

Preliminary construct validity of patient-reported outcomes to assess chronic pain in adults with sickle cell disease

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Key Points

- Pain-related PROs show preliminary construct validity in differentiating individuals with and without chronic SCD pain.
- On PROMIS PROs, individuals with chronic pain had moderate impairment, whereas those without chronic pain had no or mild impairment.

Chronic pain affects 30% to 40% of individuals with sickle cell disease (SCD) and impairs patient functioning. Clinically meaningful, practical, and valid assessment tools for investigation, evaluation, and management of chronic pain are limited, representing a barrier for advancing SCD care. We sought to determine whether patient-reported outcomes (PROs) show preliminary construct validity in identifying individuals with SCD who were a priori defined as suggestive of having chronic pain based on previously published criteria. All individuals completed the Patient-Reported Outcomes Measurement Information System (PROMIS) domains: pain interference, pain behavior, pain quality (nociceptive, neuropathic), fatigue, sleep disturbance, depression, and anxiety; the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) domains: pain impact and emotional impact; and the painDETECT questionnaire. Thirty-three adults living with SCD were enrolled, and 42.4% had chronic pain. Pain-related PROs scores distinctly differentiated individuals with chronic pain from those without. Individuals with chronic pain had significantly worse pain-related PROs scores: PROMIS pain interference (64.2 vs 54.3), PROMIS pain behavior (63.2 vs 50), and ASCQ-Me pain impact (42.9 vs 53.2). According to published PROMIS clinical cut scores for the pain-related domains, individuals with chronic pain were categorized as having moderate impairment, whereas those without chronic pain had mild or no impairment. Individuals with chronic pain had PRO pain features consistent with neuropathic pain and worse scores in fatigue, depression, sleep disturbance, and emotional impact. Pain-related PROs show preliminary construct validity in differentiating individuals with and without chronic SCD pain and could be used as valuable tools for research and clinical monitoring of chronic pain.

Introduction

Pain is the most common complication for individuals living with sickle cell disease (SCD). Pain negatively affects the health-related quality of life (HRQL) of individuals with SCD, impairing both physical and psychosocial functioning, and an increased frequency of pain is associated with mortality.¹⁻³ Individuals with SCD experience severe acute intermittent pain in addition to chronic, daily pain. The average number of acute pain episodes per year for individuals with SCD is 3, and ~30% to 40% of

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individuals with SCD experience chronic pain.⁴⁻⁶ The definition for chronic pain in SCD was constructed in 2017 by Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks-American Pain Society Pain Taxonomy Initiative and it describes chronic pain as ongoing pain on most days over 6 months in a single or multiple locations.⁷ Interviews with adults with SCD who experience chronic pain demonstrate the negative impact pain has on their overall quality of life and further interferes with adequate use of pharmacological and non-pharmacological pain management strategies.⁸

Prior studies of chronic pain in SCD have, importantly, used daily pain diaries to collect quantitative outcomes to determine the chronicity of pain.⁶ These studies are vital to describing this important clinical complication of SCD that was previously not well recognized. Although daily pain diaries are likely to be considered the “gold standard” for collecting data to define the presence of chronic pain, they are often impractical and not easily operationalized in clinical and research settings. Assessment tools that are clinically meaningful, valid, and feasible to administer and complete are essential for further scientific investigation into the cause and optimal treatment of chronic SCD pain and for the clinical evaluation and management of chronic SCD pain. The lack of these assessment tools represents a barrier for advancing chronic pain assessment and treatment for individuals with SCD. Thus, it is important to have alternative ways other than daily pain diaries to validly assess the presence of chronic pain in individuals with SCD.

Patient-reported outcomes (PROs) have previously been suggested as potentially useful assessment tools for chronic pain in SCD. Specifically, PROs have been used to fully understand the physical and emotional impact of this common SCD complication.⁹ Previous data show individuals with SCD who experience 3 or more days of pain per week have worse scores in the PROMIS domains of pain interference, anxiety, and depression compared with individuals who have pain on <3 days per week.¹⁰ However, more data are needed to support the validity of PROs for individuals with chronic SCD pain. As a next step for using PROs for assessment of chronic SCD pain, it is important to evaluate the preliminary construct validity of PROs for chronic pain. Construct validity can be supported by the known-group approach when a test can discriminate between a group known to have a specific characteristic and a group that does not. Determining the construct validity of PROs to differentiate between the groups with and without chronic pain in SCD is the next step in supporting their use to assess for the existence of chronic pain. Fully understanding the construct validity of these tools with a robust clinical anchor of defined chronic pain increases their utility for both research and clinical care.

