REGULAR ARTICLE

blood advances

Costs and impact of disease in adults with sickle cell disease: a pilot study

Sophie Lanzkron,[1] Nicole Crook,[2] Joanne Wu,[3] Sarah Hussain,[4] Randall G. Curtis,[5] Derek Robertson,[6] Judith R. Baker,[2] Diane Nugent,[2] Amit Soni,[2] Jonathan C. Roberts,[7,8] Megan M. Ullman,[9] Julie Kanter,[10] and Michael B. Nichol[3]

[1]Division of Hematology and Cardeza Foundation for Hematologic Research, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA; [2]Center for Inherited Blood Disorders, Orange, CA; [3]Leonard D. Schaeffer Center for Health Policy & Economics, University of Southern California, Los Angeles, CA; [4]Transplant/Oncology & Infectious Disease Progam, School of Medicine, Johns Hopkins University, Baltimore, MD; [5]Factor VIII Computing, Berkeley, CA; [6]Maryland Sickle Cell Disease Association, Columbia, MD; [7]Bleeding & Clotting Disorders Institute, Dills Family Foundation Center for Research at BCDI, Peoria, IL; [8]Departments of Pediatrics and Medicine, University of Illinois College of Medicine at Peoria, Peoria, IL; [9]Gulf States Hemophilia and Thrombophilia Center, The University of Texas Health Science Center at Houston, Houston, TX; and [10]Department of Medicine, University of Alabama at Birmingham, Lifespan Comprehensive Sickle Cell Center, Birmingham, AL

Key Points

- It is feasible to collect patient-reported data and extract health care utilization data via medical chart review in adults with SCD.
- The economic burden of SCD care primarily stems from outpatient clinic visits.

We assessed the feasibility to estimate illness burden in adults with SCD, investigated factors associated with health-related quality of life (HRQoL), and estimated societal burden. We recruited 32 participants and collected data on fatigue, HRQoL, and work productivity and activity impairment via patient survey. Health care utilization was abstracted for the 12 months before enrollment using medical chart review. Mean age was 36.7 years; 84.4% of participants had hemoglobin *SS* or $S\beta_{thal}^{0}$ disease, and 81.3% reported chronic pain (experiencing pain on ≥3 days per week in the past 6 months). Mean EQ-5D-3L visual analogue scale score was 63.4 and the index score was 0.79. The mean fatigue score was 57.9. Higher fatigue score was correlated with lower EQ-5D index score (correlation coefficient r = −0.35; P = .049) and Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) scores, including pain (r = −0.47; P = .006), sleep (r = −0.38; P = .03), and emotion scores (r = −0.79; P < .0001). The number of hospitalizations was negatively correlated with HRQoL (all P < .05). Patients who reported chronic pain had significantly lower mean ASCQ-Me sleep scores (48.3 vs 57.1; P = .04) and EQ-5D index scores (0.72 vs 0.89; P = .002) than those without chronic pain. Mean estimated annual per person costs were $51 779 (median, $36 366) for total costs, $7619 ($0) for indirect costs (estimated from lost earnings of participants), and $44 160 ($31 873) for medical costs. Fatigue, SCD complications, hospitalization, and chronic pain negatively affected HRQoL. This sample experienced a high economic burden, largely from outpatient doctor visits.

Introduction

Sickle cell disease (SCD) is an inherited red blood cell disorder that afflicts millions of people throughout the world.[1] People with SCD typically experience periodic episodes of severe acute and chronic pain. There are many other SCD complications such as infection, acute chest syndrome, stroke, renal disease, pulmonary hypertension, leg ulcers, and liver pathology, which have been shown to increase with age.[1,2] Approximately 1 in 1900 newborns are affected by SCD,[3] resulting in a total of 90 000 to 100 000 affected individuals (~60% are adults) in the United States,[4,5] primarily Black/African Americans. Advances in the diagnosis and

Submitted 22 December 2023; accepted 13 May 2024; prepublished online on *Blood Advances* First Edition 22 May 2024; final version published online 10 July 2024. https://doi.org/10.1182/bloodadvances.2023012477.

Original data are available on the request from corresponding author, Micheal B. Nichol (mnichol@usc.edu).

care of SCD have improved the life expectancy of people with SCD from a US average life span of 14 years in 1973 to ~40 to 60 years at the present time.[6,7] The mortality rate in the United States is low for children with SCD, but increases once they reach adulthood.[8,9]

Pain crisis is the most common debilitating manifestation of SCD, and frequently results in hospital admissions for both children and adults.[10] Increased frequency of pain associated with acute care use (emergency department [ED] and inpatient hospital visits) is associated with early death in adults with SCD.[11] Additionally, acute pain crises are associated with significantly impaired health-related quality of life (HRQoL).[12] Along with pain crises, other chronic medical complications of SCD, such as stroke and avascular necrosis, can affect social, emotional, cognitive, and physical well-being.[13,14] Avascular necrosis of the long bones (femur, humerus) caused by ischemic bone damage from vaso-occlusion due to SCD is a common comorbidity, and negatively influences HRQoL, especially in the physical activity and psychosocial domains.[15] Quality of life in persons with SCD is influenced not only by the disease itself, but also by the impairment of intrapersonal and interpersonal relationships due to the emotional and social impact of the disease.[16] To assess HRQoL, the Pain in Sickle Cell Epidemiology Study[17] enrolled 308 individuals with SCD, aged ≥16 years, who resided in Virginia. The study found that enrolled participants had much lower HRQoL scores than individuals with asthma, cystic fibrosis, and those on hemodialysis. These lower HRQoL scores were reported on all subscales except mental health, including physical function, physical and emotional role function, bodily pain, vitality, social function, and general health.[17] A recent systematic review regarding patient-reported outcomes showed that overall HRQoL for adults with SCD was poor and significantly worse in those who are prescribed opioids.[18]

The economic burden associated with SCD treatment in the United States is high, estimated at >$1.1 billion per year in 2009, which corresponds to ~$16 092 per patient-year.[19] The treatment of SCD, especially complications, result in a costly, lifetime commitment on the part of affected individuals, their providers, hospitals, and insurers. Although these cost studies provide insight into the economic burden of SCD,[19,20] contemporary costs studies are lacking.

