experience as a person with SCD." The racial biases that patients with SCD face, as well as their negative reactions to it, may have a damaging impact on their quality of life and interfere with the medical care that they receive.

In 2012, a cross-sectional, comparative analysis of data between the years 2003-2008 was performed to investigate the impact of race and disease on sickle cell patient wait times in the ED[15]. They compared the wait times to see a physician after arrival in three different groups: patients with SCD, patients with long bone fracture (LBF), and General Patient Sample. Patients with SCD generally presented with higher levels of pain and were assigned higher priority in triage compared to both the General Patient Sample and the LBF patients, however, they were found to experience longer wait times to see a physician. Regression models were then repeated with results only from an African American sample in an attempt to disentangle the effects of race. These results showed that mean wait times for patients with SCD were still about 50% longer than those found among the African American LBF patient sample. This suggests that the longer wait times experienced by patients with SCD may be due to both the race of patients with SCD, as well as their status as patients with SCD.

Disease Stigma

In addition to racial biases, patients with SCD also face stigmatization due to health status, also known as health-related stigma[42]. The sources of this judgment and devaluation may include family members, peers, the general public, and health care providers. Stigma for people with SCD is especially apparent in the Emergency Department, where these patients may present in severe pain and require compassionate providers to deliver evidence-based care[36]. Compared to the treatment of an acute cystic fibrosis exacerbation, which includes antibiotics and airway clearance, the treatment of a vaso-occlusive crisis experienced with SCD requires analgesia, usually opioids, which carries its own stigma. One study illustrated this stigma through comparing an asthmatic who knows the amount of prednisone they need to treat an acute exacerbation versus a patient with SCD who vocalizes the amount and type of pain medication they need for a pain crisis- one will be perceived as knowledgeable, while the other may be labeled as drug seeking[42].

In 2008, the Centers for Disease Control and Prevention (CDC) reported that drug overdose overtook motor vehicle accident as the number one cause of non-medical death in the United States[43]. This fact prompted researchers in 2016 to review the CDC database to determine how many patients with SCD died from opioid pain reliever (OPR) overdose[10]. They found that between the years 1999-2013, 174,959 people (not including patients with SCD) died due to OPR overdose, while in that same time period, only 95 patients with SCD died due to OPR overdose. Furthermore, the number of deaths due OPR in other chronic, non-cancer pain conditions such as fibromyalgia, low back pain, and migraine were higher than in patients with SCD. Although this research indicates that both death due to OPR and addiction are rising, this does not automatically imply that patients with SCD who take high amounts of opioids are drug addicts or abuse their medication.

Despite the relatively low rate of OPR overdose in patients with SCD compared to other chronic pain conditions evidenced above, some HCPs still hold negative attitudes towards patients with SCD[44,45,46]. One 2014 study examined attitudes of ED providers towards patients with SCD and found that 55.5% of nurses believed that patients with SCD who visited the ED were addicted to opioids[46]. The surveys analyzed in this study also revealed that both nurses and physicians had negative attitudes towards patients with SCD and uneasiness with caring for them. This trend is present not only between providers, but also among specialties. Questionnaires mailed out to hematologists listed with the National Association for Sickle Cell Disease and directors of emergency services in teaching hospitals with sizable African American populations throughout the nation were analyzed to assess provider beliefs, perceptions, and practices. Analyzation of this data revealed that about 53% of the ED physicians and 23% of the hematologists thought that more than 20% of patients with SCD are addicted to analgesics. In a survey-based assessment that was published in 2020, 243 ED providers were asked what they believed were barriers to SCD care administration – an overwhelming 62.1% of respondents identified the opioid epidemic as a barrier to caring for individuals with SCD in their ED, with 60.9% citing patient behavior[47].

While not all health care providers view patients with SCD negatively, literature demonstrates that patients report feeling discriminated against and stigmatized by HCPs, as well as being somewhat satisfied or completely unsatisfied with the care they have received[48]. A sample of 55 patients with SCD were interviewed about stigmatization they have experienced when presenting for pain management, and a majority reported that they had directly experienced this stigma[34]. Several participants even remarked that being labeled as “drug-seeking” was typical when visiting the ED for pain management. They described ED providers as doubtful regarding the existence and/or severity of their pain, which consequently created a feeling of disrespect for patients seeking pain relief. Interestingly, stigma was only mentioned by 2 of the 56 providers during their interviews.