In addition to fully understanding the construct validity of PROs for identifying those individuals with SCD who have chronic pain, it is important to understand patient-reported qualitative features of chronic pain. This knowledge will contribute to a further understanding of the biology of chronic SCD pain and could direct treatment. Although previous studies have shown that neuropathic pain plays a role in SCD pain in general, whether neuropathic pain features exist in a cohort specifically designated as suggestive of having chronic SCD pain based on published criteria is not well described.¹¹

Here, we sought to assess the preliminary construct validity of PROs for the assessment of chronic pain. Specifically, we determined whether PROs could differentiate a cohort of individuals with SCD who were a priori defined as likely to have chronic pain or not based on published diagnostic criteria. Our primary hypothesis was that PROs could differentiate individuals with SCD with and without chronic pain. Our secondary hypothesis was that individuals with chronic pain have PRO scores suggestive of neuropathic pain compared with individuals without chronic pain.

Methods

Study population and data collection

We conducted a cross-sectional study with participants from Milwaukee, Wisconsin and Memphis, Tennessee. Study participants included a convenience sample of Black individuals with SCD (all genotypes) who were 18 years of age or older. Exclusion criteria were inability to speak English, a history of stroke, chronic transfusion therapy, current pregnancy, inability to consent, crizanlizumab therapy, a pain-related disorder other than SCD, and other non-SCD-related chronic systemic illnesses. Participants consented in person when they presented to the Adult Sickle Cell Disease Clinic for care, when they were hospitalized for pain, or when they accompanied other family members to appointments. All study-related activities were completed during individuals' baseline state of health, and PRO data collection was not completed during acute care visits. All participants answered questions about pain frequency and duration to ascertain if individuals experienced chronic pain. All study participants completed PRO domains from PROMIS and ASCQ-Me and the painDETECT questionnaire. These PROs are all further described in detail below. The study questionnaires could be completed by email, on a patient's personal device, or on study tablets in person at the time of other study-related activities. Demographic and clinical data, including sex, age, sickle cell genotype, medical history, and ongoing treatment, were collected by the research team via electronic health record review. Informed written consent was obtained from the study participants. The study was approved by the institutional review board (IRB) at the Medical College of Wisconsin as a central IRB and for both study sites, Milwaukee and Memphis, as per the reliance agreement. An IRB-approved remuneration was provided to participants for the completion of study activities.

Chronic pain

To evaluate whether an individual with SCD experiences chronic pain, we a priori based our diagnostic criteria on those defined by the America Pain Society Pain Taxonomy initiative for chronic SCD pain. These criteria describe chronic pain as reports of ongoing pain present on most days over the past 6 months, either in a single location or in multiple locations. Participants completed a questionnaire that included questions on pain frequency (1) and pain duration (2) (based on previous SCD chronic pain research⁵) to capture these criteria as outlined below:

1. Pain frequency: In a typical month, how often do you have pain?
 - (1) Everyday
 - (2) 5 to 6 days per week
 - (3) 3 to 4 days per week
 - (4) 1 to 2 days per week
 - (5) than 10 times per month
 - (6) 1 to 2 times per month
 - (7) No pain at all.

2. Pain duration: Have you been experiencing this pain due to sickle cell disease for the past 6 months or more? (1) Yes (2) No.

Individuals with SCD were designated to the likely to have chronic pain group if they experienced pain due to SCD every day, 5 to 6 days per week, 3 to 4 days per week, or more than 10 times per month, with a duration of this frequency for the past 6 months or more. Individuals had to meet criteria for both frequency and duration to be designated to the likely to have chronic pain group.

