Assessment of Patient-Reported Health-Related Quality of Life among Hospitalized Adults with Sickle Cell Disease

A thesis submitted by

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Abstract

Sickle cell disease (SCD) is an inherited condition characterized by painful vaso-occlusive (VOC) episodes that lead to poor health-related quality of life and premature mortality. Currently, pain assessment is performed by the Numeric Rating Scale (NRS), with which patients rate the intensity of pain from 0 (no pain) to 10 (worst imaginable pain). Newer patient-reported outcomes (PROs) measures that assess the multidimensional impact of pain among adults with SCD have been preliminarily validated in ambulatory populations. This study described the VOC experience among hospitalized adults with VOC, using two PRO tools, the Patient-Reported Outcomes Measurement Information system (PROMIS) Global Health and the Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me).

Adults with SCD hospitalized with VOC at two academic centers in New England from April 2016-October 2017 were eligible. Participants completed PROMIS Global Health and ASCQ-Me assessments at admission and seven days after hospital discharge. We calculated means and standard deviations for the NRS and PRO scores. We described feasibility in terms of proportion of assessment ascertainment. Healthcare utilization outcomes included hospital length of stay (LOS) and 30-day readmission rates. Using multivariable linear regression, we used sociodemographic, clinical characteristics, and the novel PRO scores to predict hospital LOS.

Forty-two of 44 eligible patients (95.5%) consented and completed all admission assessments. The mean age was 30.2 years, 60% were women, 76% were black, non-Hispanic, and 64% had hemoglobin SS. Twenty-seven participants (64%) completed all assessments seven days after discharge. Seven (47%) of the missing assessments were due to hospital readmission within one week. Sixty percent of patients had four or more VOCs in the last 12 months. These participants were more likely to be younger, of non-Hispanic race, have hemoglobin SS, be prescribed hydroxyurea, and on disability. They tended to have higher pain intensity and lower ASCQ-Me scores.

All mean ASCQ-Me and PROMIS Global scores were below population norms, with the exception of Sleep Impact. There was statistically significant improvement in mean NRS ($p<0.01$) and PROMIS Physical Health ($p<0.05$) at seven days following discharge.

The overall 30-day readmission rate was 40.5% and mean LOS 8.5 days. The clinical prediction model demonstrated that 29% of the variability in LOS was accounted for by the relationship of Hb SS genotype, presence of dependent children at home, and PROMIS Global Physical Health score.

Administering PROs among adults with SCD hospitalized for VOC is feasible and informative. Participants reported recurrent, prolonged and severe VOCs. PROMIS and ASCQ-Me scores indicated substantial suffering as compared to the general U.S. and outpatient SCD populations. The striking 30-day readmission rate (40.5%) highlights that hospitalized adults with SCD are a particularly vulnerable population.

Dedication

This work is dedicated to my parents, Lee and Jesse Esham, for encouraging me to pursue my dreams and instilling in me the compassion and empathy I bring to my research and to the bedside, and to my partner, Sudhir Manchanda, for his endless encouragement and belief in me to always push beyond what I thought possible.

And to all the patients that made this work possible:

"Although the world is full of suffering,
it is also full of the overcoming of it."
Helen Keller

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List of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AIC	Akaike Information Criterion
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement System
BMC	Boston Medical Center
ED	Emergency Department
EHR	Electronic Health Record
Hb	Hemoglobin
HCUP	Healthcare Cost and Utilization Project
HRQL	Health-Related Quality of Life
logLOS	Natural Logarithm of Length of Stay
LOS	Length of Stay
NIH	National Institutes of Health
NRS	Numeric Rating Scale
PRO	Patient-Reported Outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
REDCap	Research Electronic Data Capture
SCD	Sickle Cell Disease
SD	Standard Deviation
Tufts MC	Tufts Medical Center
U.S.	United States
VOC	Vaso-Occlusive Crisis

Chapter 1: Introduction

1.1 Sickle Cell Disease and the Vaso-Occlusive Crisis

Sickle cell disease (SCD) is a group of heritable hemoglobinopathies that represents the most prevalent blood disease in the United States (U.S.), affecting upwards of 100,000 individuals.[1,2] SCD is comprised of a variety of genetic mutations, including the most severe forms of hemoglobin SS (Hb SS) and hemoglobin Sβº as well as other common genotypes including hemoglobin SC and $S\beta^+$, all primarily affecting racial and ethnic minorities. Although SCD consists of many genotypes, the disease is unified by recurrent painful episodes, referred to as vaso-occlusive crises (VOC), which are considered the hallmark clinical manifestation of SCD.[3] Sickle cell pain from VOCs has been described as worse than post-operative pain and as intense as terminal cancer pain.[4,5] Pain is an inherently subjective experience and the intensity and complexity of SCD pain is often underestimated and misunderstood by clinical providers.[6-8] Patients with SCD report frustration from provider preoccupation with concerns of opiate addiction as well as disregard, lack of sympathy and insensitivity to their pain, all of which culminate in inadequate pain assessment and mitigation.[6,7,9,10]

Pain in adults with SCD is mostly managed at home, which may contribute to underestimation of the prevalence of pain and its impact on patients by their healthcare providers.[7] As a consequence, there can be misclassification, distorted communication, and under treatment of pain.[7] In turn, undertreated pain is associated with decreased patient satisfaction, increased healthcare utilization with lengthier hospital stays, more

frequent emergency department (ED) visits and inpatient admissions, and decreased health-related quality of life (HRQL).[11-13]Although pain episodes outside of the hospital account for most days with pain, pain is the leading cause of hospitalization among patients with SCD.[3,10,14] These issues of pain assessment and management further complicate the medical care of these vulnerable patients with this highly morbid disease.

1.1.1 Hospitalizations and Healthcare Utilization in the Context of VOCs

When adult patients with SCD are hospitalized with painful VOC, all home-based therapies and supports have been exhausted, and hospital admission signals the need for escalated therapies.[10,15] Although most patients with SCD manage their pain at home outside of the view of their providers, and one-third have no hospital or ED visits in a given year, a small subpopulation of patients with SCD account for most healthcare utilization with frequent ED visits and admissions to inpatient units.[16-21] Individuals with SCD who have ≥4 hospital admissions per year constitute a population who are more likely to have SCD-related complications including acute chest syndrome, pneumonia, avascular necrosis of bone, sepsis, as well as lower HRQL.[16,18,20,22] Frequent healthcare utilization has also been shown to be associated with markers of SCD severity such as measures of low hematocrit, need for transfusion therapy, and occurrence of SCD-related complications.[22] In 2009, the annual cost of healthcare of adults with SCD, which is primarily driven by SCD-related ED visits and hospitalizations, was estimated at $34,266 per person, with overall U.S. SCD population costs exceeding $1.1 billion.[14]

In one large study from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP), analysis of State Inpatient Databases and State Emergency Department Databases for healthcare utilization among over 21,000 American adults with SCD demonstrated that publicly insured, young adults aged 18-30 years had the highest rates of utilization, with a mean of approximately five ED or inpatient encounters per patient annually.[21] This finding of highest healthcare utilization occurring among young adults was confirmed in a 2014 study where California population-based surveillance data revealed that the greatest increase in mean annual ED utilization occurred at the time of transition from pediatric to adult care. These rates increased threefold from those aged 10-19.9 years old, with an average number of annual ED visits 0.9 (range 0-46) to 2.8 (range 0-179) among 20-29.9 year-olds.[17] This higher level of ED utilization persists throughout young adulthood, later declining after the age of 50.[17]

1.1.2 Hospital Length of Stay, 30-Day Readmissions and Mortality

The average hospital length of stay (LOS) in 2004 of all admissions related to SCD from the HCUP analysis of the Nationwide Inpatient Sample was 5.5 days.[23] However, the average LOS for these patients increases with age during childhood and varies considerably among adults in the literature, ranging upwards of 8 days in some studies.[24,25] Hospital admissions for SCD also increase with age during childhood and peak in young adulthood, with two-thirds of all SCD-related admissions occurring in adults aged 18-44 years.[23,25]

The HCUP also evaluated 30-day hospital readmission rates and found that SCD has the highest readmission rate of any chronic condition, with readmissions occurring in one-third of all SCD-related hospitalizations.[21,23,26] Furthermore, young adults with SCD aged 18 to 30 years had the highest readmission rate at 41%.[21] By comparison, approximately one quarter of adults with congestive heart failure are readmitted to the hospital during this period, and one in every six patients discharged from the hospital after either acute myocardial infarction or pneumonia are readmitted.[26]

SCD has considerable impact on mortality, and healthcare utilization has been shown to be predictive of death. In a prospective, observational study of 182 patients with hemoglobin SS disease, 26 patients (14%) died over a 5-year follow up period with nearly half of all deaths occurring in patients who were readmitted within one week after hospital discharge.[24] Not only are VOCs predictive of death, increased frequency of pain-related hospitalizations has also been shown to be a key predictor of early mortality.[18,21,27,28] Thus, among adults with SCD, hospitalizations for VOC and the immediate post-discharge period are times of high vulnerability.[24]

1.2 Current Standard of Pain Assessment among Adults with SCD: the Numeric Rating Scale

For decades, the International Association for the Study of Pain has broadly defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[29] Because the experience of pain is inherently subjective, there is no objective, gold standard measurement of pain. Pain

among adults is routinely assessed with the unidimensional measure of pain intensity, known as the Numerical Rating Scale (NRS). The NRS is the most frequently used pain assessment scale and consists of a 0-10 point rating of pain intensity, where 0 signifies "no pain" and 10 signifies "worst pain."[10,30,31] Like other linear analog scales, the NRS is brief, minimizing respondent burden and maximizing user acceptability.[31] In the hospital setting, it is elicited in a face-to-face encounter, but it can also be administered via a phone interview.[31-33] The NRS has demonstrated sensitivity to change and adequate test–retest reliability.[31] A consensus meeting in 2008 by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials provided recommendations for interpreting the clinical importance of treatment outcomes in clinical trials, at which time the NRS was recommended as a core domain measure for chronic pain clinical trials.[33]