Implications

The discrimination experienced by patients with SCD in health care settings may be associated with disparate care and various adverse health outcomes. Studies conducted in the general population have indicated that racial biases lead to differential treatment in the medical system and to poorer health outcomes, including poor mental health and earlier mortality[49,50]. A study performed in 2016 discovered that racial discrimination was associated with experience of anger and decreased subjective sleep quality, which were associated with increased allostatic load[51]. The allostatic load was found to be significantly higher in African Americans than White Americans, and this difference was mediated by occurrences of racial discrimination. Results of this study suggest that experiences of racial discrimination may ultimately contribute to the exacerbation of chronic illnesses. A 2015 study recruited 71 individuals with SCD to examine the relationship between perceived racial discrimination and pain in both the clinical and laboratory settings[52]. Results showed that discrimination in health care settings was correlated with “greater clinical pain severity and enhanced sensitivity to multiple laboratory-induced pain measures, as well as stress, depression, and sleep.” This suggests that the negative experiences due to racial bias faced by those with SCD in medical settings may contribute to enhanced pain sensitization.

Provider attitudes and bias may perpetuate racial health care disparities[52]. When confidential surveys were distributed to hematology/oncology staff members from the Sickle Cell Center at Children’s Hospitals & Clinics of Minnesota, free text comments included statements such as, “Sickle cell patients often have behaviors that elicit negative reactions … I don’t think it’s a racial issue,” as well as “I do not feel sickle cell patients are treated different due to race. If anything, … it is their behavior [that causes different treatment].” Even with trained, specialized providers who dedicate their lives to treating patients with SCD, health care stigma still exists. Negative provider attitudes, such as those described above, may translate into clinical practice and mistreatment of patients. A cross-sectional survey of 655 emergency providers in 2011 revealed that negative attitudes toward individuals with SCD were associated with lower adherence to national guidelines[45]. Furthermore, ED providers in the highest quartile of negative attitudes were

20% less likely to redose opioids within 30 minutes for inadequate analgesia. Several patients with SCD report that their physician's preoccupation with reducing pain medication resulted in further stigmatization and decreased attention to their overall medical care[53]. Patients presenting with a pain crisis due to SCD who do not receive effective pain control in the Emergency Department have a higher risk of being readmitted soon after discharge, and these increased hospitalization rates contribute to higher mortality and increased healthcare costs from the visits themselves and lost work hours[47]. Negative provider attitudes and bias towards both race and disease state have led to adverse treatment and health outcomes of patients with SCD, further perpetuating disparities in care.

The discrimination faced by patients with SCD from their providers has been associated with negative effects on patient-provider relationships and delayed care-seeking behaviors[15,42]. A systematic review of 28 studies indicates that SCD-related stigma hinders patients' physiological and psychological wellbeing, has harmful social consequences, and impairs healthcare interactions. Individuals that reported discrimination in medical settings are less likely to trust their providers and therefore more likely to be non-adherent to their medical recommendations[42,55]. Increased hospitalizations due to ineffective treatments and non-adherence may be a contributing factor to the unfavorable disease course of SCD.

Gap in the Literature

As detailed above, there have been several studies examining the relationship between race and treatment of patients with SCD in the Emergency Department. Data has also demonstrated that multiple socio-demographic features of patients (such as age, race, gender, literacy, and income) and the community (primary care provider, geographic location, resource supplies) contribute to hospital admissions[56]. A retrospective review found that patients with SCD from lower socioeconomic areas were at a higher risk of readmission, and higher inpatient mortality was found amongst those readmitted[57]. One may hypothesize that the increased risk of readmission could be due to inadequate pain control, which may stem from implicit racism and bias from the provider.