PROMIS

PROMIS is a publicly available system for patient-reported health status that can measure more than 70 health symptoms and HRQL domains relevant to healthy people and to those with a variety of chronic diseases. PROMIS assesses domains such as pain, fatigue, depression, and physical functioning, among others.¹² The PROMIS domains included as part of this study are pain interference, pain behavior, pain quality-neuropathic, pain quality-nociceptive, fatigue, sleep disturbance, depression, and anxiety. PROMIS measures use a T-score metric where 50 is the mean of a relevant reference population (general population for domains fatigue, anxiety, and depression; general and clinical population for domains pain interference, pain behavior, pain quality, and sleep disturbance; and clinical sample with painful conditions for domains pain quality-nociceptive and pain quality-neuropathic), and 10 is the standard deviation (SD) of that population. Higher T-scores for PROMIS measures indicate more of the concept being measured (eg, higher T-score for the domain of pain interference indicates higher interference due to pain). PROMIS cut scores have been constructed for clinical interpretation by PROMIS scientists, who reviewed the collected large-scale calibration data and evaluated 0.5, 1.0, and 2.0 SDs as thresholds to use across domains.¹³ We analyzed the severity categorization of our median and interquartile range scores according to these cut points.

ASCQ-Me

ASCQ-Me is a SCD-specific patient-reported quality of life measurement system developed to assess the physical, social, and emotional impact in adults with SCD. ASCQ-Me includes questions that enable adults to describe their function and well-being according to 7 domains: pain episodes, pain impact, emotional impact, sleep impact, social functioning impact, stiffness impact, and SCD medical history checklist.¹⁴ The ASCQ-Me domains included as a part of this study were pain impact and emotional impact. ASCQ-Me measures use a T-score metric where 50 indicates the health score, and the value of 10 represents 1 SD unit of the average respondent in the diverse sample of 561 adult individuals with SCD.¹⁵ Higher T-scores on the ASCQ-Me measures for the pain impact and emotional impact domains indicate better self-reported health.

painDETECT

The painDETECT questionnaire is a validated neuropathic pain screening tool developed for use in individuals ages ≥ 14 years to differentiate neuropathic from non-neuropathic pain.¹⁶ painDETECT scores range from -1 to 38, with higher scores indicating an increased probability of neuropathic pain. Scores from -1 to 12 indicate a neuropathic pain component does not exist, 13 to 18 indicate a probable neuropathic pain component, and 19 to 38 indicate a definite neuropathic pain component.¹⁶

Analyses

We used summary statistics to report the demographic and clinical characteristics of the individuals included in our study. Continuous variables are summarized using the median and interquartile range, and categorical variables are summarized using percentages. The median scores of the included PROs (PROMIS, ASCQ-Me, and painDETECT) were compared between the group with chronic pain and the group without chronic pain using the Mann-Whitney U test, whereas differences in the categorical variables (demographic characteristics: sex, genotype, and hydroxyurea use) were compared using χ^2 or Fischer exact test. False discovery rate correction was performed to adjust for multiple comparisons. A P value of $< .05$ was considered significant. We performed additional analyses, excluding patients with a reported pain frequency of "more than 10 times per month" from the suggestive chronic pain group. To increase the clinical interpretation of the pain-related PROMIS domain scores, we analyzed data obtained from the pain interference and pain behavior domains in the 2 groups (chronic pain, no chronic pain) in the context of previously described validated published PROMIS severity T-score cut points (within normal limits: up to 55, mild: 55-60, moderate: 60-70, severe: above 70).¹³

Results

A total of 33 adults living with SCD were enrolled. The median age of our entire sample population was 33.4 (SD 10.0) years, with a range of 19 to 58 years, and 45.5% ($n = 15$) were female. We found that 42.4% ($n = 14$) of the study cohort met criteria that suggest the existence of chronic pain. Table 1 displays the demographic and clinical characteristics of study participants divided into 2 groups: those that likely have chronic pain and those that likely do not have chronic pain. Individuals with chronic pain were older than individuals without chronic pain, and there were no significant differences in sex ($P = .65$), genotype ($P = .162$), or hydroxyurea use ($P = .106$) between the 2 groups. Most individuals with chronic pain took at least 1 type of opioid (85.7%), and half of them took acetaminophen, ibuprofen, or naproxen. Among individuals without chronic pain, 68.4% took at least 1 type of opioid, and 73.7% took acetaminophen, ibuprofen, or naproxen. A significantly higher proportion of individuals with chronic pain were treated in the clinic or hospital for pain in the past 3 months compared with individuals without chronic pain (78.6% vs 36.8%, $P = .017$). In the chronic pain group, 14.3% of the individuals experienced pain more than 10 times a month, 28.6% reported pain 3 to 4 times a week, and 57.1% reported pain every day. In the no chronic pain group, 15.8% did not experience any pain, 47.4% had pain 1 to 2 times a month, and 26.3% had pain 1 to 2 times a week. Further, 5.3% of individuals in the no chronic pain group experienced pain more than 10 times a month or 5 to 6 times a week, but these individuals did not report a pain duration of 6 months, thus they did not meet the a priori criteria for chronic pain and were thus designated to the no chronic pain group.