HRQoL research is still new in the field of SCD. Before the development of the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) in 2014, there were no disease-specific instruments to measure HRQoL in SCD.[21,22] Thus, research using ASCQ-Me is still relatively limited. The National Academies of Sciences, Engineering, and Medicine consensus study report on SCD released in September 2020 found a lack of data to characterize SCD-related disease burden, outcomes, and unmet needs.[23] These findings motivated the present pilot study, which is intended to implement standardized data collection tools from patient self-report and clinical chart review. The objectives of this article are to (1) assess the feasibility of collecting data to estimate illness burden in adults with SCD, (2) investigate the factors associated with HRQoL in SCD, and (3) estimate the societal burden of SCD, including direct and indirect costs.

Methods

Design

We used a cross-sectional study design. Patient surveys were developed using validated instruments and questionnaires related to SCD clinical characteristics and treatment. A clinical data collection tool was developed to obtain clinical and health care utilization data, based on the experience gained from studies conducted by a national hemophilia research consortium.[24,25] Institutional review board approvals were obtained from the University of Southern California and Johns Hopkins University. Participants met the following inclusion criteria: (1) age ≥18 years; (2) people with a diagnosis of SCD (any genotype); (3) people who have received their SCD care at a specialty SCD treatment center at least 1 year before the enrollment; (4) people who speak either English or Spanish; and (5) people who provide written informed consent. Individuals who were judged by the clinician to be cognitively impaired or who had any additional blood disorder that was not SCD-related were excluded.

Recruitment and procedures

Two SCD specialty centers (Johns Hopkins Hospital and Center for Inherited Blood Disorders) located in the eastern and western United States recruited participants. Eligible participants were identified by the study coordinator during clinic visits or through retrospective clinical chart review. After obtaining informed consent, the study coordinator administered the baseline participant survey and entered data into the web-based REDCap data management system. The survey collected data on sociodemographic and SCD clinical characteristics and treatment, HRQoL, fatigue, Work Productivity and Activity Impairment (WPAI), access to care, physical activity, anxiety, and depression. Participants received a $20 gift card for completing the survey. Recruitment began on 31 July 2019, and was completed on 5 August 2020.

The study coordinator abstracted information from the medical chart review using standardized chart abstraction forms developed specifically for this study. Data were abstracted for the period of 1 year before enrollment for clinical characteristics and health care utilization. We also abstracted prescription information focusing on antibiotics and opioid analgesics for the 6-month period preceding enrollment.

Measures

Demographics. The survey completed by study participants collected sociodemographic data including marital status, employment, education, ethnicity, race, health insurance status, and household income.

HRQoL. ASCQ-Me is a validated disease-specific measure of HRQoL for patients with SCD.[21,22] The overall measurement system assesses 7 different health domains, 6 of which are assessed through 5-item questionnaires (emotional impact, pain impact, sleep impact, social functioning impact, stiffness impact, and pain episode). The seventh domain is assessed through a 9-item questionnaire (SCD Medical History Checklist [MHC]). Except for the MHC, each health domain was scored according to the ASCQ-Me user manual and transformed to T-scores.[26] T-scores are standardized to have a mean of 50 and a standard deviation (SD) of 10, with a score of 50 representing the average HRQoL of patient with SCD from a benchmark population of adults with SCD.[26] Higher domain scores represent a more favorable status for the emotional, pain, sleep, social functioning, and stiffness impact domains. Lower domain scores represent a more favorable status for the pain episode frequency and pain episode severity scores.

The EQ-5D-3L is the 3-level version of EQ-5D developed by the EuroQol Group, and consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has the following 3 levels: no problems, some problems, and extreme problems. The US-based valuation algorithm was used to generate a time trade-off index score.[27] Higher scores represent better health.

Fatigue. Patient-Reported Outcomes Measurement Information System Short Form Fatigue 4a is a 4-item instrument measuring fatigue. The total raw score for each participant is translated into a T-score. The T-score rescales the raw score into a standardized score with a mean of 50 and an SD of 10. Therefore, a person with a T-score of 40 is 1 SD below the population mean. For negatively worded concepts such as fatigue, a T-score of 60 is 1 SD worse than the population mean. By comparison, a fatigue T-score of 40 is 1 SD better than the population mean.[28]

Anxiety and depression. The 7-item Generalized Anxiety Disorder (GAD-7) questionnaire was used to measure anxiety,[29] and the 8-item Patient Health Questionnaire depression scale (PHQ-8) was used to measure depression.[30] If scores on either of these measures reach ≥10, they are considered as potentially diagnostic for the respective mental health condition in the general population.[29,30] GAD-7 and PHQ-8 had been used previously in a study on adults with SCD to measure the symptoms of depression and anxiety.[31]

Chronic pain and SCD severity. A question worded "do you experience pain on 3 or more days a week in the past 6 months?" was used to measure chronic pain. The ASCQ-Me MHC sums 9 SCD complications and the patient's treatment history. Score cutoffs (low, medium, and high) for the SCD MHC are based on quartiles of the distribution of scores. Cutoffs for low, medium, and high groups were SCD-MHC scores <2, equal to 2, and >2, respectively.[32] Because of our small sample size, we combined the low and medium groups.

Opioid used. Medical chart review documented opioid medication prescriptions for 6 months before enrollment. Both short- and long-acting opioid prescriptions were captured in these data.

