Journal Article

Indirect cost burden of sickle cell disease on patients and caregivers in the United States

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Abstract: Sickle Cell Disease (SCD) is a genetic condition resulting in abnormal red blood cells that block blood vessels and reduce oxygen flow. In 2020 the Institute for Clinical and Economic Review (ICER) assessed three newer medications, Crizanlizumab, Voxelotor, and L-Glutamine for SCD. In collaboration with ICER, Sick Cells, a U.S. based advocacy organization, developed and fielded an online survey to gather U.S. patient and caregiver work and activity impairment, and out of pocket costs (OOPCs) to include in the review of the medications as contextual information. Analyses included 452 respondents, representing 287 patients and 165 caregivers. Results showed that patients and caregivers spend an average of $388.10 and $226 per month, respectively, in OOPCs and lost an estimated $1,659.80 and $1,496.90 in monthly wages, respectively, due to time missed from work because of SCD. Patient estimated lost wages and work impairment score were associated with the number of patients last year pain crises (wages: β=9.5; p=0.00; work: β=0.48; p=0.04). Patient and caregiver estimated lost wages and work impairment scores were associated with the duration of recent patient pain crises (wages [patient: β=245.5; p=0.00; caregiver: β=241.4; p=0.00]; work: [patient: β=14.8; p=0.00; caregiver: β=8.3; p=0.02]). Incorporating patients' and caregivers' perspectives provide a more comprehensive assessment of health status value but these perspectives are often missing from health economic reviews.

Keywords: keyword 1; Sickle cell disease; 2 Indirect cost 3 ICER

1. Introduction

1.1. Sickle Cell Disease in the United States

Sickle cell disease (SCD) is a group of inherited disorders characterized by abnormal hemoglobin resulting in crescent or sickle shaped red blood cells. SCD is considered rare in the United States, affecting an estimated 100,000 individuals and is more common among Black/African American and Hispanic/Latinx populations as compared to the White population [1,2]. Latinx is a gender-neutral term used in the United States to describe people who are of or relate to Latin American origin or descent. However, the true prevalence of people living with SCD in the U.S. is unknown [3].

Persons with SCD experience a multitude of medical complications because of the underlying hemolysis and vascular damage that results in acute and chronic injury to multiple end organs, including brain, kidney, and the cardiopulmonary system [4]. Most patients experience significant lifelong morbidities associated with high health care costs and reduced life expectancy. Life expectancy for patients with SCD is 54 years compared to 76 years in the U.S. general population [5]. Increased mortality is due to lifelong SCD

comorbidities and lack of an appropriate 'medical home' to provide comprehensive care [6,7].

Blood,bone marrow transplants, and recently gene therapies are the only known cures for SCD; other treatments manage SCD symptoms and comorbidities. Long standing treatment for SCD includes penicillin, primarily for children, to reduce the risk of pneumococcus bacterial infection; transfusions to increase the number of red blood cells and reduce the risk of stroke; and hydroxyurea to reduce the number of acute pain crises and acute chest syndrome [8]. More recently, the U.S. Food and Drug Administration (FDA) approved several new medications. L-glutamine, approved in 2017, helps prevent damage to red blood cells and can decrease the frequency of acute pain crises [9]. Voxelotor, approved in 2019, prevents red blood from assuming the sickle shape [10]. Crizanlizumab, also approved in 2019, helps prevent blood flow blockages and reduces acute pain crises [11]. These are the first SCD-specific medications and the first new medications in over 20 years for the treatment of SCD.

1.2. The Institute for Clinical and Economic Review (ICER) of Sickle Cell Disease

The Institute for Clinical and Economic Review (ICER), a U.S. based, independent, non-profit research organization, evaluates medical evidence to improve patient outcomes and control costs. ICER uses comparative clinical effectiveness, feedback from patients and families, input from clinicians, manufacturers, and health care payers to assess the costs and benefits of new health care interventions provided to patients and their families who receive care in the U.S. healthcare system. ICER's reports are used by health care payers such as Medicaid and private insurers to inform formulary decisions, coverage criteria, and intervention price negotiations. Medicaid is a U.S. public insurer that provides health coverage to millions of Americans, including eligible low-income adults, children, pregnant people, older adults, and people with disabilities.