Table 2 displays a comparison of the median PROMIS, ASCQ-Me, and painDETECT scores between the chronic pain and no chronic pain groups. In the chronic pain group, scores in the pain-related PROMIS domains of pain interference and pain behavior and the ASCQ-Me pain impact domain were significantly worse, collectively suggesting the ability of these PROs to differentiate these

Table 1. Demographic and clinical characteristics of participants who likely have chronic pain and those who likely do not have chronic pain

Participant characteristics	Chronic pain (n = 14) N (%)	No chronic pain (n = 19) N (%)	P value
Age (median, IQR)	36 (23-36)	29 (30.5-44)	.042*
Sex, female	7 (50.0)	8 (42.1)	.65†
Genotype			
HbSS	7 (50.0)	14 (73.6)	.364†
HbSC	6 (42.9)	4 (21.1)	
HbSβ+	1 (7.1)	1 (5.3)	
Hydroxyurea use	9 (64.3)	17 (89.4)	.106†
Taking at least 1 type of opioid	12 (85.7)	13 (68.4)	.416†
Taking acetaminophen, ibuprofen, or naproxen	7 (50.0)	14 (73.7)	.459†
Treated for pain in the hospital or clinic in the past 3 months	11 (78.6)	7 (36.8)	.017†
Pain frequency in a typical month			
No pain at all	0	3 (15.8)	N/A
1-2 times a month	0	9 (47.4)	
1-2 times a week	0	5 (26.3)	
More than 10 times a month	2 (14.3)	1 (5.3)	
3-4 times a week	4 (28.6)	0	
5-6 times a week	0	1 (5.3)	
Everyday	8 (57.1)	0	

Significant P values are shown in bold.

*Mann-Whitney U test.

†χ² test or Fisher exact test.

2 groups. Importantly, all pain-related PROs scores in the chronic pain group denote impaired functioning. For the pain quality domains, scores that assess the neuropathic component were significantly higher in individuals with chronic pain, whereas there was no significant difference between the 2 groups in scores that assess the nociceptive component. Further, the painDETECT scores were significantly higher in the chronic pain group. The median score of 15 on the painDETECT questionnaire in the chronic pain group is indicative of a probable neuropathic pain component, whereas the median score of 9 in the no chronic pain group suggests that a neuropathic pain component does not exist. These data, taken together with data from the PROMIS pain quality domains, collectively suggest that neuropathic pain features may be more likely to exist in those with chronic pain. Scores in the nonpain-related PROMIS domains fatigue, sleep disturbance, depression, and the ASCQ-Me emotional impact domain were significantly worse in individuals with chronic pain, also collectively supporting the negative impact of chronic pain on overall HRQL. The PROMIS anxiety domain was not significantly different between the 2 groups. Additional analyses that excluded 2 individuals who reported pain more than 10 times per month during the past 6 months from the suggestive of chronic pain group are shown in supplemental Table 1. Our findings from the original analysis did not change after the exclusion of these individuals.

Table 2. Comparison of PRO scores between adults with SCD who likely have chronic pain and those who likely do not have chronic pain