Direct costs. Annual health care utilization data were obtained from medical charts. The number of hospital admissions, length of stay, and primary diagnosis recorded in the charts were used to calculate inpatient costs. Direct SCD-related health care costs were determined by multiplying measured units of health care utilization, for example number of utilizations, by the representative unit price associated with each service.[33] SCD treatments received outside the patients' designate treatment center and nonmedical direct costs (eg, transportation to a health care provider) were not considered. Inpatient cost was estimated on the basis of the mean costs associated with diagnosis of SCD with crisis from the 2017 Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project National Inpatient Sample given that 68% of persons in the sample who were hospitalized had a diagnosis of acute pain crisis.[34] The costs of outpatient or doctor visits and ED visits were based on the latest available data for 2018 from the Medical Expenditure Panel Survey reports.[35] Outpatient or doctor visits include annual multidisciplinary comprehensive visits and acute provider (physician and nursing), physical therapy, social work/psychology, genetic counseling, outpatient procedure, transfusion, and other visits. Total direct medical costs were summed from outpatient doctor visits, ED visits, and hospitalizations. Because individuals with SCD were prescribed many medications during the 6-month period before enrollment, assessments of fill rate were not available. Given that the medical chart records may not include inpatient prescriptions, we decided to exclude prescription cost data because of the likelihood of incomplete reporting.

Indirect costs. Indirect costs were imputed using the human capital approach,[36] in which productivity loss is measured in terms of lost earnings of participants, using wages as a proxy measure for the output of work time. Indirect costs include lost wages from missed work for employed participants and lost wages due to working part-time or being unemployed because of SCD. Missed work days due to SCD were calculated from the WPAI: Specific Health Problem patient survey.[37] The average hourly earnings for 2018, as reported by the US Bureau of Labor Statistics,[38] were $27.1. Total costs included both direct and indirect costs and were presented as 2018 costs.

Statistical analysis

Descriptive analyses were performed, and results were compared with the general US population when such data were available. Descriptive statistics, such as frequencies and proportions (for categorical variables) and means, SDs, medians, and ranges (for continuous variables), were used to describe the sample in terms of patient characteristics, HRQoL, fatigue, WPAI scores, and health care utilization. Descriptive statistics were also used to describe participants' clinical characteristics and treatments. The factors associated with HRQoL scores were assessed by Pearson correlation or Student T-tests for differences between 2 groups.

Institutional review board approvals were obtained from the University of Southern California and Johns Hopkins University.

Results

Participant characteristics

We recruited and collected data from 32 adults aged ≥18 years. Mean age was 36.7 (standard deviation [SD] 10.6) years, and 65.6% were female (Table 1). Half of the sample reported working at a job or business in the week before taking the survey, 50% had completed a 4-year college degree or higher, and 31.3% earned $25 000 or less annual household income; 84.4% of the participants were Black or African American, and 6.2% of the overall sample reported that they were of Hispanic, Latino, or Spanish origin. Of the 31 participants who completed the insurance question, 6.5% reported that they did not have any health insurance, and 93.5% had some coverage through public and private sources, although 23.3% reported having difficulty in finding adequate health insurance. More than 10% of respondents reported that they or their spouse needed to make work-related adjustments to obtain or maintain health insurance due to SCD. According to the

Table 1. Participants' sociodemographic characteristics

Variable	Frequency	Percentage
Sex		
Male	11	34.4
Female	21	65.6
Marital status		
Single, divorced, separated	23	71.9
Married, with a partner	9	28.1
Employment		
Working at a job or business	16	50.0
With a job or business but not at work	4	12.5
Looking for work	1	3.1
Not working at a job or business	9	28.1
Choose not to answer	2	6.3
Education level		
Less than high school diploma	2	6.3
High school diploma/equivalency (eg, GED)	7	21.9
Less than bachelor's degree (<4-year college)	7	21.9
More than bachelor's (4-year college) degree	16	50.0
Household income in the last 12 mo		
≤$25 000/y	10	31.3
≥$25 000/y	17	53.1
Do not know	1	3.1
Choose not to answer	4	12.5
Hispanic, Latino, or Spanish origin		
Yes	2	6.3
No	30	93.8
Race		
Black or African American	27	84.4
Other, specify*	5	15.6
Health insurance type†		
No insurance	2	6.5
Public	16	51.6
Private	11	35.5
Public and private	2	6.5
Difficulty in finding adequate health insurance*,†		
Yes	7	23.3
No	21	70.0
Do not know	2	6.7

Data were obtained from participants' surveys.
GED, general educational development.
*Other races included Afro-Latina, Middle Eastern, West Indian, and multiple race.
†Variables have missing data because of underreporting. Total sample does not sum up to 32 because of missing data.

Table 2. Participants' clinical characteristics from clinical chart review

Variable	Frequency	Percentage
SCD type		
Hb *SS* disease	25	78.1
Hb *SC* disease	5	15.6
Hb $S\beta_{thal}^{0}$	2	6.3
Received a red blood cell transfusion to treat an acute complication	10	31.3
Received chronic transfusion	4	12.5
Participant has been prescribed the following treatment		
Folic acid	29	90.6
Hydroxyurea	17	53.1
Prophylactic penicillin or other antibiotics to prevent infection	10	31.3
Short-acting opioid analgesics	24	75.0
Long-acting opioid analgesics	10	31.3
Iron chelation medication	9	28.1
CPAP machine	3	9.4
Most common prescribed drugs from 483 records*		
Short-acting opioid analgesics	304	62.9
Long-acting opioid analgesics	68	14.1
Antibiotics	58	12.0
Hydroxyurea	49	10.1
L-glutamine	4	0.8
Most common diagnosis for ED visits†		
Acute pain crisis	65	89.0
Acute chest syndrome	1	1.4
Pneumonia	1	1.4
Other	6	8.2
Most common diagnosis for hospitalization from 73 records†		
Acute pain crisis	50	68.5
Pneumonia	3	4.1
Acute chest syndrome	2	2.7
Heart disease (heart failure)	1	1.4
Other	17	23.3

Data were obtained from clinical chart review for 12 months before enrollment.
CPAP, continuous positive airway pressure.
*Analysis was performed on the basis of chart review for 483 prescription records during the 6 months before the enrollment period.
†Analysis was performed based on chart review for 73 records from the 12 months before enrollment.

survey responses, 90.6% of participants used prescription pain medications to treat SCD in the past 6 months.