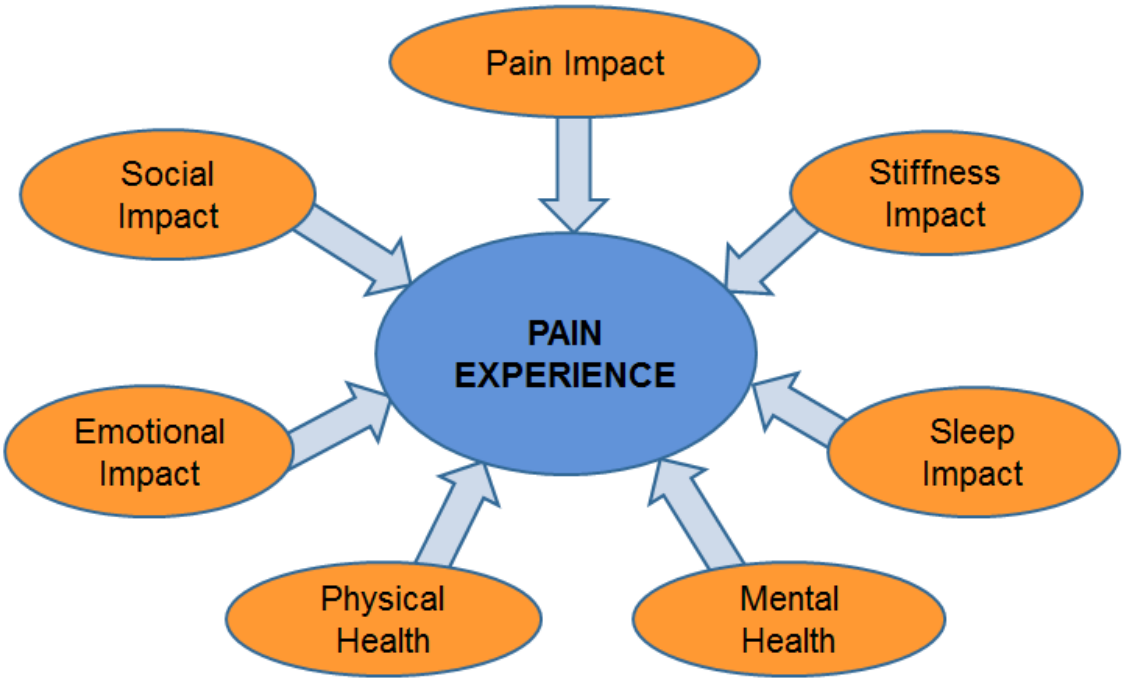
Although the NRS is useful in detecting changes in an individual's pain intensity, it does not provide any information regarding other dimensions of pain such as the timing, frequency, duration, functional impact, or interference of pain on an individual.[8,33,34] In the current context of the U.S. opioid epidemic, the Joint Commission has moved away from advocating for "pain as a fifth vital sign" in lieu of new standards calling for incorporation of assessment of psychosocial factors in addition to self-reported pain intensity.[35]

1.3 Improved Measurement Tools

Adults with SCD experience multiple disease-related complications and the effects of the pain experience reaches beyond what is captured by the NRS. The pain experience is

interwoven with domains of physical functioning, emotional distress, and social functioning, resulting in substantially impaired HRQL (see Figure 1.1).[2,11,12,36] Prior studies have suggested that more effective treatments of pain would improve HRQL in patients with SCD, thereby highlighting the need for a comprehensive assessment of the individual's pain experience in those with SCD.[2,11,12,36] In response, new tools for the measurement of the multidimensional experience of pain in SCD for use in outcomes research and clinical practice have been developed, including the Patient-Reported Outcomes Measurement Information System (PROMIS) and the Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) .[8,34,37-39]

Figure 1.1 Pain Experience in SCD



In 2004, a National Institutes of Health (NIH) initiative was established to enhance the tools of clinical research in the measurement of patient-reported outcomes (PROs). Through the PROMIS initiative, new measures were developed and tested across several chronic conditions, including SCD.[34,37,40,41] These measures focus on domains of physical, mental and social health, as well as symptoms, such as pain and fatigue.[34,37,40,41] Several of the PROMIS measures are generic, such as PROMIS Global Health, meaning that they can be used across conditions and populations.[34,42] In contrast, disease-specific measures are used to evaluate disease impact among those with a particular health condition. To complement the generic instruments, ASCQ-Me was developed contemporaneously with PROMIS to assess the physical, social and emotional impact of SCD on adults.[38,43] ASCQ-Me scores present a profile of the effects of SCD on adult functioning and well-being, with potential clinical research applications of more fully characterizing the efficacy of therapies in randomized controlled trials, evaluating and comparing effectiveness of therapies, and evaluating the effectiveness of healthcare delivery.[39]

ASCQ-Me development was a multi-step process that involved a comprehensive literature review, 11 focus groups of 84 adults with SCD, in-depth individual interviews with 36 adults with SCD and 15 clinical providers.[39] ASCQ-Me was initially validated in 2014 in a cross-sectional sample of 561 adults with SCD at seven outpatient sites in the U.S.[39] Since its initial release in 2015, ASCQ-Me has yet to be administered to other populations with SCD, particularly hospitalized adults with SCD. In addition, prior to this present work, there has been no repeated administration of ASCQ-Me in adults with

SCD, and ASCQ-Me has not previously been applied to an inpatient sample of patients during an acute VOC episode.[8,39,44]

As SCD pain assessment is critical to the management of this disease, in this prospective, longitudinal study, we sought to better understand the pain experience among adults with SCD admitted with painful VOC, as informed by self-reported measures of PROMIS Global Health and ASCQ-Me. This study relies on novel, yet preliminarily validated measures to yield information in three key areas: 1) feasibility of the assessment of the pain experience using PROs among adult patients with SCD, hospitalized for VOC; 2) the comparison of PROMIS Global Health, ASCQ-Me and SCD severity, defined by frequency of VOCs over the prior year, among hospitalized adults with VOC; and 3) the relationship between HRQL scores, as measured by PROMIS Global Health and ASCQ-Me, and prediction of a key hospital utilization outcome, hospital LOS.

Chapter 2

Assessment of Health-Related Quality of Life among Adults Hospitalized with Sickle Cell Disease Vaso-Occlusive Crisis[1]

[1] Esham KS, Rodday AM, Smith HP, Noubary F, Buchsbaum RJ, Parsons SK. To be submitted to *Blood*.

2.1. Introduction

Sickle cell disease (SCD) is a group of heritable hemoglobinopathies that represents the most prevalent blood disease in the United States (U.S.), affecting upwards of 100,000 individuals.[1,2] SCD is characterized by recurrent painful episodes, known as vaso-occlusive crises (VOC), which are considered the hallmark of the disease.[3,11-13]

2.1.1 SCD and the VOC

Although most SCD patients manage their pain at home, and one-third of SCD patients have no hospital or ED visits in a given year, VOC is the leading cause of hospitalization.[3,10,14,21] In 2009, the annual cost of healthcare of adults with SCD, which is primarily driven by SCD-related ED visits and hospitalizations, was estimated at $34,266 per person, with overall U.S. SCD population costs exceeding $1.1 billion.[14] Although there is no uniform definition of disease severity in SCD, adult SCD patients with four or more hospital admissions per year constitute a subgroup more likely to have SCD-related complications as well as lower HRQL.[16,18,22,44] This subpopulation of adults with SCD, estimated at approximately 29% of adults aged 18 to 30 years old, account for most healthcare utilization with frequent ED visits and admissions to inpatient units.[16-19,21] Furthermore, the Agency for Healthcare Research and Quality (AHRQ) Healthcare Utilization Project (HCUP) analysis of State Inpatient Databases found that SCD accounts for 57% of hospital stays among all Medicaid patients aged 1-64 years with ≥ 4 hospitalizations annually.[20] When adult patients with SCD are hospitalized with painful VOC, all home-based therapies and supports have been exhausted, and hospital

admission signals the need for escalated therapies.[10,15] However, at present, a comprehensive pain assessment for adults with SCD experiencing a VOC is lacking.

2.1.2 Pain Assessment in SCD

Pain assessment in adults is most commonly performed with the Numeric Rating Scale (NRS), where individuals rate the intensity of pain from 0 signifying "no pain" to 10 signifying "worst imaginable pain."[10,30,31] As pain is inherently subjective and multidimensional, new tools for the measurement of the experience of pain in SCD for use in outcomes research and clinical practice have been developed.[8]

2.1.3 Improved Measurement Tools

The National Institutes of Health (NIH) Patient-Reported Outcomes Information System (PROMIS) initiative improved tools for clinical research with the development of measures to be used across the general population and in those with chronic illness, including SCD.[41] Several of the PROMIS measures are generic, such as PROMIS Global Health, meaning that they can be used across conditions and populations.[34,42] Specifically, PROMIS Global Health is a generic measure of health-related quality of life (HRQL) that generates separate physical health and mental health subscales. To date, PROMIS Global Health items have been shown to be predictive of key outcomes and future events such as healthcare utilization and mortality.[34,45]

In contrast, disease-specific measures are used to evaluate disease impact among those with a particular health condition. To complement the generic instruments, the Adult

Sickle Cell Quality of Life Measurement System (ASCQ-Me) was developed contemporaneously with PROMIS to assess the physical, social and emotional impact of SCD on adult functioning and well-being.[38,39,43]

ASCQ-Me development was a multi-step process that involved a comprehensive literature review, 11 focus groups of 84 adults with SCD, and in-depth individual interviews with 36 adults with SCD and 15 clinical providers.[39] ASCQ-Me was initially validated in 2014 among a cross-sectional sample of 561 outpatients with SCD across seven sites in the U.S.[39] Since its initial release in 2015, ASCQ-Me has yet to be administered to other populations, particularly hospitalized adults with SCD. In addition, prior to this present work, there has been no longitudinal administration of ASCQ-Me in adults with SCD.[8,39,44]

As SCD pain assessment is critical to the management of this disease and the HRQL among adults hospitalized with VOC has yet to be described with PROMIS Global Health or ASCQ-Me, in this prospective study of pain, we sought to measure the VOC pain experience and its effect on HRQL and healthcare utilization among adults with SCD admitted with painful VOC, as informed by self-reported measures of PROMIS Global Health and ASCQ-Me.

2.2. Methods

2.2.1 Study Design

The study utilized an inception cohort of adults with SCD hospitalized at Tufts Medical Center (Tufts MC) and Boston Medical Center (BMC) with VOC from April 2016-October 2017.

2.2.2 Subject Characteristics

Adults aged 18 years or older with SCD (genotypes hemoglobin (Hb) SS, Hb SC, Hb $S\beta^+$ thalassemia, Hb $S\beta^0$ thalassemia, and other/unspecified) admitted to Tufts MC or BMC inpatient services with VOC were eligible. No incentives were offered for study participation. Subjects were excluded it they were unable to provide written informed consent or were non-English speaking, as ASCQ-Me is presently only available in English.

2.2.3 Study Measures

Self-reported sociodemographic and medical history information included participants' age, gender, insurance payer, highest level of education, living situation, dependency status, employment status, disability status, disease genotype and hydroxyurea prescription.