In 2019-2020, ICER reviewed the health and economic outcomes of crizanlizumab, voxelotor, and L-glutamine compared to usual care [12]. Using the published literature and data from clinical trials, ICER assessed the medications' clinical benefits, potential harms, and cost-effectiveness, including direct costs and the quality and length of life. At the initiation of the review, crizanlizumab and voxelotor were not yet approved by the FDA. Several advocacy organizations noted the prematurity of the review given the lack of post-market, peer review literature on the medications and the lack of clarity on how ICER intended to capture patients' and caregivers' perspectives on the health and economic effectiveness model and indirect costs. Advocates expressed concerns with the timing of the ICER review given the historic under-investment in SCD research [13] and drug development and minimal explanation of how health equity would be incorporated into the health economic review. Health equity is a crucial point given SCD disproportionately affects racial and ethnic minorities and people of color are not well represented in clinical trials [14.15], the data in which ICER relies on.

ICER's model did not include patient and caregiver out of pocket costs (OOPCs), patient activity impairment, and patient and caregiver time missed from school and work. The medical costs to treat SCD are substantial [17-20] with lifetime costs totaling several hundred thousand dollars per patient [21]. Much of the literature on SCD costs uses claims data which does not include lost educational potential, time missed from work [22], or OOPCs despite the financial burden on patients [23]. A recent study by Holdford and colleagues showed the substantial indirect economic burden of SCD [24] and also called for more economic studies to fully characterize the burden of the disease [24,25], particularly studies that assess both direct and indirect costs. To address this gap, the study authors collaborated with ICER to develop and field an online survey to capture patient and caregiver indirect costs to include in the health and economic effectiveness review of the SCD medications. The results showed that patients and caregivers had a monthly average of $388.10 and $226 in OOPCs, respectively. Additionally, due to SCD, patients and caregivers lost an estimated respective average monthly income of $1,659.80 and $1,496.90.

Results of the regression analysis suggest that estimated lost wages and work impairment scores were statistically significantly associated with the number and duration of patient pain crises.

2. Materials and Methods

In collaboration with ICER, Sick Cells, designed and fielded a survey – the My Life with Sickle Cell: Patient and Caregiver Survey – to evaluate the personal and socioeconomic impact of sickle cell disease on patients and caregivers. The questionnaire was developed through stakeholder consultation and a community task force of ten community-based organizations (CBOs). The questionnaire included 20 questions on several key domains, including 1) demographics, socioeconomic characteristics, and insurance coverage 2) health status, comorbidities, and severity of SCD 3) employment status, productivity, and activity impairment, 4) experiences with pain and fatigue, and 5) non-medical costs and annual earnings.

Sick Cell piloted the survey with patients and caregivers to assess the data collection method and the difficulty of answering the survey questions. The final survey was imported into an online survey platform and the link was distributed to CBOs that have constituents around the country. The data were collected from January 16-31, 2020. The survey did not include any personally identifiable information. The survey relied on a convenience sample and was not evaluated by an ethics committee. There was an active consent process by which participants consented to participate in the study by advancing to the survey questions after reading the survey instructions. The instructions specified that the survey was anonymous and responses would be reported in aggregate.

2.1. Sample

A total of 547 people responded, 93 respondents were excluded because they were from an individual who was not a patient or caregiver, the respondent did not reside in the United States, did not answer the exclusion questions, or was not at least 18 years old. The final sample for analysis was 452, representing 287 patients and 165 caregivers.

2.2. Analysis

2.2.1. Descriptive statistics

Information on patient and caregiver demographics (age, gender, race, health insurance type, employment status; Table 1), treatment type, SCD health and income burdens, and work and activity impairments are presented as percentages, means, and standard deviations as appropriate.

2.2.2. Multiple regression analysis

Separate regression models for patients and caregivers were used to examine the association between estimated lost wages and work impairment score on the number and duration of patient pain crises along with age, gender, and race. The multicollinearity test showed the number of last year pain crises was not correlated with the duration of the last seven-day pain crises.

Statistical analyses were performed using the statistical package program SAS 9.2. P-values equal to or less than 0.05 were considered statistically significant.

2.3. Measures

Out of pocket costs (OOPC): We calculated OOPC [26] as the sum of medical appointments and hospitalizations, medications, home care, other costs, vitamins/supplements, paid care, accommodations, devices, and transportation, including parking.