The chart review revealed that 78.1% of the participants had hemoglobin (Hb) homozygous for the *S* mutation (*SS*), 15.6% were compound heterozygote for Hb *S* and *C* mutations (*SC*), and 6.3% were compound heterozygote for Hb *S* and a beta null thalassemia mutation ($S\beta_{thal}^{0}$) variant (Table 2). Among the sample, 53.1% were on hydroxyurea, 31.3% have been prescribed prophylactic penicillin or other antibiotics to prevent infection, and 9.4% of participants have been prescribed a treatment involving the use of a continuous positive airway pressure machine in the last 12 months. In addition, 31.3% of participants received a red blood cell transfusion to treat an acute complication, whereas 12.5% were on long-term transfusion therapy. Chart review of prescriptions from the 6 months preceding enrollment showed that of

the total 483 prescription records, the most commonly prescribed drugs were short-acting opioid products (62.9%), followed by long-acting opioid products (14.1%), antibiotics (12.0%), hydroxyurea (10.1%), and L-glutamine (0.8%; Table 2).

HRQoL

In our sample, the mean (SD; range) reported EQ-5D VAS was 63.4 (SD, 22.6; range, 10.0-95.0), which is 18.4 points lower than the mean score of 81.8 in the US population for the 35- to 44-year age group.[39] The mean reported EQ-5D index was 0.79 (SD, 0.20; range, 0.26-1.0), which is lower than the US 35- to 44-year age group population norm of 0.853.[39] The reported ASCQ-Me scores were comparable to the mean scores of patients with SCD in the ASCQ-Me field test sample.[26] The mean fatigue T-score was 57.9 (SD, 11.5), which is worse than the US population average for this age group by 7.9 points.[28]

Mean Hb was 9.24 (SD, 1.87; range, 6.3-13.4). Hb was not correlated with fatigue score or HRQoL scores (all $P > .06$). Fatigue score was negatively correlated with EQ-5D index score (correlation coefficient r = −0.35; $P = .049$) and ASCQ-Me scores, including pain impact (r = −0.47; $P = .006$), sleep impact (r = −0.38; $P = .03$), emotion impact (r = −0.79; $P < .0001$), and social functioning impact (r = −0.61; $P = .0002$) scores (Table 3). The sum of the MHC was negatively correlated with EQ-5D VAS (r = −0.53; $P = .002$) and index scores (r = −0.50; $P = .004$), and ASCQ-Me pain (r = −0.41; $P = .02$) and stiffness (r = −0.63; $P = .0001$) scores. There was no correlation between the number of ED visits and HRQoL scores. The number of hospitalizations was negatively correlated with EQ-5D index score (r = −0.56; $P < .001$) and ASCQ-Me sleep impact (r = −0.64; $P < .0001$), emotion impact (r = −0.38; $P = .03$), stiffness impact (r = −0.36; $P = .04$), and pain impact (r = −0.35; $P = .048$) scores.

Table 4 shows the HRQoL scores stratified by status on MHC, ED visits, hospitalization, opioid use, and chronic pain. Except for ASCQ-Me pain episode severity and fatigue score, the patients with MHC >2 had significantly lower mean ASCQ-Me and EQ-5D VAS and index scores than those with MHC ≤2 (all $P < .01$). HRQoL scores were not significantly different between the patients who had ED visits and those without ED visits. However, for those with ED visits, mean pain episode severity scores were significantly higher than for those without ED visits (51.61 ± 4.28 vs 45.28 ± 9.64; $P = .03$). Compared with those without hospitalization,

Table 3. Correlation of HRQoL scores with Hb, MHC, ED visits, and hospitalization

HRQoL	Hb	Fatigue	ASCQ-Me MHC	ED visits	Hospitalization
EQ-5D VAS					
Correlation coefficients	0.03	−0.32	−0.53	0.21	−0.05
P value	.89	.07	.002	.25	.79
EQ-5D index score					
Correlation coefficients	−0.06	−0.35	−0.50	−0.18	−0.56
P value	.73	.049	.004	.32	.0009
ASCQ-Me pain impact					
Correlation coefficients	0.16	−0.47	−0.41	−0.12	−0.35
P value	.39	.006	.02	.50	.05
ASCQ-Me stiffness impact					
Correlation coefficients	−0.002	−0.22	−0.63	0.07	−0.36
P value	.99	.23	.0001	.69	.04
ASCQ-Me sleep impact					
Correlation coefficients	0.06	−0.39	−0.30	−0.17	−0.64
P value	.76	.03	.09	.36	<.0001
ASCQ-Me emotion impact					
Correlation coefficients	0.18	−0.79	−0.29	−0.08	−0.38
P value	.32	<.0001	.11	.67	.03
ASCQ-Me social functioning impact					
Correlation coefficients	0.002	−0.61	−0.31	−0.07	−0.33
P value	.99	.0002	.0795	.72	.07
ASCQ-Me pain episode frequency					
Correlation coefficients	0.25	0.45	0.31	0.24	0.32
P value	.18	.01	.09	.18	.08
ASCQ-Me pain episode severity					
Correlation coefficients	−0.33	0.32	0.18	0.13	0.23
P value	.06	.08	.32	.48	.20

ED, emergency department.