The NRS is an 11-point scale that measures pain intensity, where 0 signifies "no pain" and 10 signifies "worst imaginable pain."[10,30,31] A minimal clinically important difference on the NRS was found to be a 1-point score change.[33]

The PROMIS SF v1.1 – Global Health measure is a 10-item assessment that generates separate Physical and Mental Health subscale scores.[34] PROMIS scores for each subscale range from 0-100 and are standardized to a U.S. population mean of 50 and standard deviation (SD) 10.[42] For both of the subscales, higher scores connote better functioning and a change of 3 to 5 points (0.3-0.5 SD) is considered clinically meaningful. [33,34,46-50]

ASCQ-Me is a SCD-specific patient-reported outcomes (PRO) measurement system that begins with a 5-item assessment of the frequency, timing and severity of sickle cell pain events, the Pain Episode scale, which serves as an indicator of SCD severity over the prior year. The Pain Episode scale generates separate Frequency and Severity subscale scores.[38,39,51] ASCQ-Me Pain Episode scores for each subscale range from 0-100 and are standardized to a SCD-population mean of 50 (SD, 10) as per published algorithm.[43,46,51,52] In contrast to the other PROMIS and ASCQ-Me scales in which higher scores connote better health, higher scores for the Pain Episode subscales connote worse impact with more frequent and more severe disease, respectively.[43,52]

The remainder of ASCQ-Me is composed of five short forms, each comprised of 5 items, which assess the Emotional Impact, Social Functioning Impact, Pain Impact, Stiffness Impact, and Sleep Impact of SCD, respectively.[39,51] In keeping with PROMIS methodology, scores for each of the ASCQ-Me scales range 0-100 with a standardized SCD-population mean of 50 (SD, 10), where lower scores connote worse disease impact, except where noted.[43,46,51,52] Of note, the ASCQ-Me Social Functioning Impact measure was not analyzed in the 7-day post-discharge assessment, as its recall period of 30 days

overlaps with the admission assessment. Since there is currently no published minimal clinically important difference for the ASCQ-Me measures, we assumed a minimal clinically important difference to be a point score change of 3 to 5 points (0.3-0.5 SD), which is the standard for interpretation of PROMIS scores.[48-50]

Known group comparisons by VOC frequency were performed on the basis of response to the number of self-reported VOCs during the preceding year (ASCQ-Me Pain Episode Item 1). High and low frequency groups were categorized as ≥4 VOCs in the prior year and <4 VOCs in the prior year, respectively.

Healthcare utilization outcomes of interest included hospital length of stay in days and frequency of 30-day hospital readmissions to Tufts MC and BMC, collected from the electronic health record (EHR).

2.2.4 Study Procedures

Participants provided sociodemographic and medical history information upon hospital admission for VOC, at which time the ASCQ-Me Pain Episode Frequency and Severity measure was also completed. On admission and seven days following hospital discharge, participants completed the PROMIS Global Health and ASCQ-Me questionnaires (see Figure 5.1). In the event of hospital readmission within one week from discharge, PROMIS and ASCQ-Me were not collected for the 7-day post-discharge assessment.

The NRS is part of usual standard care and was collected upon admission from the EHR for each participant. The NRS was also collected 7-days post-discharge (with window period of up to +2 days). In the event of hospital readmission within one week from discharge, the NRS upon readmission was collected from the EHR.

All assessments at the time of hospital admission were collected with pen and paper and all assessments following discharge were collected via telephone report by a trained investigator of the research team (K.S.E). If participants did not respond on the first telephone call follow-up attempt, participants were phoned once daily during the 7-day post-discharge study window for a maximum of three telephone calls.

2.2.5 Statistical Analysis

Descriptive statistics were used to describe feasibility of PRO collection in terms of assessment ascertainment at the time of hospital admission and seven days following hospital discharge for VOC.

Descriptive statistics were used to describe the frequencies of sociodemographic and SCD characteristics among the study population.

ASCQ-Me Pain Episode Frequency and Severity scores are reported in addition to summary of Pain Episode Items 1, 3, 4 and 5 separately, since respondents commonly asked for clarification regarding whether to respond based on the current VOC or the "last pain attack (crisis)" for Item 2, raising concerns regarding the relevance of those

items to participants at time of an acute VOC.[43] In addition, study sample ASCQ-Me scores are presented in comparison to the outpatient ASCQ-Me validation sample scores, the reference population for ASCQ-Me.[39,43]

Means and SDs for the NRS and PROs were calculated for assessments collected at the time of hospital admission and again at seven days after hospital discharge. Using a one-sample t-test, change scores (7-day post-discharge minus admission) for PROMIS and ASCQ-Me measures were calculated using a complete case analysis and two-sided alpha of 0.05. Summary statistics with means and SDs were reported by scale for both assessment time points for the overall cohort and separately among the high and low VOC frequency groups.

Summary statistics for hospital length of stay (LOS) and 30-day readmission rates were calculated in our study sample and compared to results from the AHRQ HCUP analyses of the Nationwide Inpatient Sample, State Inpatient Databases and State Emergency Department Databases comprised of encounter-level information on several thousands of SCD-related admissions.[21,23]

Study data were collected and managed using Research Electronic Data Capture (REDCap), a secure, web-based application for electronic data capture tool hosted at Tufts MC.[53] The study protocol was approved by the Tufts Health Sciences Institutional Review Board (IRB) at Tufts MC. The study was approved by BMC and Boston University Medical Campus IRB with a data sharing agreement in place. All statistical

analyses were performed at Tufts MC using R statistical software version 3.4.2 (RStudio version 1.1.383).[54]

2.3. Results

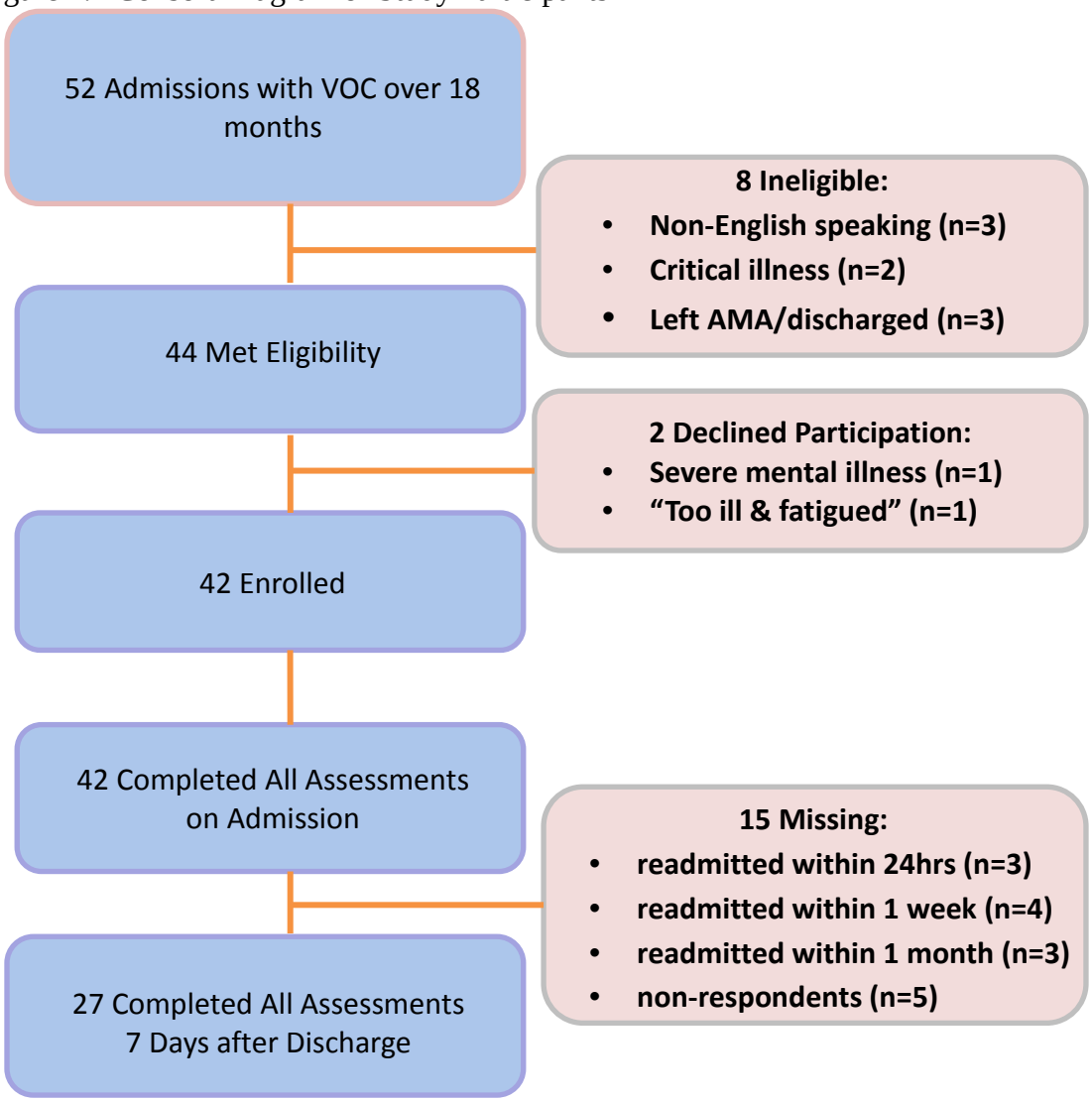
2.3.1 Feasibility

Of 44 eligible participants, 42 unique individuals were enrolled (see Figure 2.1). Two participants declined, citing reasons of severe mental illness and inability to participate due to fatigue. All of the enrolled participants completed the admission assessments. However, there was 64% data completeness at one week following discharge, with complete data on 27 participants. Most missing assessments were meaningful, as they were due to hospital readmissions (n=10). The remainder of participants were non-respondents 7-days post-discharge (n=5).

2.3.2 Participant Sociodemographic and SCD Characteristics

Baseline participant characteristics of the study sample reflect the young adult population of minorities that comprises SCD in the U.S. The mean age was 30.2 years, 60% were women, and there was a predominance of Hb SS genotype, consistent with more clinically severe disease manifestation. In this cohort, no patients were uninsured due to enrollment in the MassHealth Medicaid program in the Commonwealth of Massachusetts. Sixty percent of participants reported being on disability and one-third of participants had achieved a high school or less level of education. Additional participant sociodemographic and disease characteristics are provided in Table 2.1.

Figure 2.1 Consort Diagram of Study Participants



Abbreviations: VOC, vaso-occlusive crisis; AMA, against medical advice

2.3.3 Baseline ASCQ-Me Pain Episode Scores among Adults Hospitalized with VOC

Baseline ASCQ-Me Pain Episode scores among this sample of 42 inpatient adults hospitalized with VOC demonstrated more frequent and more severe VOCs as compared to the initial outpatient validation sample (Table 2.2).[39] The study sample ASCQ-Me Pain Episode Frequency score was 56.8 and Severity score 55.7, both of which were more

than 0.5 SD from the validation sample mean of 50, reflecting worse VOC episodes. Raw ASCQ-Me Pain Episode scores can be found in the Appendix, Table 5.1.