PRO domains	Chronic pain (n = 14) Median (IQR)	No chronic pain (n = 19) Median (IQR)	P value*
Pain-related			
PROMIS pain interference	64.2 (60.5-68.7)	54.3 (45.7-59)	.001
PROMIS pain behavior	63.2 (61.9-65)	50 (35.3-60.1)	.004
ASCQ-Me pain impact	42.9 (37.3-48.4)	53.2 (42.5-65.8)	.013
Pain quality			
PROMIS nociceptive	47.5 (44.4-50.5)	37 (30-64.9)	.305
PROMIS neuropathic	51.8 (50.4-54.4)	37 (37-50.4)	.006
painDETECT	15 (11.8-22.8)	9 (6-12)	.011
Nonpain-related			
PROMIS fatigue	60.7 (56.5-69.7)	52.8 (45.2-60.4)	.032
PROMIS sleep disturbance	63 (57-65.8)	56.5 (44.2-60.2)	.014
PROMIS depression	54.9 (51.2-62.2)	48.2 (34.2-57.5)	.026
PROMIS anxiety	59.7 (52.4-70.8)	53.1 (38.4-65.6)	.078
ASCQ-Me emotional impact	45.3 (39.2-51.7)	60.3 (44.5-67.4)	.019

Significant P values are shown in bold.

FDR, false discovery rate.

*FDR adjusted P values based on Mann-Whitney U test.

PROMIS PROs have published validated score cut points for determining severity in the pain interference and pain behavior domains. These published criteria categorize severity by the following T-score cut points: within normal limits up to 55, mild 55 to 60, moderate 60 to 70, and severe above 70.¹³ Figure 1 shows that for both of the PROMIS pain-related domains, we found individuals with chronic pain fall into the moderate severity category (pain interference: median 64.2, IQR 60.5-68.7; pain behavior: median 63.2, IQR 61.9-65), whereas individuals without chronic pain fall into the mild or within normal limits severity category (pain interference: median 54.3; IQR, 45.7-59; pain behavior: median, 50; IQR, 35.3-60.1). Very importantly, we found distinct ranges of scores for the 2 groups without overlap (Figure 1).

Discussion

Our data show that pain-related PROs (including PROMIS pain interference, PROMIS pain behavior, and ASCQ-Me pain impact) are valid for distinguishing between adults with SCD who likely do and do not experience chronic pain. To our knowledge, this is the first published study to show that PROs can differentiate between these 2 groups where published criteria for chronic SCD pain were used as a clinical anchor.⁷

The utility of using PRO tools for the assessment of chronic pain is evolving. PROs have been recommended for use by the PhenX Toolkit for SCD,¹⁷ and they are also recommended for use as end points in clinical trials by both the American Society of Hematology and the US Food and Drug Administration.^{18,19} The expansion of the use of PROs includes building a body of evidence that supports the validity of these tools in a particular clinical context, namely, chronic pain. Specifically, these domains designed to assess pain-related functional impact all show significantly worse

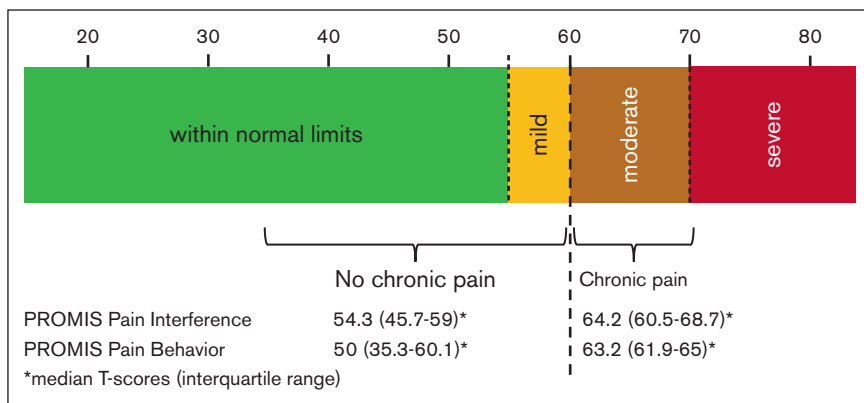


Figure 1. Severity categorization for PROMIS pain interference and pain behavior scores in individuals with SCD who likely have chronic pain and those who likely do not have chronic pain. Displayed are median T-scores and interquartile ranges of the PROMIS pain interference and pain behavior domains in the chronic pain group and no chronic pain group according to published validated PROMIS score cut points. Data show distinct ranges of scores for both domains without overlap, indicating moderate impairment for those with chronic pain and mild impairment or normal functioning for those without chronic pain.