Table 4. HRQoL scores stratified by status on MHC, ED visits, hospitalization, used opioid, and chronic pain

		MHC			ED visits			Hospitalizations			Used opioid			Chronic pain		
Variable	All (N = 32)	MHC ≤2 (n = 18)	MHC >2 (n = 14)	*P* value*	No (n = 15)	Yes (n = 17)	*P* value	No (n = 16)	Yes (n = 16)	*P* value*	No (n = 6)	Yes (n = 26)	*P* value*	No (n = 6)	Yes (n = 26)	*P* value*
EQ VAS																
Mean	63.41	73.61	50.29	.005	61.33	65.24	.63	66.56	60.25	.43	63.33	63.42	.99	72.50	61.31	.28
SD	22.58	14.55	24.68		22.44	23.22		18.82	26.03		17.22	23.93		12.94	23.96	
EQ-5D index																
Mean	0.75	0.87	0.60	.0005	0.79	0.72	.30	0.83	0.68	.03	0.78	0.74	.69	0.89	0.72	.06
SD	0.20	0.10	0.21		0.17	0.23		0.15	0.23		0.27	0.19		0.09	0.21	
Emotion†																
Mean	48.88	52.40	44.36	.02	49.15	48.65	.89	53.93	43.83	.002	50.63	48.48	.63	54.88	47.50	.10
SD	9.90	8.02	10.52		10.88	9.29		8.71	8.52		11.73	9.66		8.96	9.74	
Pain†																
Mean	50.68	53.73	46.75	.02	53.09	48.55	.14	53.04	48.31	.12	52.92	50.16	.49	62.47	47.96	<.0001
SD	8.63	7.43	8.70		7.99	8.83		8.57	8.27		9.86	8.44		3.27	7.00	
Sleep†																
Mean	49.98	54.72	43.87	.002	52.61	47.65	.18	54.95	45.00	.005	49.43	50.10	.89	57.10	48.33	.06
SD	10.37	8.61	9.41		7.88	11.91		7.91	10.34		17.33	8.56		9.14	10.09	
Social†																
Mean	49.99	52.52	46.74	.06	50.04	49.95	.98	53.41	46.58	.02	56.02	48.60	.06	58.30	48.08	.008
SD	8.74	9.30	7.01		9.42	8.40		9.57	6.45		9.79	8.06		6.73	8.09	
Stiffness†																
Mean	50.35	55.56	43.65	.0003	52.10	48.80	.36	51.89	48.81	.39	53.37	49.65	.42	57.02	48.81	.07
SD	10.03	7.85	8.57		9.17	10.76		10.18	9.95		11.69	9.73		5.79	10.24	
PEF†																
Mean	50.75	47.31	55.18	.046	47.44	53.68	.12	46.99	54.52	.05	40.19	53.19	.008	42.78	52.59	<.05
SD	11.14	12.02	8.33		12.54	9.13		12.73	7.99		13.24	9.26		12.45	10.20	
PES†																
Mean	48.64	47.36	50.29	.30	45.28	51.61	.03	44.99	52.30	.006	47.23	48.97	.09	39.04	50.86	.0003
SD	7.86	8.97	6.08		9.64	4.28		7.73	6.28		5.21	8.40		6.22	6.45	
Fatigue																
Mean	57.89	54.94	61.69	.10	58.86	57.04	.66	54.58	61.21	.10	49.95	59.73	.06	49.78	59.77	.05
SD	11.48	11.23	11.03		11.83	11.45		11.70	10.57		14.10	10.25		15.63	9.75	

PEF, pain episode frequency; PES, pain episode severity.
**P* value were calculated using the Student *t* tests.
†ASCQ-Me health domains include emotional impact, pain impact, sleep impact, social functioning impact, stiffness impact, and pain episodes.

participants who were hospitalized had significantly lower HRQoL scores, higher pain episode frequency or severity scores, or higher fatigue scores (all $P < .05$). Individuals who were prescribed opioid medications for pain anytime over the course of the 6-month chart review had a significantly higher mean ASCQ-Me pain episode frequency score (53.19 ± 9.26 vs 40.19 ± 13.24; $P = .008$) than those without prescriptions of opioid medications. Participants who reported chronic pain (81% of sample) had significantly lower mean ASCQ-Me pain and social impact scores (47.96 ± 7.00 vs 62.47 ± 3.27 [$P < .0001$] and 48.08 ± 8.09 vs 58.30 ± 6.73 [$P = .008$], respectively). They also had higher pain episode frequency and pain severity scores (50.86 ± 6.45 vs 39.04 ± 6.22 [$P < .05$] and 50.86 ± 6.45 vs 39.04 ± 6.22 [$P = .0003$], respectively) than those without chronic pain. The fatigue score was lower among the participants who did not report chronic pain than among those who reported chronic pain (mean, 49.78 ± 15.63 vs 59.77 ± 9.75; $P = .05$).

Anxiety and depression

In our sample, 81.3% of participants met the anxiety threshold and 68.8% met the depression threshold with scores ≥10 on the GAD-7 and PHQ-8, respectively.

WPAI

Nineteen participants (59.4%) reported that they were currently employed (working for pay). Among these, the mean work time missed because of SCD problems was 26.2% ± 34.5% of the time on average. Impairment while working due to SCD was 42.9% ± 29.3%, and on average, overall work impairment was 46.8% ± 31.4%. The mean degree of SCD problems affecting regular activities was 43.1% ± 27.9%.

Health care utilization and costs

The 1-year chart review revealed a total of 73 ED visits and 73 hospitalizations for all 32 participants. The most common reason for ED visits or hospitalizations was acute pain crisis: 89% for ED visits and 68% for hospitalizations.

Table 5 shows the analytic results of health care utilization and costs. The mean annual number of visits included outpatient or doctor visits (14.3 ± 11.3), ED visits (2.3 ± 4.8), and hospitalizations (2.3 ± 3.7). Mean outpatient or doctor visit cost per person per year was $21 028 ± $16 530, whereas emergency room cost was $3499 ± $7323 and hospitalization cost was $19 633 ± $31 847. The mean total direct medical care cost was $44 160 ± $44 262, and the estimated mean annual indirect cost from lost work was $7619 ± $16 214. The estimated mean total cost (the sum of direct and indirect costs) was $51 779 ± $50 278.