Table 2.1: Participant Sociodemographic and Disease Characteristics

Hospitalized Cohort, n(%)	**Participants (n=42)**
Age in Years, mean (SD)	30.2 (9.1)
Female	25 (59.5%)
Non-Hispanic Black	32 (76.2%)
Hemoglobin SS Genotype	25 (59.5%)
Prescribed Hydroxyurea	27 (64.3%)
Publicly Insured	37 (88.1%)
Self-Reported Disability	25 (59.5%)
Employed	16 (38.1%)
≤ High School Education	13 (30.11%)
Lives Alone	7 (16.7%)
Primary Caregiver of Dependent Child	9 (21.4%)
Tufts MC Study Site	33 (78.6%)

Categorical variables are binary: gender (male/female), race/ethnicity (non-Hispanic black/other), genotype (Hb SS/other), prescription of hydroxyurea (yes/no), publicly insured (yes/no), self-reported disability (yes/no), employed (yes/no), ≤ high school level of education (yes/no), lives alone (yes/no), primary caregiver of dependent children (yes/no), and study site (Tufts MC/BMC).

Regarding item responses to the Pain Episodes measure, in contrast to the initial ASCQ-Me validation sample of 561 outpatients in which 20% of participants reported two or more VOCs in the prior year, in the current study, 90% reported two or more VOCs in the prior year (see Table 2.2). Further, 60% of study participants reported 4 or more VOCs in the last 12 months. The mean score for the most severe pain during the last pain attack was 8.9 (SD = 1.3) on a scale from 0-10, as compared to 7.8 among the validation sample. The duration of the most recent pain crisis was at least a week for 50% of study participants, as compared to only 21% in the validation sample. In addition, a greater proportion of study participants reported duration of VOC lasting longer than two weeks

(21% vs. 7% in the validation group). There were similar rates of those reporting inability to care for themselves during a pain crisis (43%), among the study and validation samples (Table 2.2).

Table 2.2: Pain Episode Frequency and Severity Items: More Frequent and Severe VOCs among Hospitalized Cohort

	ASCQ-Me Validation Sample (n=561)	Hospitalized Cohort (n=42)
Pain Episode Frequency Item 1		
≥ 2 VOCs in the past 12 months, %	20%	90%
Pain Episode Severity Item 3		
Pain severity during last crisis (0-10), mean(SD)	7.8 (2.3)	8.9 (1.3)
Pain Episode Severity Items 4 & 5		
How much did your last pain crisis interfere with your life?, %		
I've never had a crisis	2%	0%
Not at all, I did everything I usually do	10%	9%
I had to cut down on some things…	21%	29%
I could not do most things…	30%	19%
I could not take care of myself…	18%	19%
.....needed some help…		
I …needed constant care…	19%	24%
About how long did your most recent pain attack (crisis) last?, %		
I've never had a crisis	2%	0%
Less than 1 hour	4%	0%
1-12 hours	18%	5%
13-24 hours	8%	0%
1-3 days	22%	21%
4-6 days	25%	24%
1-2 weeks	14%	29%
More than 2 weeks	7%	21%

Abbreviation: VOC, vaso-occlusive crisis

2.3.4 NRS, PROMIS and ASCQ-Me Profiles at Hospital Admission, 7-Days after Discharge, and Change Scores

The admission NRS, PROMIS and ASCQ-Me scores of the 27 respondents with complete follow-up were similar to the scores of the overall cohort (Table 2.3). The mean NRS on admission was 8.4, signifying severe pain intensity among study participants. There was statistically significant and clinically meaningful improvement in the NRS 0-10 pain score from severe to moderate pain intensity by seven days following discharge among the 27 respondents with complete follow up (Table 2.3).

Mean PROMIS Global Physical Health subscale scores were more than a full standard deviation below the U.S. population mean upon admission (38.9), with statistically significant improvement by seven days following hospital discharge among respondents (40.9), although mean scores following discharge still remained well below population norms (Table 2.3). Mean PROMIS Global Mental Health subscale scores were significantly below U.S. population norms on admission (42.2) and seven days following discharge (44.7), however there was no statistically significant improvement in change scores among study respondents (Table 2.3).

Scores on all of the ASCQ-Me scales, with the exception of Sleep Impact, were below SCD-specific population norms. Emotional Impact scores were a full standard deviation below the population mean at both admission (40.5) and seven days following discharge (40.8). None of the ASCQ-Me change scores (admission to seven days post discharge) were statistically significant (see Table 2.3).

Table 2.3: Comprehensive Pain Assessment at Hospital Admission, 7-Days Following Discharge and Change Scores among Adults Hospitalized with VOC

	All Patients, n=42	**Restricted to Complete Follow-Up, n=27**		
NRS, PROMIS, & ASCQ-Me Domains	**Admission, mean(SD)**	**Admission, mean(SD)**	**Discharge+7 mean(SD)**	**Change[1], mean(SD)**
NRS Pain Score (0-10)	8.4 (1.9)	8.5 (2.1)	5.6 (3.1)	- 2.9 (4.2) *
PROMIS-Global Physical Health	38.9 (5.0)	39.8 (5.6)	40.9 (4.7)	2.1 (5.5) *
PROMIS-Global Mental Health	42.2 (6.0)	43.5 (6.5)	44.7 (5.8)	1.6 (6.0)
ASCQ-Me Emotional Impact	40.5 (9.1)	42.5 (8.3)	40.8 (7.5)	0.1 (12.8)
ASCQ-Me Social Functioning	46.5 (7.7)	43.4 (7.2)	-	-
ASCQ-Me Pain Impact	42.2 (6.5)	41.5 (6.3)	44.1 (8.0)	2.8 (8.1)
ASCQ-Me Stiffness Impact	47.8 (7.3)	45.4 (7.6)	45.9 (8.6)	- 0.5 (8.0)
ASCQ-Me Sleep Impact	52.1 (4.5)	51.1 (4.7)	51.2 (5.5)	0.05 (5.4)

Abbreviation: VOC, vaso-occlusive crisis
[1]Change scores restricted to respondents with complete follow-up, n=27
*Denotes $p<0.05$ on one-sample t-test

2.3.5 Known Groups Comparisons by Frequency of VOCs

Sixty percent of study participants reported four or more pain crises in the prior year, constituting the high VOC frequency group. In general, participants with high VOC frequency tended to be younger, of non-Hispanic black race, have Hb SS genotype, be prescribed hydroxyurea and on disability, as compared to the low VOC frequency group (Table 2.4).

Table 2.4: Patient and Disease Characteristics by Frequency of VOCs over the Prior Year

Patient & Disease Characteristic	< 4 VOC/year n=17	≥ 4 VOC/year n=25
Age, years (SD)	33.1 (11.3)	28.2 (6.7)
Female	59%	60%
Non-Hispanic Black	75%	88%
Hb SS	53%	52%
Prescribed Hydroxyurea	47%	76%
Publically Insured	88%	88%
Self-Reported Disability	35%	76%
≤ High School Education	47%	20%
1° Caregiver of Dependent Child	18%	24%

Abbreviation: VOC, vaso-occlusive crisis
Categorical variables are binary: gender (male/female), race/ethnicity (non-Hispanic black/other), genotype (Hb SS/other), prescription of hydroxyurea (yes/no), publicly insured (yes/no), self-reported disability (yes/no), employed (yes/no), ≤ high school level of education (yes/no), lives alone (yes/no), primary caregiver of dependent children (yes/no), and study site (Tufts MC/BMC).

Known groups comparison by VOC frequency in the prior year, as a marker of clinical disease severity, demonstrate that participants in the high VOC frequency group tended to have, on average, lower HRQL scores on admission in all scales except PROMIS Physical Health, where the scores were similar to the low frequency VOC group, and PROMIS Mental Health, where the low VOC frequency group had statistically significant worse Mental Health as compared to the high VOC frequency group, mean scores 39.4(SD 6.2) vs. 44.2(SD 5.2), respectively (p=0.01, see Table 2.5).

Compared to analyses from the HCUP, the mean LOS in the study cohort was 8.5 days (median 7 days, range 1-44 days) vs. 5.5 days, and the 30-day rate of hospital readmissions was 40.5% in the study cohort vs. 41.1% (among adults aged 18-30 years).[21,23] Of those participants with hospital readmissions within 30 days, 18% occurred

within 24 hours, 29% occurred within one week, and the remaining 53% occurred between one and four weeks following hospital discharge (Table 2.6).

Table 2.5: Known Groups Comparisons by Frequency of VOCs over the Prior Year

Measure/Domain at Admission	< 4 VOC/yr, mean(SD) n=17	≥ 4 VOC/yr, mean(SD) n=25
Pain Score (0-10)	8.1 (2.5)	8.6 (1.3)
PROMIS-Global Physical	38.7 (5.5)	39.0 (4.7)
PROMIS-Global Mental	39.4 (6.2)	44.2 (5.2)*
ASCQ-Me Emotional Impact	42.2 (10.1)	39.4 (8.1)
ASCQ-Me Social Functioning	47.4 (7.7)	45.9 (7.8)
ASCQ-Me Pain Impact	42.2 (8.6)	41.9 (4.9)
ASCQ-Me Stiffness Impact	50.2 (7.1)	46.1 (7.1)
ASCQ-Me Sleep Impact	53.2 (3.6)	51.2 (4.9)

Abbreviation: VOC, vaso-occlusive crisis
*p=0.01 on two-sample t-test

Table 2.6: Healthcare Utilization as Compared to the HCUP Databases^

Healthcare Utilization	HCUP Databases SCD Samples	Hospitalized Cohort (n=42)
Average Length of Stay[a]	5.5 days	8.5 days (SD 8.1)
30-day Readmission Rate[b]	41.1%	40.5%
≤ 24hrs	-	3 (7%)
≤ 1 week[c]	9.8%	5 (12%)
≤ 30 days	-	9 (21%)

^Abbreviations: HCUP, Healthcare Utilization Project; NIS, National Inpatient Sample; SID, State Inpatient Databases; SEDD, State Emergency Department Databases; NRD, National Readmissions Database
[a]Average length of stay was 5.5 days from the NIS analysis of hospitalizations for sickle cell disease from 1994 - 2004.[23]
[b]30-day readmission rate was 41.1% from the SID and SEDD among adults aged 18-30 years[21] from 2005-2006 with an overall 30-day readmission rate of 33.4%.[21] The 30-day readmission rate from was 34.4% from the NRD analysis of Medicaid patients in 2014.[55]
[c]7-day readmission rate from the NRD analysis among Medicaid patients in 2014 was 9.8%.[55]

2.3.6 Healthcare Utilization Outcomes

The mean hospital LOS was similar between high and low VOC frequency groups. Although participants in the high VOC frequency group tended to be readmitted more frequently as compared with the low VOC frequency group, (44% vs 36% 30-day readmission rate) this did not reach statistical significance, given the limited sample size (p=0.81; Table 2.7).