The potential correlation between different socioeconomic factors of patients with SCD and discrimination with subsequent disparities in health care management in the ED has not been greatly studied. In the general population, it has been found that physicians' feelings of affiliation toward patients were significantly associated with socioeconomic status[58]. This research also demonstrated that patient SES was associated with physicians' perceptions of patients' personality, abilities, behavioral tendencies, and role demands. However, the association between these negative perceptions of patients of low and middle SES groups and treatment in the ED setting, especially in those with SCD, has not been greatly studied.

Several studies have included patient sex when assessing for discrimination in the medical setting. A systematic review and meta-analysis assessed the health-related quality of life (HRQL) in pediatric patients diagnosed with SCD and found that female sex was associated with worse HRQL[49]. However, the HRQL is a general assessment of an individual's perception of the physical, psychological, and social aspects of their life- and is therefore subjective. One cross-sectional study used data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) between 2006-2015 to determine sex differences in analgesic use among patients with SCD presenting to the ED[13]. The goal of this study was to evaluate the effect of sex on any opioid and non-opioid medication use in the SCD population. Though they did not find any statistical significance in sex disparities in analgesic use, results did show that the odds that male patients were prescribed opioids was 1.5 times more than female patients. This study may have been impacted by bias through the utilization of NHAMCS to obtain their dataset, as it is limited in collection and sample size. Additionally, the utilization of analgesics in patients with SCD as a proxy to measure implicit bias of providers may not show direct causation. It is possible that patients with a primary diagnosis of SCD may have visited the ED for complaints that may not have required opioid or non-opioid analgesia.

Education and employment are additional socioeconomic factors that may contribute to preconceived notions and judgment about a patient. Between 2006 to 2007, a provider questionnaire was administered to evaluate health care provider attitudes towards patients with acute vaso-occlusive crisis due to SCD[42]. After factor analysis, they created a 7-item scale called the Positive Prover Attitudes towards Sickle Cell Patients Scale (PASS); higher scores indicated more positive attitudes. Their findings revealed that higher patient educational attainment and employment were significantly associated with higher PASS scores. Given the association between positive attitudes and higher education and employment, further research needs to be done to determine any clinical significance.

METHODS

Study design

This retrospective study will be a cross-sectional, comparative analysis of data from public-use datasets of the National Hospital Ambulatory Medical Care Survey (NHAMCS) ED sample between the years 2008-2018. This research aims to study the relationship between socioeconomic status and the amount of time patients with SCD who present to the Emergency Department of a hospital with a pain crisis wait to see a provider, taking into account factors such as sex, education, and employment. Covariates such as time of day, age, race, and acuity as measured by the Emergency Severity Index (ESI) score will be considered to account for potential confounding influences on the outcome variable.

Study population and sampling

The analysis will include patients aged 18 years and older with a diagnosis of SCD (ICD-9-CM codes 282.41, 282.42, and 282.60 through 282.69 for years 2008-2015 and ICD-10-CM codes D57.0 through D57.9 from 2015-2018) who present to the ED with a vaso-occlusive pain crisis (pain being the chief complaint at the time of presentation). Time to provider will be identified and further stratified by sex, employment, and education level. Patients under the age of 18 years will be excluded from the analysis with the reasoning that the vast majority of pediatric patients will not yet have had the opportunity for employment or higher education, and thus will not be a reliable group to draw generalizable conclusions from.

Study variables and measures

The outcome variable will be time to provider (TTP), which will be defined as the length of time between patient arrival to the ED and the first interaction with a medical provider (physician or midlevel provider) in minutes. As prior studies have examined times patients with SCD wait to see a provider in the Emergency Department, this would allow for direct comparison, making it an ideal measurement for this proposed study[59]. Additionally, time to provider is recorded in every patient visit in a consistent fashion (minutes), therefore, it may be easily identified in datasets and there is a low chance of distorting the data. The predictors of interest for this study will be sex (male vs. female), employment (employed vs. unemployed), and education (at least some high school education vs. high school/GED degree vs. at least some college).