Discussion

Analyses of data collected for this project demonstrate the feasibility of collecting data to evaluate HRQoL and burden of illness in persons with SCD using validated, standardized data collection tools. The data collection from the current study provides important insights into the emotional and social disease burden associated with SCD, as measured in a pilot sample of patients treated at 2 comprehensive sickle cell centers.

Many individuals with SCD experience significant pain. As reported elsewhere,[40,41] most patients with SCD experience vaso-occlusive crises, otherwise known as sickle cell pain crises, and as many as 30% of patients experience chronic pain. In our sample, ~91% of participants reported that they used prescription pain medications to treat SCD, and 81% reported having chronic pain, both of which are higher than reported in other studies.[40,41] Fifty percent of our sample had required ED visits or hospitalization due to their SCD (most of these visits due to acute pain crisis and not including infusion center treatment) in the last 12 months. The data analyses indicated that fatigue, SCD medical history, hospitalization, and chronic pain negatively impact HRQoL. Chronic pain was associated with higher fatigue score. Thus, although pain is a major factor in HRQoL, fatigue is also important and should be considered in determining treatment. In this study, fatigue was not correlated with Hb levels, which may be due to sample size. Further investigation into the causes of fatigue in this population is needed. According to these data, it is possible that treatment strategies to prevent SCD

Table 5. Mean annual health care utilization and costs among persons with SCD

Variable	Minimum	Maximum	Median	Mean	SD
No. of outpatient/doctor visits	0.0	46.0	11.5	14.3	11.3
No. of ED visits	0.0	21.0	1.0	2.3	4.8
No. of hospitalizations	0.0	16.0	0.5	2.3	3.7
No. of prescriptions*	0.0	72.0	7.5	15.1	18.5
Missed work h due to SCD†	0.0	40.0	3.0	9.6	14.1
Outpatient/doctor visit costs ($)	0.0	67 436.0	16 859.0	21 027.9	16 529.8
ED visit costs ($)	0.0	32 214.0	1 534.0	3 499.4	7 323.0
Hospitalization costs ($)	0.0	137 701.9	4 303.2	19 633.3	31 846.5
Indirect costs ($)‡	0.0	56 368.0	0.0	7 618.5	16 213.6
Total medical costs ($)	0.0	208 205.9	31 872.7	44 160.7	44 262.2
Total costs ($)	0.0	208 205.9	36 365.6	51 779.1	50 277.9

The table presents the results for the study sample, N = 32. Total medical costs included costs of outpatient or doctor visits, ED visits, and hospitalizations.

*Number of prescriptions was counted for the 6-month period only for the following prescription drugs: antibiotics, short-acting opioid products, long-acting opioid products, hydroxyurea, and L-glutamine.

†Missed work hours due to SCD for a week were estimated from the WPAI: Specific Health Problem patient survey.

‡Indirect costs were imputed as annual missed work days multiplied by the average hourly earning rate of $27.1 in 2018.

complications may reduce pain, fatigue, and hospitalization, thus improving HRQoL.

The strength of an association between 2 variables can be described using correlation coefficients. Absolute magnitude of the correlation coefficient of 0 to 0.39 indicates negligible to weak correlation, 0.40 to 0.69 indicates moderate correlation, and 0.70 to 1.0 indicates strong correlation.[42] Although our pilot study sample is small, the ASCQ-Me pain domain displayed statistically significant moderate correlations with the fatigue score, ASCQ-Me MHC, and number of hospitalizations. The stiffness impact score was moderately correlated with MHC, and was weakly correlated with the number of hospitalizations. The sleep score was weakly correlated with fatigue and moderately correlated with the number of hospitalizations. The emotion and social scores were moderately correlated with the fatigue score. These results provide some indication that ASCQ-Me domain measures were correlated with SCD severity and its associated health care utilization.

The EQ-5D-3L is a generic instrument widely used to measure HRQoL. The EQ-5D VAS and index score were both moderately correlated with the ASCQ-Me MHC. Like the ASCQ-Me, the EQ-5D index score was lower in persons who reported chronic pain than in those without chronic pain. In this study, the EQ-5D index score was associated with SCD-related conditions. Using a generic HRQoL measure such as the EQ-5D allows for a comparison of SCD patients' well-being with the general US population and with populations affected by other disease conditions. Further research is needed to validate the use of the EQ-5D in the SCD population.

The anxiety and depression rates in our sample were much higher than those among the general US population in 2019, when a 7.1% rate of moderate/severe symptoms of anxiety (GAD-7 score $\geq$10)[43] and a 7.0% rate of depression (PHQ-8 score $\geq$10) were reported.[44] They were also much higher than the rates reported in a population of adults with SCD who participated in the National Survey of American Life, which used structured diagnostic interviews and criteria of DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition and found that 24.7% of participants had an anxiety disorder and 38.8% had a mood disorder.[45] Fatigue and pain can lead to anxiety and depressive disorders.[46] Given that the PHQ-8 and GAD-7 are screening tools, they likely led to an overreporting of both depression and anxiety in this study, as not all participants underwent formal psychological assessments. As both somatic and psychological disturbances are considered to interfere with patients' HRQoL,[46] further investigation of the effect of mental health disorders on outcomes is needed. Future studies should consider the validation of PHQ-8 and GAD-7 for measuring depression and anxiety in the SCD population.

Persons with SCD experienced high annual medical costs and loss of work productivity. We should note that infusion procedures were included in outpatient visits. Outpatient and doctor visits comprised the largest portion of medical costs (~50%). According to our analyses, patients with SCD used many prescription medications, including opioid analgesics. The extensive use of prescription medications makes it difficult to abstract prescription information manually to estimate prescription costs. Therefore, we have not included prescription costs in estimating the total burden of illness. This pilot work illustrates the importance of using other sources, such as administrative data, to evaluate drug use costs in the SCD population.