Table 2.7: Healthcare Utilization Outcomes by Frequency of VOCs over Prior Year

Healthcare Utilization	< 4 VOC/yr, n=17	≥ 4 VOC/yr, n=25
Length of Stay (days), median (q1,q3)*	7 (4,9)	7 (3,12)
30-day Readmission Rate	36% (n = 6)	44% (n = 11)
≤ 24hrs	6% (n =1)	8% (n =2)
≤ 1 week	18% (n =3)	8% (n =2)
≤ 30 days	12% (n =2)	28% (n =7)

Abbreviation: VOC, vaso-occlusive crisis
*Median length of stay (LOS) is reported in days with corresponding first (q1) and third quartiles (q3)

2.4 Discussion

PROMIS Global Health and ASCQ-Me scores profile the pain experience of adults with SCD admitted with painful VOC. In the present study sample, the baseline ASCQ-Me Pain Episode scores reflect recurrent, prolonged and severe VOC episodes over the prior year. All generic and disease-specific scores as measured by PROMIS Global Health and ASCQ-Me were well below population norms on admission and at one week following hospital discharge, with the exception of Sleep Impact. The negative valence on the ASCQ-Me Stiffness Impact scale, although not a statistically significant change, may imply worsening stiffness among respondents following hospital discharge. These

findings are indicative of ongoing substantial suffering from the VOC pain experience as compared to the general U.S. population and to outpatients with SCD.

We demonstrate the acceptability and feasibility of collecting PROs from adults with SCD as the participants in this study wanted to be "asked" about their pain experience, demonstrated by the high enrollment and 100% data completion on admission, despite the intensity and severity of participants' clinical status at the time of hospital admission. However, we encountered potentially non-ignorable missing data at the 7-day post discharge assessment, primarily due to hospital readmissions, that limits the interpretability of change in scores over time. We restricted analyses to complete-cases, which is likely not representative of the more medically ill participants who required hospital readmission during the study interval. Future studies with larger sample sizes may employ pattern mixture modeling conditioned on the reason for missingness or multiple imputation to analytically address missing data. In addition, future studies of the responsiveness of PROMIS and ASCQ-Me measures to changes in the pain experience over time should take into consideration the duration of acute VOCs, the high readmission rate within seven days following hospital discharge, the time to recovery from an acute VOC, as well as the potential for individuals to experience incremental decrements in HRQL with each VOC, reflective of the accumulation of end-organ damage.

Although pain intensity (NRS) and PROMIS Physical Health improved seven days following hospital discharge, other HRQL scores did not. This likely reflects the

incomplete resolution of the acute VOC one week following hospital discharge. In addition, although acute pain (e.g. NRS scores) and its impact on overall physical functioning may improve, some domains may not recover following an acute VOC, and some may even worsen. For instance, the negative valence on ASCQ-Me Stiffness Impact seven days following hospital discharge suggests that some patients deteriorate following hospital discharge. PROMIS Mental Health and ASCQ-Me Emotional Impact scores remained low, supporting the need to assess the impact of the pain experience on individuals with SCD patients above and beyond the current standard of pain intensity, to identify other areas in need of clinical attention.

Participants with low VOC frequency had worse mental health scores as measured by PROMIS, as compared to the high VOC frequency group. Future study of this finding is needed. Although this may be counterintuitive, one hypothesis is that mental health is more severely impacted at the time of hospital admission by the sudden and disruptive occurrence of an acute VOC among individuals who are infrequently affected by pain crises. One could speculate that mental health scores among individuals with infrequent crises would be better than those who have frequent crises, if assessed at times outside of an acute VOC.

Adults with SCD experience multiple disease-related complications as the effects of the VOC pain experience are predominating and interwoven with the domains of physical functioning, emotional distress, and social functioning, resulting in substantially impaired HRQL.[2,11,12,36] The lack of a standard, comprehensive pain assessment of the individual's

pain experience in SCD further complicates the ability to meaningfully study and provide quality medical care to these vulnerable individuals with a highly morbid disease.[2,11,12,36]

New tools for the measurement of the multidimensional experience of pain in SCD for use in outcomes research and clinical practice have been developed, namely PROMIS Global Health and ASCQ-Me.[8,29,34,38] As these newer measures were developed in ambulatory populations, prior to this work, they have not been studied longitudinally among adults with SCD hospitalized for painful VOC.

The lengthy hospital stays and strikingly high 30-day readmission rate highlight that adult SCD patients hospitalized with VOC are a particularly vulnerable population. In an analysis from the Bethesda Sickle Cell Cohort Study, among 264 adults with Hb SS disease, the self-reported number of severe VOCs over the prior year was shown to be a relevant measure of both the severity of SCD and the risk of death.[18] Furthermore, frequent hospitalizations have been shown to be predictive of early mortality, and hospital readmission within one week from discharge was associated with death in an earlier study.[24,56]

In the current landscape of SCD care marked by decreasing life-expectancy, poor availability of comprehensive SCD care centers, and challenges of prescription access and pain management in the midst of our national opioid crisis, comprehensive pain assessment utilizing standard pain intensity measurement combined with new PRO tools

including PROMIS and ASCQ-Me, is key to the conduct of meaningful research and implementation of interventions aimed at improving outcomes in SCD.[57,58]

Chapter 3

Development of a Clinical Prediction Model of Hospital Length of Stay among Adults Hospitalized with Sickle Cell Disease Vaso-Occlusive Crisis[1]

[1] Esham KS, Rodday AM, Smith HP, Noubary F, Buchsbaum RJ, Parsons SK. To be submitted to *Blood*.

3.1 Introduction

Sickle cell disease (SCD) is a group of heritable hemoglobinopathies that represents the most prevalent blood disease in the United States (U.S.), affecting upwards of 100,000 individuals.[1,2] SCD is characterized by recurrent painful episodes, known as vaso-occlusive crises (VOC), which are considered the hallmark of the disease.[3,11-13]

3.1.1 SCD and the VOC

Although most SCD patients manage their pain at home, and most SCD patients have no hospital or emergency department (ED) visits in a given year, VOC is the leading cause of hospitalization.[3,10,14] When adult patients with SCD are hospitalized with painful VOC, all home-based therapies and supports have been exhausted, and hospital admission signals the need for escalated therapies.[10,15] Although the average hospital length of stay (LOS) for diagnosis of sickle cell disease (SCD) has been reported in the literature to be approximately six days, some studies have reported that adults with SCD with chronic complications and psychosocial comorbidities may experience longer hospital stays.[23,24] Furthermore, internal, unpublished data from Tufts Medical Center (Tufts MC) in 2015 revealed a mean LOS of seven days, standard deviation (SD) 6.1 among adults with SCD hospitalized with vaso-occlusive crisis (VOC).

There is a paucity of understanding of what aspects of the pain experience drive LOS among the hospitalized adult SCD population. New clinical research tools employing patient-reported outcomes (PRO) methodology to measure health-related quality of life

(HRQL) are now available, however, at present, a comprehensive pain assessment for adults with SCD experiencing a VOC utilizing these newer measures is lacking.

3.1.2 Improved Measurement Tools

The National Institutes of Health (NIH) Patient-Reported Outcomes Information System (PROMIS) initiative improved tools for clinical research with the development of measures to be used across the general population and in those with chronic illness, including SCD.[41] Several of the PROMIS measures are generic, such as PROMIS Global Health, meaning that they can be used across conditions and populations.[34,42] Specifically, PROMIS Global Health is a generic measure of HRQL that generates separate physical health and mental health subscales. To date, PROMIS Global Health items have been shown to be predictive of key outcomes and future events such as healthcare utilization and mortality.[34,45]

In contrast, disease-specific measures are used to evaluate disease impact among those with a particular health condition. To complement the generic instruments, the Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) was developed contemporaneously with PROMIS to assess the physical, social and emotional impact of SCD on adult functioning and well-being.[38,39,43]

As SCD pain assessment is critical to the management of this disease and the HRQL among adults hospitalized with VOC has yet to be described with PROMIS Global Health or ASCQ-Me, in our inception cohort, we sought to capture baseline factors,

including measures of HRQL at the time of hospital admission, to determine if scores during an acute VOC could predict key utilization outcomes, such as hospital LOS. This has both clinical utility for accounting for the conflicting reports of expected LOS in the literature, identifying areas of potential future interventions to reduce hospitalization lengths, as well as financial implications for hospital reimbursement, particularly when institutional LOS exceeds the "expected" six days commonly referenced in this population.

3.2 Methods

3.2.1 Data Source

This is a prospective study of a cohort of adults with SCD hospitalized with painful VOC, from April 2016-October 2017 across two academic institutions, Tufts MC and Boston Medical Center (BMC). Study data were collected and managed using Research Electronic Data Capture (REDCap), a secure, web-based application for electronic data capture tool hosted at Tufts MC.[53]

3.2.2 Study Participants

Eligibility criteria included any adult over the age of 18 with history of any SCD hospitalized with a VOC. Individuals were excluded if they were unable to provide written informed consent due to critical medical illness or unable to read in English, as the HRQL questionnaires require literacy in English. No incentives were offered for study participation and all participants received usual medical care as per the discretion of their treating clinicians. The study protocol was approved by the Tufts Health Sciences

Institutional Review Board (IRB) at Tufts MC. The study was approved by BMC and Boston University Medical Campus IRB with a data sharing agreement in place.

3.2.3 Outcome

Hospital LOS in days was calculated as the discharge date and time minus admission date and time, as reported in the electronic health record (EHR). As unpublished internal data from Tufts MC in 2015 was consistent with skewed LOS among hospitalized adults with SCD-related admissions, a natural log transformation was applied to the outcome of LOS in this study sample to approximate a normal distribution as shown in the Appendix, Figure 5.2. The final outcome variable is thus the continuous variable, logLOS.

3.2.4 Predictors

Predictor variables were defined *a priori* based on literature review and clinical expertise.

Demographic variables included age (date of birth) at time of hospital admission, sex, health insurance coverage at the time of admission (public/private), highest level of education, living/housing status, dependent children status, employment status and disability status. Of note, race/ethnicity is not included herein as a predictor because the SCD genotype reflects the racial and ethnic makeup of this genetic disease, which uniquely affects minorities.

SCD characteristics included genotype, hydroxyurea prescription and ASCQ-Me SCD Pain Episode Frequency and Severity scores.

HRQL measures included PROMIS Global Physical and Mental Health subscales, and the five ASCQ-Me scales of Emotional Impact, Social Impact, Pain Impact, Stiffness Impact, and Sleep Impact. PROMIS Global and ASCQ-Me scores have a population mean of 50 (SD=10), with higher scores signifying better functioning and score differences of 3-5 points (1/3-1/2 SD) considered clinically meaningful.[48-50]

All variables were collected via patient-report upon hospital admission, allowing for a 2-day window period, including sociodemographic information, SCD characteristics, and HRQL measures. A complete list of candidate predictor variables can be found in the Appendix, Table 5.2.