scores in the group a priori designated as suggestive of having chronic pain. Interestingly, based on prior established thresholds for PROMIS pain interference and pain behavior domain, all individuals with chronic pain have moderate impairment, whereas individuals who likely do not have chronic pain have mild or no impairment. Importantly, there was no overlap of the median scores or interquartile ranges between the 2 groups, which further underscores their ability to validly discriminate between the presence or absence of chronic pain. Collectively, these data support the idea that these pain-related PROs could be used to screen for the presence of chronic pain in research and clinical settings and provide confidence in the scores to delineate this group from those without chronic pain. This is especially important because daily pain diaries are not always feasible for research or clinical use. Further, the validity of PROs for the assessment of chronic pain in SCD would allow for robust evaluations across different trials, both comparing data from SCD populations enrolled in different studies/trials and comparing SCD to other chronic pain populations. In addition, the assessment of frequency and duration used in our study will likely not have been incorporated uniformly across studies, whereas PRO tools are standardized and can be implemented and scored consistently across study populations. Finally, using PROs to evaluate chronic pain in SCD goes beyond frequency and duration and describes the quality of pain as well as the multifunctional impact of chronic pain on the quality of life in individuals with SCD.

The construct validity of the pain-related PROs is strengthened by previous published work that indicates the substantial negative impact of chronic pain on individuals' daily life. Data show that worse scores in the PROMIS pain interference domain occur in individuals who experience pain on 3 or more days per week compared with individuals who experience pain on <3 days per week.¹⁰ Although this study did not define chronic pain as per the published criteria because the duration of the pain was not assessed, increased pain frequency was demonstrated. Another study that assessed chronic pain in individuals with SCD via electronic health records and pain interference on a scale of 0 to 10 (0 indicating no interference and 10 indicating an inability to carry on with activities) found that chronic pain had a negative impact on the ability to perform daily activities.²⁰ With most patients in this study identified as experiencing chronic pain, one-third of the patients rated the level of pain interference in daily

activities in the past 6 months between 7 and 10. Further, one-third of the patients also described the strong negative impact of chronic pain on their ability to take part in recreational, social, and family activities and their ability to work.²⁰ Our data indicated moderately impaired functioning in the chronic pain group, which is consistent with these published data.

In addition to determining the construct validity of PROs for chronic pain, our findings suggest that a neuropathic component is present in individuals with SCD who have chronic pain. Importantly, neuropathic pain features were present in the chronic pain group using 2 independent assessment measures, PROMIS pain quality-neuropathic and painDETECT, which supports cross-consistency and further underscores our findings. Studies in chronic pain populations other than SCD describe the prevalence of neuropathic pain in almost 20% of patients.²¹⁻²³ Neuropathic pain in SCD has already been shown to affect HRQL. A study evaluating the impact of neuropathic pain in SCD on HRQL as assessed by ASCQ-Me found that neuropathic pain was associated with significantly lower emotional functioning, social functioning, worse sleep, and stiffness.²⁴ Another study described worse HRQL in individuals with SCD who experienced neuropathic pain in the physical domain, psychological domain, social relationships, and environment but not in pain intensity, as measured by the abbreviated version of the World Health Organization (WHOQOL-brief).²⁵ In adolescents, a significant correlation was found between the likelihood of neuropathic pain and lower scores on the PedsQL SCD Pain and Hurt module, further supporting the negative impact of neuropathic pain on HRQL.²⁶ Our data expand on these previously reported findings and reveal that in those that are a priori defined as having chronic pain,⁷ a neuropathic pain component appears more likely as compared with those that do not have chronic pain, as reflected by significantly higher PROMIS pain quality-neuropathic and painDETECT scores in the chronic pain cohort. These data contribute to the increasing body of evidence that suggests the existence of nervous system sensitization as one of the underlying etiologies of chronic SCD pain by reporting phenotypic features of neuropathic pain in those who experience chronic SCD pain via validated PRO tools. To our knowledge, this is the first study to describe the neuropathic component in chronic SCD pain as defined by established diagnostic criteria.²⁷⁻²⁹ Interestingly, although we do observe higher scores in the PROMIS nociceptive domain in the chronic pain

group, this finding did not reach statistical significance. It is possible that nociceptive pain plays less of a role in chronic SCD pain, whereas a neuropathic component is more prominent. However, this is speculative based on these data and requires further investigation in future work.