Limitations

This study used a convenience sample. Thus, the patients who visited the clinic most frequently were the most likely to be enrolled. In addition, there is insufficient power for some group comparisons because this was a pilot study of a small sample. Furthermore, given that the current data collection effort included only adults with SCD, additional studies should assess children with SCD to fully understand the disease burden for the entire SCD population.

Conclusion

The data collection tools developed from this pilot study illustrate the feasibility of evaluating HRQoL and economic burden for people with SCD, laying the foundation for better characterization of important health and economic effects in this understudied population. Further, these data continue to highlight the need for a national, longitudinal clinical registry to track outcomes. This should include patient-reported outcomes to enhance our understanding of the disease course, its emotional/social effects, and the relationship of these effects with biologic findings. These data provide some evidence that fatigue, SCD complications, hospitalization, and chronic pain negatively impact HRQoL. Similarly, our data demonstrate that SCD is associated with high economic burden, largely from direct medical costs incurred through outpatient and transfusion visits. Although these data are derived from limited sample sizes, they suggest specific areas where SCD health care teams, SCD community-based organizations, affected individuals, and caregivers can begin to create interventions to improve the HRQoL of affected individuals. These data add to the emerging evidence that quantifies the economic burdens of SCD, which is vital to setting baselines for future policy interventions that could address innovations to reduce costs while retaining health care quality.

Acknowledgments

The authors thank Steven Carrasco from the University of Southern California (USC) and Rajalakshmi Ganapathy from the Center for Inherited Blood Disorders. The authors also thank Mary Brown from the Sickle Cell Disease Foundation and the Hemotology Utilization Group Studies Sickle Cell Disease Advisory Group for her advice and contributions.

The study was supported by investigator-initiated research agreements between the USC and Pfizer Inc, and USC and Global Blood Therapeutics (current Pfizer Inc).

Authorship

Contribution: M.B.N. acted as the principal investigator (PI) of the study; S.L. and A.S. acted as the co-PIs of the study; M.B.N., J.W., S.L., and N.C. conceived the project and developed the methodological approach and data collection tool; S.H. and N.C. collected the data; J.W. and M.B.N. developed the key parameters and analysis approach, interpreted the data, and drafted the manuscript; J.W. analyzed the data; and all authors edited and revised the manuscript and approved the final manuscript.

Conflict-of-interest disclosure: S.L. received research funding from Global Blood Therapeutics (current Pfizer Inc), Shire, Novartis, and CSL Behring, and consulting fees from ICON, bluebird bio, Magenta, Novartis, Novo Nordisk, and Pfizer. J.W. received financial support through the project funding provided by Pfizer Inc and

Global Blood Therapeutics (current Pfizer Inc). R.G.C. received consulting fees from the University of Southern California (through the project funding provided by Pfizer), Bayer, and Novo Nordisk. M.B.N. is the principal investigator for the Hemotology Utilization Group Studties research group and has received grant funding from Pfizer, Genentech Inc, Baxalta US Inc (Bannockburn, IL; a Takeda company), Octapharma, CSL Behring, Global Blood Therapeutics (current Pfizer Inc), and Novo Nordisk. The remaining authors declare no competing financial interests.

ORCID profiles: S.L., 0000-0002-2878-0251; N.C., 0000-0003-1960-7323; J.W., 0000-0003-0932-4979; S.H., 0000-0002-8255-9005; R.G.C., 0000-0002-6859-6432; J.R.B., 0000-0002-7850-0027; D.N., 0000-0002-1109-0879; J.C.R., 0000-0002-9415-9543; M.M.U., 0000-0002-6621-0137; J.K., 0000-0001-7002-8891; M.B.N., 0000-0003-4989-9806.

Correspondence: Michael B. Nichol, University of Southern California, 650 Childs Way, RGL 212, Los Angeles, CA 90089; email: mnichol@usc.edu.