3.2.5 Statistical Analysis

To identify baseline factors associated with hospital LOS, we assessed the relationship between candidate predictor variables and logLOS using multivariable linear regression following accepted standards for clinical prediction model development.[59,60] Although ten events per variable is commonly cited as the threshold needed for accurate prediction of binary outcomes in logistic regression and Cox proportional hazards models, the minimum number of subjects per variable in linear regression is much less.[61] With multivariable linear regression, models require only two subjects per predictor variable for adequate estimation of regression coefficients, thus with the sample size of 42, all 19 candidate predictor variables were included for analysis.[61] Model development utilized complete case analysis and predictor variables associated with logLOS at $p<0.2$ on univariate analysis were considered in the multivariable model. The final model was

developed using backward selection with Akaike information criterion (AIC). Final model performance was evaluated with a calibration plot which, for linear regression, is a simple scatterplot that graphically portrays the extent of agreement between observed vs. model-predicted values of logLOS.[62] Perfect model-predictions would fall along the 45º line, and lack of calibration would appear as a random scatter.[62] Internal validation was performed using 200 randomly selected bootstrap samples with replacement.

Study data were collected and managed using Research Electronic Data Capture (REDCap), a secure, web-based application for electronic data capture tool hosted at Tufts MC.[53] All statistical analyses were performed at Tufts MC using R statistical software version 3.4.2 (RStudio version 1.1.383).[54]

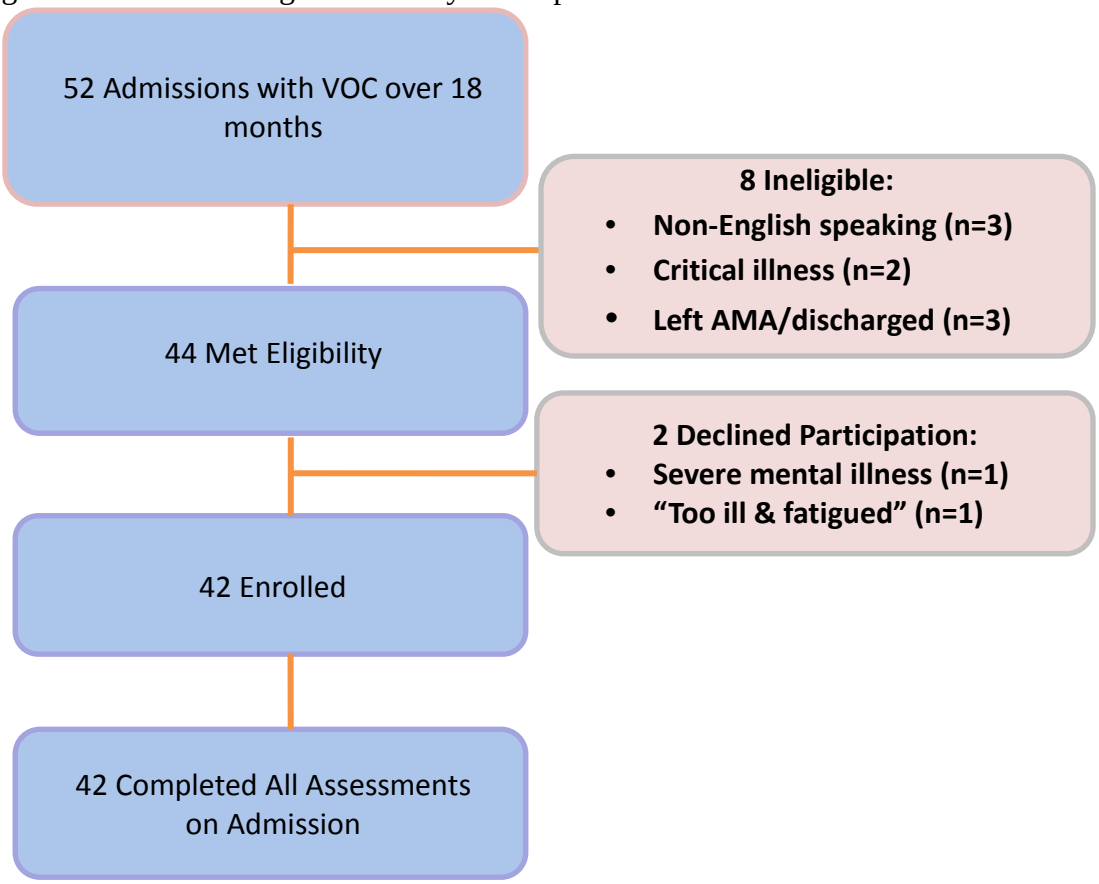
3.3 Results

3.3.1 Description of Participant Baseline Sociodemographic, Disease and HRQL Characteristics

Among the 44 eligible individuals, two declined participation citing reasons of mental illness and fatigue (see Figure 3.1). The final study cohort is comprised of 42 unique adult patients with SCD. All 42 participants completed all of the baseline assessments including collection of sociodemographic information, disease characteristics, and HRQL scores as measured by PROMIS Global Health and ASCQ-Me. Thus, no participants are missing data for the outcome variable or any of the predictor variables.

Participant baseline demographic and disease characteristics revealed that the study sample was on average 30.2 years old with most participants being female, non-Hispanic black, publicly insured, on disability, and unemployed. Most patients had the Hb SS genotype and reported having been prescribed hydroxyurea (Table 3.1).

Figure 3.1: Consort Diagram of Study Participants



Abbreviations: VOC, vaso-occlusive crisis; AMA, against medical advice

Participant baseline HRQL scores reflected severe impairment. The mean 0-10 pain score on admission was 8.1, signifying severe intensity of pain in the context of acute VOC. Participants, on average, had meaningfully impaired HRQL across all PROMIS and

ASCQ-Me domains, except Sleep Impact, upon hospital admission as compared to general and SCD-specific population means of 50 (see Table 3.2).

Table 3.1: Baseline Patient and Disease Characteristics

Patient and Disease Characteristic	**Participants, n=42 (%)**
Age in Years, mean (SD)	30.2 (9.1)
Female	25 (59.5%)
Hispanic	10 (23.8%)
Non-Hispanic Black	32 (76.2%)
Hb SS Genotype	25 (59.5%)
Prescribed Hydroxyurea	27 (64.3%)
Publically Insured	37 (88.1%)
Self-Reported Disability	25 (59.5%)
Employed	16 (38.1%)
≤ High School Education	13 (30.11%)
Lives Alone	7 (16.7%)
Primary Caregiver of Dependent Child	9 (21.4%)
Tufts MC Study Site	33 (78.6%)

Categorical variables are binary: gender (male/female), ethnicity (Hispanic/non-Hispanic), race (non-Hispanic black/other), genotype (Hb SS/other), prescription of hydroxyurea (yes/no), publicly insured (yes/no), self-reported disability (yes/no), employed (yes/no), ≤ high school level of education (yes/no), lives alone (yes/no), primary caregiver of dependent children (yes/no), and study site (Tufts Medical Center/Boston Medical Center).

Table 3.2: Participant Baseline HRQL

Measure/Domain at Admission	**Mean (SD) n=42**
Pain Score (0-10)	8.1 (1.9)
PROMIS-Global Physical	38.9 (5.0)
PROMIS-Global Mental	42.2 (6.0)
ASCQ-Me Emotional Impact	40.5 (9.1)
ASCQ-Me Social Functioning	46.5 (7.7)
ASCQ-Me Pain Impact	42.0 (6.5)
ASCQ-Me Stiffness Impact	47.8 (7.3)
ASCQ-Me Sleep Impact	52.1 (4.5)

Abbreviation: HRQL, health-related quality of life

3.3.2 Hospital LOS

Among the study cohort, the mean LOS was skewed at 8.5 days (range 1-44), whereas the median LOS was 7 days (first quartile 3.3 days; third quartile 9.8 days).

3.3.3 Descriptive Summary of Baseline Predictor Variables in Relation to Hospital LOS

Baseline predictor variables in relation to hospital LOS demonstrated a trend toward longer LOS among females and participants with the Hb SS genotype. Those not prescribed hydroxyurea, with high school or less education, publically insured, unemployed or on disability also tended to have longer hospital stays (Table 3.3).

Table 3.3: Descriptive Summary of Baseline Characteristics and LOS in Days

Baseline Characteristics & LOS in Days (n=42)	
Candidate Variable	LOS in days Median (q1, q3))
Female Male	7 (3,10) 6 (4,8)
Hb SS Genotype Other Genotypes	8.5 (6.25,13) 5.5 (2,7)
Not Prescribed Hydroxyurea Prescribed Hydroxyurea	6 (2,8.5) 7 (1,10)
≤ High School Education > High School Education	7 (3,10) 6.0 (3,9)
Not Primary Caregiver Primary Caregiver of Dependent Child	7 (5,10) 3 (2,6)
Self-Reported Disability Not on Disability	7 (6,12) 6 (2,8)
Unemployed Employed	7 (4.5,9) 6 (2,10)
Publically Insured Privately Insured	7 (3,10) 6 (7,9)

Median length of stay (LOS) is reported in days with corresponding first (q1) and third quartiles (q3)

3.4 Clinical Prediction Model Development

3.4.1 Univariate Screen

All 42 complete cases were included in the model development. Thus with a sample size of 42 study participants, all 19 candidate predictor variables were included. The unadjusted association between each candidate predictor and the logLOS outcome using linear regression is shown in Table 3.4. Hb SS genotype, high school or less education, primary caregiver status of a dependent child, disability, and PROMIS Global Physical Health score were all associated with the logLOS outcome at the $p<0.2$ level and considered in the multivariable linear regression model.

3.4.2 Model Specification

Following the univariate screen, we used multivariable linear regression with backward selection for specification of the final model. After backward selection, the multivariable regression model at the time of hospital admission included presence of Hb SS genotype, primary caregiver status of dependent children at home and PROMIS Global Physical Health subscale score (Table 3.5).