The significantly worse scores for nonpain-related domains among individuals with SCD who have chronic pain compared with those who do not have chronic pain further underscore that chronic pain has a multidimensional impact on patients' physical and emotional functioning. This is consistent with prior literature focused on recurrent and chronic pain. Worse scores in the anxiety and depression domains were previously shown in individuals with SCD who experienced pain on 3 or more days a week compared with individuals with SCD who experienced pain on <3 days a week.¹⁰ Another study described relationships between quality of life and chronic pain grade.²⁰ Chronic pain grade considers intensity and disability and ranges from grade 0 (no intensity-no disability) to grade IV (high disability-severely limiting).³⁰ Researchers have found a significant correlation between chronic pain grade and fatigue and low energy.²⁰ In a study where pain was assessed via a 28-day diary that assessed pain rated on a 10-point scale, data show that patients with a higher rating of daily pain also have worse scores in many domains of the SF-36 questionnaire, including anxiety, depression, and fatigue.³¹ Our findings are also similar to those from a study evaluating functional and psychosocial outcomes among children and adolescents with SCD who experienced chronic pain. Youth with SCD experiencing chronic pain had significantly greater functional disability and increased depressive symptoms compared with youth who experienced episodic SCD or no pain at all.⁵ Collectively, our data further support the importance of mental health, emotional health, and other physical functioning screening in individuals with SCD who have chronic pain to ensure all aspects of their health are being addressed in this clinical context.

Our study based the classification of chronic pain on the published definition for SCD chronic pain, which strengthens our findings.⁷ Using this consensus definition, we found that 42.4% of our adult cohort reported chronic pain. The prevalence of chronic pain in individuals with chronic pain varies from study to study based on the definition.³² A precise method to estimate the prevalence of chronic pain includes evaluating longitudinal patient-reported data from daily pain diaries. A study from 2008 using this method over 6 months found that 56% of adults with SCD experienced pain on more than 51% of the days, whereas 29% of them experienced pain nearly every day.⁶ The prevalence of chronic pain in our study is close to what was found in this daily diary study, confirming the method we used for chronic pain assessment in our data collection.³²

Here, we classified individuals who experienced pain more than 10 times per month for the past 6 months in the suggestive of chronic pain group. Although a precise interpretation of the term "most days" would include "more than 15 times per month," the authors of the published consensus definition for chronic SCD pain state there are not adequate data to definitively support precise cut-offs for both frequency and duration, and pain more than 10 times per month still reflects a substantial amount of pain. Our additional analyses, which excluded individuals who had pain more than 10 times per month, showed the same results when these individuals were included in the analyses. These

additional analyses further underscore that experiencing pain more than 10 times a month could be considered for inclusion in the definition.

This study is limited by its cross-sectional design. Our data are not able to determine causality, thus it is possible that the chronicity of pain affects many of the PRO domains assessed and vice versa. The sample size is small; thus, the findings should be interpreted as preliminary and hypothesis-generating data for further investigation and validation within a larger cohort of patients. Recall bias in assessing individuals' pain frequency and duration is possible. There is also the possibility of misclassification of individuals into the a priori designated groups (ie, likely have chronic pain group, likely do not have chronic pain group). However, the prevalence of chronic pain in our study is comparable to that found in a large daily diary study, supporting the appropriateness of the method we used to ascertain the existence of chronic pain in a more practicable way. Further, multiple significant PRO domain differences using distinct and independent measures between the 2 groups also validate our approach. A larger study is warranted to definitively validate and establish cut points of PRO scores that identify those with chronic pain and make the scores more clinically meaningful. Future studies should also examine the effect that genotype, the use of hydroxyurea, and opioid therapy have on the development and pathophysiology of chronic pain. Our data support the use of PROs in studies examining chronic pain in individuals with SCD.

In conclusion, pain-related PROs show preliminary construct validity in differentiating between adults with SCD with and without chronic pain. These data contribute to the growing literature supporting the use of PROs as valuable and practical tools for research and clinical evaluation of chronic pain in individuals living with SCD.

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Authorship

Contribution: L.M., A.S., and A.M.B. designed the project; J.H., J.S.H., J.J.F., and H.K. helped with collecting data; L.M., A.S., and A.M.B performed statistical analysis; L.M., A.S., and A.M.B wrote the first version of manuscript; and L.M., A.S., A.M.B, J.H., J.S.H., J.J.F., and H.K. edited the manuscript.

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