Additional covariates in the analysis will include patient age, race, acuity, and time of presentation to the ED. Age will be defined as a continuous measure. Race will be categorical, based on how it is organized in the NHAMCS database (Black, White, Asian or Native Hawaiian/Other Pacific Islander, American Indian/Alaska Native, and more than one race reported). Acuity will be determined from the emergency severity index (ESI) score, a five-level scale used by Emergency Departments to classify patients from low urgency (level 5) to high urgency (level 1). This study will group ESI scores into three categories: the lowest acuity will be defined as ESI levels 4-5, moderate acuity will be defined as ESI level 3, and high acuity will be defined as ESI levels 1-2. Time of presentation will be grouped into three categories: 7am-3pm shift vs. 3-11pm shift vs. 11pm-7am shift.

Data analysis

The study will employ a variety of statistical analyses to examine these relationships.

1. Student T-tests will be used initially to evaluate the difference in mean wait times across binary predictors, such as between male and female patients, and employed and unemployed patients.
2. One-Way Analysis of Variance (ANOVA) will be performed to compare wait times across education levels. This is a more appropriate test than a T-test for a categorical variable with more than two levels. It assesses whether the mean waiting time significantly differs across the three education levels. Post-hoc tests (such as Tukey's HSD test, for example) will be used to conduct pairwise comparisons if the overall ANOVA result is significant.
3. Multiple Linear Regression will be used to predict the wait time based on multiple independent variables. The advantage of multiple linear regression is that it allows for the examination of the effects of multiple predictors on an outcome, while controlling for the effects of other variables. The regression will help determine the extent to which sex, education, and employment status can predict wait times while controlling for covariates like age, race, acuity, and time of presentation. Assumptions of multiple linear regression, including linearity, independence, homoscedasticity, and normality of residuals, will be checked and addressed as necessary. While the generalized linear model and

logistic regression could be used in certain scenarios, in this case, given that the outcome variable is continuous (waiting time in minutes), a linear regression model is more suitable.

4. Interaction effects, for instance, the interaction between time of day and other predictor variables or covariates, will also be evaluated. This can shed light on how the relationships between predictors and waiting time might change under different conditions (for example, does the influence of socioeconomic status on waiting time vary by time of day?).

In summary, the combination of T-tests, One-Way ANOVA, and Multiple Linear Regression will provide a robust examination of the relationship between socioeconomic factors and wait times in the emergency department. These methods will help to identify key predictors and understand the complexity of the relationships among variables while controlling for potential confounders.

Timeline and resources

The retrospective study will analyze data over a ten-year period (2008-2018), terminating before the start of the COVID-19 pandemic, as TTP in EDs may vary during this time, potentially affecting the validity of the data. An approximate timeline for data gathering, cleaning, and statistical analysis is three to four months. Personnel resources include: a primary investigator and clerical assistants to clean data, if necessary. Physical resources include a computer with appropriate statistical software.

Institutional Review Board

Due to the de-identified nature of the publicly available NHAMCS dataset, this research will likely be exempt from review by the Institutional Review Board. However, the primary investigator should research the particular guidelines of their institution.

CONCLUSION

Discussion

Limitations to this study include the examination of time to provider as a proxy to provider bias. There may be other confounding factors contributing to the variance in wait times, such as patient volumes in the Emergency Department at the time of patient presentation, staff availability, the mode of patient transportation to the hospital (ex: ambulance vs. self-presenting), amongst others. Future studies may also evaluate time to first analgesic administration and/or adequate pain control on reassessment.

Another point of consideration is how patient status is tracked on medical record systems. Typically, patients are marked by individual staff members, which may contribute to variation in the intervals being recorded. However, the large sample size that will be included in this study should minimize the potential for error.

Furthermore, the measurement of acuity using the Emergency Severity Index (ESI) score is determined by the provider and is therefore subjective. Although ESI scores are valuable in that they are relatively simple and clear to use, there may be rates of under and over-triage, and the reliability of such scale may be questionable. This may lead to shorter wait times due to a specific provider's perception of one's condition and pain they are experiencing. Pain is a subjective experience, and patients with SCD who suffer from daily pain may have developed coping mechanisms, resulting in the lack of quantifiable signs of pain such as moaning or writhing. The discrepancy between reported levels of pain and quantifiable signs may lead to misperceptions about "drug seeking" behavior and a subsequent delay in time to provider and analgesia administration[15]. This proposed study attempts to mitigate the potential confounding factor of acuity determined from the ESI score through a linear regression model.