The final model is as follows:

$$\widehat{\text{logLOS}} = -0.002 + 0.56 * (\text{HbSS Genotype}) - 0.66 * (\text{Presence of Dependent Children}) + 0.04 * (\text{PROMIS Global Physical Health Subscale Score})$$

Table 3.4: Univariate Screen of Candidate Predictor Variables and logLOS

Univariate Relationship Between Candidate Variables and log LOS (n=42)		
Candidate Variable	**Beta (SE)**	**p-value**
Age (continuous)	0.01 (0.02)	0.49
Gender (reference: male)	0.17 (0.28)	0.54
Hb SS Genotype	0.66 (0.25)	0.01*
Hydroxyurea Prescription	0.13 (0.29)	0.65
≤ High School Education	-0.39 (0.29)	0.18*
Lives Alone	-0.25 (0.37)	0.50
Primary Caregiver of Dependent Child	-0.69 (0.32)	0.03*
Employed	-0.14 (0.28)	0.63
Publicly Insured	-0.14(0.42)	0.74
Self-Reported Disability	0.41 (0.27)	0.14*
ASCQ-Me Pain Episode Item 1 Score	0.04(0.28)	0.90
ASCQ-Me Pain Episode Item 4 Score	-0.03(0.28)	0.92
PROMIS Global Physical Health Score	0.05(0.03)	0.09*
PROMIS Global Mental Health Score	0.01(0.02)	0.56
ASCQ-Me Emotional Impact Score	0.004 (0.02)	0.79
ASCQ-Me Social Impact Score	-0.01(0.02)	0.50
ASCQ-Me Pain Impact Score	0.01(0.02)	0.53
ASCQ-Me Stiffness Impact Score	-0.01 (0.02)	0.48
ASCQ-Me Sleep Impact Score	-0.001(0.03)	0.96

Abbreviations: SE, standard error; Hb, hemoglobin; PROMIS, Patient-Reported Outcomes Measurement Information System; ASCQ-Me, Adult Sickle Cell Quality-of-Life Measurement Information System

*$p<0.02$ on univariate screen

Table 3.5: Multivariable Relationship of Predictor Variables and logLOS

Multivariable Relationship Between Variables and logLOS (n=42)		
Candidate Variable	**Beta (SE)**	**p-value**
Hb SS Genotype	0.56 (0.24)	**0.03***
Primary Caregiver of Dependent Child	-0.66 (0.29)	**0.03***
PROMIS Global Physical Health Score	0.04(0.02)	**0.10***

*Multivariable logistic regression utilizing predictor variables with $p<0.02$ on univariate screen followed by backward selection using Akaike Information Criterion.

3.4.3 Interpretation

Since the outcome variable is the logarithmic transformation of LOS, interpretation of the beta coefficients requires exponentiation.[63] Exponentiation of the beta coefficients suggests that, holding all else constant, the mean LOS among patients with Hb SS is 75% longer than those without Hb SS. In addition, for patients with dependent children at home, mean LOS is 52% shorter, holding all else constant. For a 5-point increase in the PROMIS Global Physical Health subscale score, mean LOS is increased by 22%, holding all else constant.

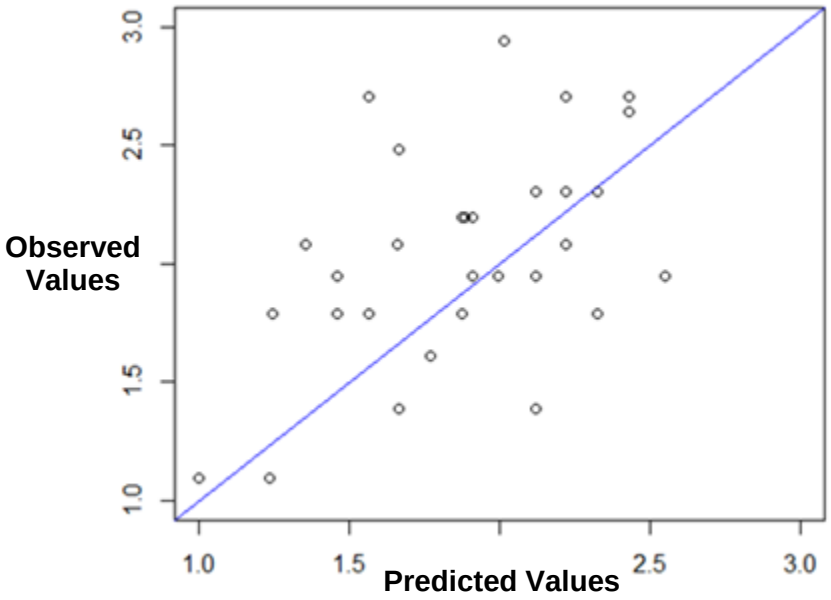
3.4.4 Model Performance

Applied at the time of hospital admission, the multiple R^2 of this model suggests that 29% of the variability in logLOS is explained by the relationship of Hb SS genotype, primary caregiver status of dependent children at home, and PROMIS Global Physical Health score. The calibration, although not perfect, appears acceptable without random scatter (See Figure 3.2).

3.4.5 Model Validation

We performed internal validation with a bootstrapping technique with replacement. Internal validation produced similar slopes for all linear regression models.

Figure 3.2 Calibration Plot of Observed vs. Model-Predicted Values of logLOS



Model-predicted values (x-axis) and observed values (y-axis) of logLOS are plotted above, where perfect model calibration would appear as all values falling along the 45º straight line.

3.5 Discussion

This clinical prediction model, consistent with what we know from other populations, demonstrates that HRQL scores can predict healthcare utilization among adults with SCD. Applied at time of hospital admission for VOC, our final clinical prediction model explained 29% of the variability of hospital LOS by presence of Hb SS genotype, primary caregiver status of dependent children, and PROMIS Global Physical Health subscale score. Hb SS is the most severe phenotype of the group of genetic mutations that cause SCD, therefore it is not surprising that individuals with Hb SS would have longer hospital LOS as compared to less-severe genotypes.[24,64] Adults serving as primary caregivers for dependent children are likely motivated to return home as soon as possible following hospital admission, possibly accounting for the shorter LOS observed in this

study. Presence of dependent children at home should be considered in future study of social drivers of hospital utilization.

PROMIS Global Health items have previously been shown to be predictive of key outcomes and future events such as healthcare utilization and mortality, however this is the first application in the adult SCD population.[34,45] We observed increased LOS with higher (i.e., better) PROMIS Physical Health subscale scores in this observational study, as this is counterintuitive, further evaluation is needed in future studies.

As this clinical prediction model does not account for all of the variability in LOS, future study of the influence of additional factors such as SCD-related complications as markers of disease severity, such as those captured by the ASCQ-Me Medical History Checklist, as well as additional measures of mental health and cognitive functioning may improve the understanding of hospital LOS.[43,44]

Patterns of hospital utilization among adults with SCD hospitalized with VOC are incompletely characterized, although several studies have reported on number of hospitalizations, ED visits and hospital LOS.[16,17,21,23,24,26] Although a small proportion of adults with frequent hospitalizations account for the greatest healthcare utilization, information on implementation of PROs to prospectively identify individuals at highest risk of adverse outcomes such as frequent or prolonged hospitalizations, or hospital readmission is lacking. In addition, a recent sentinel study demonstrated that PRO implementation improved survival among patients with advanced solid malignancies

receiving usual cancer treatment, indicating that future application of PROs to identify and target individuals with risk factors for adverse outcomes may improve survival.[65]

Future directions would ideally include external validation and model updating as part of a larger prospective study. In addition, a larger study sample could allow for clinical prediction modeling in another area of active interest, hospital readmissions, as we observed a strikingly high rate of 30-day readmissions (40.5%) in this sample. In addition, it is unknown how steady-state HRQL scores such as PROMIS Global Health and ASCQ-Me during non-VOC intervals inform hospital utilization at the time of an acute painful episode.

Limitations of this model include the possibility of a non-representative sample, given the sample size across two study academic medical centers. This study may have selected for the sickest participants during the study interval, as participants with frequent hospitalizations were more likely to be recruited, as compared to those with infrequent hospitalizations who may have been missed. In addition, the final model has not been replicated or externally validated. Although only two subjects per variable are required for accurate predictions in linear regression models, this study was likely underpowered to detect additional meaningful effect sizes to account for the remaining 71% of variability not explained by this model. Strengths, however, of this clinical prediction model include the complete ascertainment of the outcome and all predictor variables, despite the modest sample size. Future studies using these predictor variables are likely

feasible and practical, as this information was easily elicited via participant self-report at the time of enrollment, evidenced by the high participation rate.

In conclusion, this study fits within the national dialogue of PRO implementation among individuals with SCD to reflect individuals' experience of pain and its impact as a key driver of healthcare utilization.

Chapter 4: Discussion

4.1 Comprehensive Pain Assessment for Adults with SCD

Assessing the pain experience from the perspective of patients with SCD with a brief and comprehensive assessment is critical to our enhanced understanding of the pain experience and its impact on those living with SCD. Utilization of PROs are an important step toward advocacy for adults with SCD to help address the stigmatization associated with SCD and to give voice to the experience of pain and the impact of VOC on wellbeing and quality of life in a standardized fashion.[66-68] This information can also be used to help establish a baseline for shared decision making regarding pain management plans between providers and patients.[66,69] In 2014, the NIH guidelines for the management of SCD supported listening to the patient's voice regarding their pain experience to guide pain mitigation.[70]

Furthermore, there is growing evidence that assessment of HRQL with PROs improves communication between patients and their providers, and in a recent seminal randomized controlled trial, PRO implementation was shown to improve survival among patients with advanced solid malignancies receiving usual cancer treatment.[65,66,69,71-73]

In this study, we demonstrate that the prospective, longitudinal collection of these novel yet preliminarily validated PROs is feasible and informative, enriching our understanding of the individual pain experience among adults with SCD admitted with pain from an acute VOC, as informed by self-reported measures of PROMIS Global Health and

ASCQ-Me. This assessment is brief and sufficiently comprehensive to capture the pain experience of an acute VOC and the multidimensional impact on well-being and functioning.

4.2 HRQL Profile of Adults with SCD Hospitalized with VOC

This study deepens our understanding of the assessment of pain among adults with SCD above and beyond the current standard of 0-10 pain intensity as reported by the NRS through the use of PROs. In this study, adults with SCD hospitalized with painful VOC had recurrent, prolonged VOCs over the prior year with associated severe impairments across most-all HRQL domains as measured by PROMIS Global Health and ASCQ-Me both upon hospital admission and seven days following discharge, thereby adding to the evidence establishing validity of these PROs among the adult SCD population.

The study results may not be generalizable to the entire U.S. population of adults with SCD, as only adults hospitalized for pain, indicative of more severe manifestation of SCD, were included. In addition, a national registry of adults with SCD, delineated by disease and sociodemographic characteristics does not exist at this time. Consequently, comparisons of the study sample to the larger population on factors such as disability and employment status, living situation, and hydroxyurea use cannot be performed. However, consistent with available data, approximately 60% of study participants had Hb SS followed by Hb SC, with most individuals identifying as black, non-Hispanic.[1] Similar to prior studies, most participants were young adults and publicly insured.[20,23] Adult women

may have been over-represented in the current sample (59.5%), although this gender difference in study participation is consistent with prior studies.[36,38,43,74]

Understanding the pain experience as profiled by self-reported HRQL measures such as PROMIS Global Health and ASCQ-Me is the next step in better equipping the research and clinical communities to assess the multidimensional experience of pain in adults with SCD. This study provides insights into the assessment of the VOC pain experience of adult patients living with SCD that is critical to both clinicians caring for these patients in times of health and during acute VOCs and to clinical researchers developing therapeutics to meaningfully improve outcomes in this vulnerable population.