References

1. Centers for Disease Control and Prevention. Sickle Cell Disease. Accessed 8 December 2021. https://www.cdc.gov/ncbddd/sicklecell/index.html
2. Adams-Graves P, Bronte-Jordan L. Recent treatment guidelines for managing adult patients with sickle cell disease: challenges in access to care, social issues, and adherence. *Expert Rev Hematol*. 2016;9(6):541-552.
3. Therrell BL Jr, Lloyd-Puryear MA, Eckman JR, Mann MY. Newborn screening for sickle cell diseases in the United States: a review of data spanning 2 decades. *Semin Perinatol*. 2015;39(3):238-251.
4. Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med*. 2010;38(suppl 4):S512-S521.
5. Brousseau DC, Panepinto JA, Nimmer M, Hoffmann RG. The number of people with sickle-cell disease in the United States: national and state estimates. *Am J Hematol*. 2010;85(1):77-78.
6. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330(23):1639-1644.
7. Lanzkron S, Carroll CP, Haywood C Jr. Mortality rates and age at death from sickle cell disease: U.S., 1979-2005. *Public Health Rep*. 2013;128(2):110-116.
8. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. *Medicine (Baltimore)*. 2005;84(6):363-376.
9. Paulukonis ST, Eckman JR, Snyder AB, et al. Defining sickle cell disease mortality using a population-based surveillance system, 2004 through 2008. *Public Health Rep*. 2016;131(2):367-375.
10. Ballas SK. Current issues in sickle cell pain and its management. *Hematology Am Soc Hematol Educ Program*. 2007;2007(1):97-105.
11. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med*. 1991;325(1):11-16.
12. Brandow AM, Brousseau DC, Pajewski NM, Panepinto JA. Vasoocclusive painful events in sickle cell disease: impact on child wellbeing. *Pediatr Blood Cancer*. 2010;54(1):92-97.
13. Dampier C1, Lieff S, LeBeau P, et al. Health-related quality of life in children with sickle cell disease: a report from the comprehensive sickle cell centers clinical trial consortium. *Pediatr Blood Cancer*. 2010;55(3):485-494.
14. Fisak B, Belkin MH, von Lehe AC, Bansal MM. The relation between health-related quality of life, treatment adherence and disease severity in a paediatric sickle cell disease sample. *Child Care Health Dev*. 2012;38(2):204-210.
15. Malheiros CD, Lisle L, Castelar M, Sá KN, Matos MA. Hip dysfunction and quality of life in patients with sickle cell disease. *Clin Pediatr*. 2015;54(14):1354-1358.
16. Edwards CL, Scales MT, Loughlin C, et al. A brief review of the pathophysiology, associated pain, and psychosocial issues in sickle cell disease. *Int J Behav Med*. 2005;12(3):171-179.
17. McClish DK, Penberthy LT, Bovbjerg VE, et al. Health related quality of life in sickle cell patients: the PiSCES project. *Health Qual Life Outcomes*. 2005;3:50.
18. Lee S, Vania DK, Bhor M, Revicki D, Abogunrin S, Sarri G. Patient-reported outcomes and economic burden of adults with sickle cell disease in the United States: a systematic review. *Int J Gen Med*. 2020;13:361-377.
19. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. *Am J Hematol*. 2009;84(6):323-327.
20. Mvundura M, Amendah D, Kavanagh PL, Sprinz PG, Grosse SD. Health care utilization and expenditures for privately and publicly insured children with sickle cell disease in the United States. *Pediatr Blood Cancer*. 2009;53(4):642-646.
21. Treadwell MJ, Hassell K, Levine R, Keller S. Adult sickle cell quality-of-life measurement information system (ASCQ-Me): conceptual model based on review of the literature and formative research. *Clin J Pain*. 2014;30(10):902-914.
22. Keller SD, Yang M, Treadwell MJ, Werner EM, Hassell KL. Patient reports of health outcome for adults living with sickle cell disease: development and testing of the ASCQ-Me item banks. *Health Qual Life Outcomes*. 2014;12:125.

23. National Academies of Sciences, Engineering, and Medicine. Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action. The National Academies Press; 2020.
24. Zhou ZY, Wu J, Baker J, et al. Haemophilia utilization group study - part Va (HUGS Va): design, methods and baseline data. *Haemophilia*. 2011;17(5):729-736.
25. Chen CX, Baker JR, Nichol MB. Economic burden of illness among persons with hemophilia B from HUGS Vb: examining the association of severity and treatment regimens with costs and annual bleed rates. *Value Health*. 2017;20(8):1074-1082.
26. Keller S, Yang M, Evensen C, Cowans T. *ASCQ-Me user's manual*. American Institutes for Research; 2017.
27. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care*. 2005;43(3):203-220.
28. National Institutes of Health. Patient-reported outcomes measurement information system (PROMIS) fatigue scoring manual. Accessed 11 April 2021. http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Fatigue_Scoring_Manual.pdf
29. Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Inern Med*. 2006;166(10):1092-1097.
30. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord*. 2009;114(1-3):163-173.
31. Kroenke K, Spitzer RL, Williams JB, Löwe B. The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatry*. 2010;32(4):345-359.
32. Keller S, Yang M, Treadwell MJ, Hassell KL. Sensitivity of alternative measures of functioning and wellbeing for adults with sickle cell disease: comparison of PROMIS to ASCQ-Me. *Health Qual Life Outcomes*. 2017;15(1):117.
33. Zhou ZY, Koerper MA, Johnson KA, et al. Burden of illness: direct and indirect costs among persons with hemophilia A in the United States. *J Med Econ*. 2015;18(6):457-465.
34. HCUPnet. Healthcare cost and utilization project. Agency for healthcare research and quality, rockville, MD. Accessed 18 March 2021. https://hcupnet.ahrq.gov/
35. Center for Financing. Access and cost trends, agency for healthcare research and quality, medical expenditure panel survey. 2018. Accessed 18 March 2021. https://www.ahrq.gov/data/meps.html
36. Hodgson TA, Meiners MR. Cost-of-illness methodology: a guide to current practices and procedures. *Milbank Mem Fund Q Health Soc*. 1982;60(3):429-462.
37. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353-365.
38. U.S. Bureau of Labor Statistics. Employer costs per hour worked for employee compensation. Accessed 18 March 2021. www.bls.gov/
39. Szende A, Janssen B, Cabases J, eds. *Self-Reported Population Health: An International Perspective based on EQ-5D [Internet]*. Springer; 2014.
40. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease daily pain in sickle cell disease. *Ann Intern Med*. 2008;148(2):94-101.
41. Jordan L, Adams-Graves P, Kanter-Washko J, et al. Multicenter COMPACT study of complications in patients with sickle cell disease and utilization of iron chelation therapy. *Curr Med Res Opin*. 2015;31(3):513-523.
42. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. *Anesth Analg*. 2018;126(5):1763-1768.
43. Terlizzi EP, Villarroel MA. *Symptoms of generalized anxiety disorder among adults: United States, 2019. NCHS Data Brief, no 378*. National Center for Health Statistics; 2020.
44. Villarroel MA, Terlizzi EP. *Symptoms of depression among adults: United States, 2019. NCHS Data Brief, no 379*. National Center for Health Statistics; 2020.
45. Jonassaint CR, Lukombo I, Feldman R, et al. Differences in the prevalence of mental health disorders among Black American adults with sickle cell disease compared to those with non-heritable medical conditions or no medical conditions. *Br J Haematol*. 2022;196(4):1059-1068.
46. Toumi ML, Merzoug S, Boulassel MR. Does sickle cell disease have a psychosomatic component? a particular focus on anxiety and depression. *Life Sci*. 2018;210:96-105.