As discussed with an earlier study analysis[13], this study may be impacted by bias through the utilization of NHAMCS to obtain the data, as it is limited in collection and sample size. It is important to note that the dataset undergoes weight smoothing in respect to patient visits to produce national estimates from sample data. However, given the variety of hospitals in different regions of the United States, the results should be fairly generalizable. The study may be replicated and performed in an experimental fashion in multiple hospital settings to obtain a larger sample size with comprehensive datasets.

Summary

Sickle cell disease is a genetic condition that occurs due to a mutation of the beta-globin gene, which forms an abnormal variant of hemoglobin and causes erythrocytes to adapt a "sickled" shape. One important clinical manifestation includes vaso-occlusive crises, which are often treated in the Emergency Department with parenteral opioids. Racial bias, disease stigma, and the opioid epidemic contribute to the barriers that exist for patients with SCD, ultimately resulting in disparate care and adverse health outcomes. Negative provider attitudes may translate into clinical practice and mistreatment of patients. This will be the first study to investigate the impact of socioeconomic factors (namely sex, employment, and education) on the treatment of patients with SCD who present to the Emergency Department with a pain crisis, using time to provider as the outcome variable. The results of this study may highlight further inequities faced by patients with SCD in addition to the well-studied issues of racial bias and disease stigma.

Clinical and public health significance

Implicit racism and bias may manifest as increases in time to see a provider and ultimately delayed care, causing potentially detrimental downstream effects. Patients may have a worse quality of life due to the treatment they receive in medical settings, which can affect their psychological and social well-being. In order to decrease bias and improve healthcare outcomes, it is essential to increase provider awareness of the implicit biases they may harbor against race, disease state, and socioeconomic status. Interventions for education include sessions/workshops that can be held for ED providers to address misconceptions, teach bias-reduction strategies (ex: running through hypothetical scenarios and the consequential outcomes), and review NHLBI national guidelines to best manage patients with SCD. Case managers and pain services/PMNR specialists may also be included in the multi-disciplinary care team to ensure adequate acute and chronic pain management. In one study, a Day Hospital facility was established for patients with SCD with uncomplicated painful crises and found to be effective and rapid for painful crisis management and reduced unnecessary hospital admissions[60]. Specially trained staff who had a deep awareness of the bias and stigma these patients carry may contribute to the success of such a facility.

Though mitigating provider bias may improve time to provider, protocols for pain management in patients with SCD in the ED setting may further facilitate care. For example, individualized pain plans, embedded care alerts, and FYI flags may notify an ED provider of the pain regimen recommended by a patient’s hematologist to simplify ordering and expedite the process. This personalized method can be beneficial, as each patient’s experience with pain may be unique. However, in settings where individualized pain plans are not yet implemented, standardized order sets that include recommendations from national guidelines to treat pain associated with SCD may help ED providers treat this subset of patients that they may not encounter commonly.

While integrating the clinical practices mentioned above may improve the quality of healthcare that patients with SCD receive in the ED, several other interventions directed at the patient-level may further increase the patient’s quality of life. For instance, individual psychological support and support groups/advocacy organizations for patients with SCD and their families may provide a safe space to voice their concerns and relate to others who have had similar treatment experiences. Stress associated with stigmatization can have negative effects on one’s mental health and well-being[42], therefore, social support and appropriate coping strategies may be useful for patients with SCD to address these challenges. Lastly, particularly vulnerable patients within the SCD community (ex: groups that may be identified as a result of this proposed study) may be screened to ensure they have access to primary care providers, social support, and other services, such as transportation and insurance, that have been previously identified as barriers to care. Further research may be done to identify if other subgroups of the SCD community experience increased bias and elucidate whether these interventions have positive impacts on this population.

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