4.3 Predictive Value of HRQL Scores: VOC and Healthcare Utilization

This study also demonstrates that HRQL scores predict healthcare utilization as measured by LOS, although the results should be externally validated with model updating from larger prospective samples. Future prospective study of incorporation of HRQL scores to predict key healthcare utilization outcomes such as LOS and 30-day readmissions rates could help identify and target individuals at greatest risk of adverse outcomes. For instance, the ASCQ-Me Pain Episode measure could be used to prospectively identify young adults who report frequent and severe VOCs (e.g. four or more annually). This is a particularly important subset of SCD patients as young adults are at increased risk of death and account for the highest healthcare utilization costs.[14,16-18,20,23]

Although the reported average LOS varies in the literature, the finding of mean LOS of 8.5 days is in keeping with a 5-year observational study of 182 adults with hemoglobin SS disease, in which LOS was notably longer as compared to earlier data from the HCUP.[23,24] Increased frequency and duration of pain-related hospitalizations has been shown to be a key predictor of early mortality.[18,21,27,28] Thus, among adults with SCD, hospitalizations for VOC and the immediate post-discharge period are times of high vulnerability.[24]

The HCUP found that among young adults with SCD aged 18 to 30 years, the readmission rate was 41.1%.[21] By comparison, congestive heart failure has a 25% 30-day readmission rate, acute myocardial infarction 17%, and pneumonia 16%.[26] These data highlight that SCD has the highest readmission rate of any chronic condition. Furthermore, hospital admissions for SCD peak in young adulthood, with two-thirds of all SCD-related admissions occurring in adults aged 18-44 years.[23] Although the 30-day readmission rate of 40.5% in this study is comparable to that of young adults with SCD from HCUP, 19% of participants in our sample were readmitted within one week from hospital discharge. This compares to a seven-day readmission rate of only 9.8% among Medicaid patients with SCD from the 2017 HCUP analysis of the Nationwide Readmissions Database, likely reflective of increased hospital readmissions within seven-days among young adults as compared to other age groups.[55] Multiple studies have demonstrated that increased frequency of VOCs, lengthier hospitalizations, and hospital readmission within one week from discharge are associated with risk of death.[24]

4.4 Future Directions

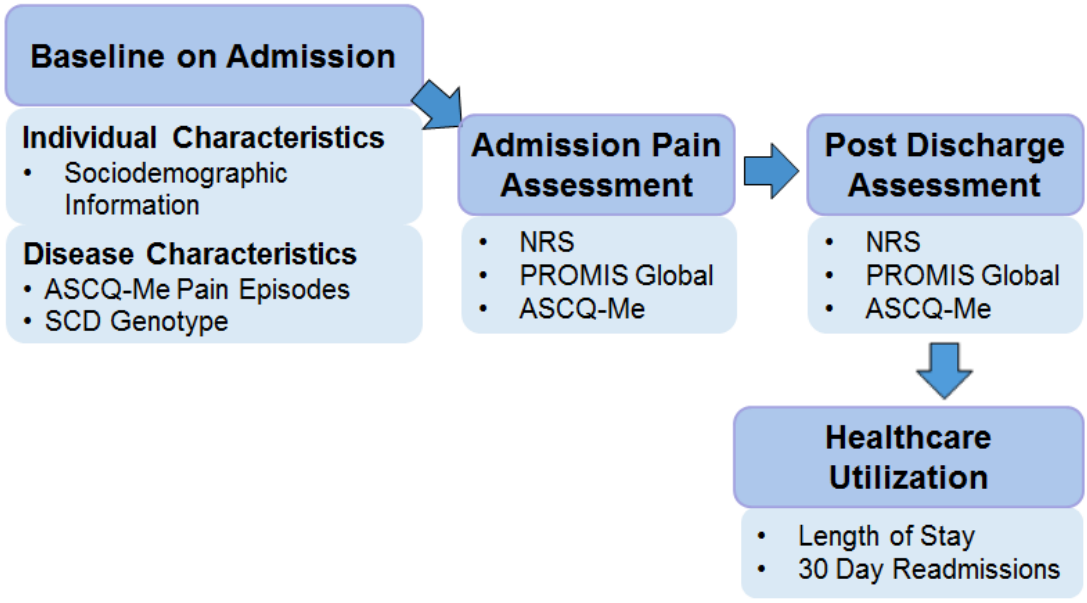
In conclusion, this study relied on novel, yet preliminarily validated PRO measures that were developed with robust methodology in keeping with the PROMIS initiative standards to accurately capture the impact of SCD on adults in the context of VOCs requiring hospitalization. In this study, the analysis of within-individual responsiveness to change of the ASCQ-Me measures is limited due to unavoidable missing data for the 7-day post-discharge assessment. Future studies may consider within-individual study of the ASCQ-Me measures at times with and without acute VOC. In addition, this study did not collect information on baseline pain intensity outside of the seven days immediately preceding admission for acute VOC. Inasmuch, this study cannot distinguish between those with and without underlying chronic pain, although most individuals with SCD develop chronic pain by adulthood.[7,67]

Future areas of research should include further study of the associations between PROMIS Global Health, ASCQ-Me and SCD severity as measured by the Pain Episode Frequency and Severity assessment, prospective implementation of PROMIS Global Health and ASCQ-Me collection in the ambulatory, emergency department and inpatient settings to identify severely impacted areas of functioning and well-being to target specific interventions aimed at improving HRQL, and determination minimum clinically meaningful differences for use in the interpretation of ASCQ-Me scores.

Chapter 5: Appendix

5.1 Supplementary Material for Manuscript

Figure 5.1 Flow Diagram of Study Procedures upon Admission with VOC[1]



[1]VOC: Vaso-occlusive crisis
The figure depicts study procedures upon hospital admission with vaso-occlusive crisis. At time of hospital admission, participants provided sociodemographic and disease characteristics. Participants then completed the admission pain assessment consisting of NRS collected from the electronic health record, and PROMIS Global and ASCQ-Me measures. Seven days following hospital discharge, participants completed NRS, PROMIS Global and ASCQ-Me assessments via telephone report. Healthcare utilization outcomes of hospital length of stay and 30-day readmission rates were collected from the electronic health record.

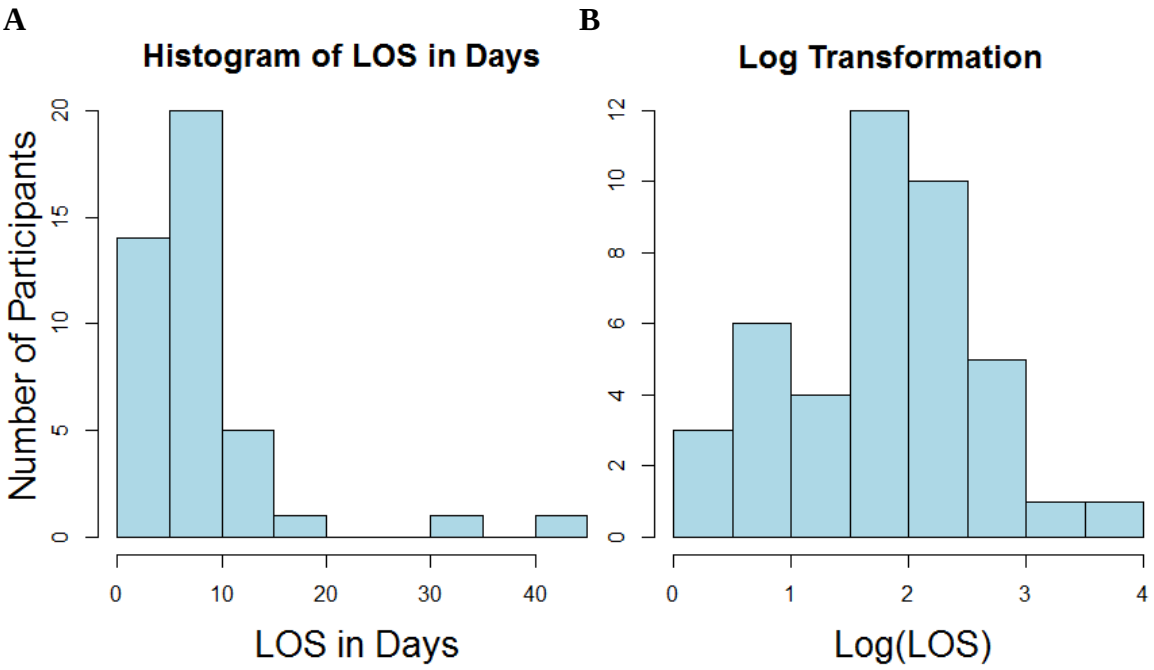
Table 5.1: Raw Pain Episode Scores Comparing the Validation to Study Samples

ASCQ-Me Pain Episode	ASCQ-Me Validation Sample (n=490) mean(SD)	Hospitalized Cohort (n=42) mean(SD)
Pain Episode Frequency[1]	7.5 (2.6)	9.3 (2.2)
Pain Episode Severity[2]	15.0 (4.3)	17.5 (2.8)

[1] Raw Pain Episode Frequency scores range 0-11
[2] Raw Pain Frequency scores range 0-22

5.2: Supplementary Material for Clinical Prediction Model Development

Figure 5.2: Natural Logarithmic Transformation of Hospital LOS in Days



Panel A shows histogram of hospital length of stay (LOS) in days (x-axis) and number of participants on the y-axis. Panel B shows the natural logarithmic transformation of LOS, which results in a more normal distribution.

Table 5.2: Candidate Predictor Variables

Candidate Variables	**Type of Variable**
Age (by DOB)	continuous
SCD Genotype (SS/ other)	binary
Prescribed Hydroxyurea (yes/no)	binary
Gender (male/female)	binary
Insurance (pubic, private)	binary
Lives Alone (lives alone/with others)	binary
Primary Caregiver Dependent Children (yes/no)	binary
Employment status (yes/no)	binary
Self-Reported Disability status (yes/no)	binary
≤ High school Education (yes/no)	binary
ASCQ-Me Pain Episode Item 1 score (Frequency)	continuous
ASCQ-Me Pain Episode Item 4 score (Severity)	continuous
PROMIS Global Physical Health score	continuous
PROMIS Global Mental Health score	continuous
ASCQ Me Emotional Impact score	continuous
ASCQ Me Social Impact score	continuous
ASCQ Me Pain Impact score	continuous
ASCQ Me Stiffness Impact score	continuous
ASCQ Me Sleep Impact score	continuous

Abbreviations: DOB, date of birth; SCD, sickle cell disease; VOC, vaso-occlusive crisis; ASCQ-Me, Adult Sickle Cell Quality-of-Life Measurement Information System; PROMIS, Patient-Reported Outcomes Measurement Information System

The table contains the 19 candidate predictor variables and their categorization that were used in clinical prediction model development.

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