Work impairment: The Work, Productivity, and Activity Impairment (WPAI) [27] instrument is a publicly available, validated, six-item measure of past seven-day

productivity and activity limitations for specific health conditions. We used the WPAI to calculate a past seven-day work impairment score using the established WPAI scoring frame [27]. Higher scores represent greater levels of impairment due to a health condition. The score is calculated below.

Question 8. Are you currently employed (working for pay)?
Question 9. How many hours did you miss from work because of SCD and its complications?
Question 10: **how many hours** did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this survey?
Question 11. How many hours did you actually work?
Question 12. On a scale of 0 to 10, how much did SCD and its complications affect your productivity while you were working?
Question 13. During the past seven days, how much did sickle cell disease and its complications affect your ability to do your regular daily activities other than work at a job?

Percent work time missed due to SCD = (Q9/(Q9+Q11))
Percent impairment while working due to SCD = Q12/10
Percent activity impairment due to SCD = Q13/10
Work impairment score = [(q9/(q9+q11)) + (1-(q9/(q9+q11)))*q12/10]*100 only for those who are employed Q8=1

Number of days a pain crisis lasted: We categorize the number of days pain crises lasted into four categories: less than 1 day; 1 to 2 days; 3 to 4 days; and more than 4 days.
Duration of last 7 days pain crises: The duration of last seven days pain crises represents the number of days the patient was in pain due to SCD in seven days prior to completing the survey.

Lost income/wages due to SCD impairment: We calculated lost income per month and reported as mean monthly lost days of income. To determine the number of working hours lost per month due to SCD, we multiplied the work impairment score, a score of past seven-day impairment, by 40 hours, a culturally common full-time, non-overtime, five-day workweek in the U.S., and divided by 100 to convert the score to the number of hours worked per week. Most employed individuals in the sample reported working full time. A 40-hour workweek is commonly considered full-time in the U.S. because working more hours will trigger overtime pay for eligible employees [28]. We multiplied the estimated hours worked per week by 2.79 to convert to the number of hours worked per month based on 235 workdays per year. Income loss was calculated as number of lost working days per month multiplied by the national average daily income rate for 40 hours per week based on the average hourly wage of $25.72 [29].

3. Results

The results showed that 79% of patients and 56% of caregivers were female. Seventy-five percent of patients were between the ages of 18 and 45 years. Ninety-four percent of patients self-identified their race as Black/African American. Most patients had some form of health insurance with Medicaid (28.9%), Medicare (23.3%), and commercial insurance (41.8%) being the primary patient insurers. Fewer than half of patients were employed (43.4%) and 65.5% of caregivers were employed. Most caregivers were the child or grandchild of patients (77%) or close family members (17%). Paid caregivers and non-paid care advocates each represented 1.3% of caregivers. The remaining caregivers did not specify their relationship to the patient (data not shown).

Table 1. Demographic Characteristics of Patients.

		Patient Respondents (N=287)	Patient Characteristics Reported by Caregiver Respondents (N=165)	Total (452)
		N (%)	N (%)	N (%)
Gender	Male	57 (19.9)	69 (41.8)	126 (27.9)
	Female	227 (79.0)	93 (56.3)	320 (70.8)
	Non-binary/other	3 (1.0)	3 (1.8)	6 (1.4)
Patient age in years	Less than 18		72 (43.6)	72 (15.9)
	18-30	82 (28.5)	44 (26.7)	126 (27.8)
	31-45	135 (47.0)	38 (23.0)	173 (38.3)
	46-54	37 (12.9)	7 (4.2)	44 (9.7)
	55+	33 (11.5)	4 (2.4)	37 (8.2)
Race/ethnicity	Hispanic, Latinx, or Spanish origin	8 (2.8)	4 (2.4)	12 (2.6)
	Black/African American	271 (94.4)	154 (93.3)	425 (94.1)
	White	5 (1.7)	1 (0.6)	6 (1.3)
	Other	3 (1.0)	6 (3.6)	9 (2.0)
Health insurance	Medicaid	83 (28.9)	69 (41.8)	152 (33.7)
	Medicare	67 (23.3)	19 (11.5)	86 (19.0)
	Dually eligible for both Medicaid and Medicare	2 (0.7)		2 (0.4)
	Veterans Administration	3 (1.0)	3 (1.8)	6 (1.3)
	Commercial	120 (41.8)	66 (40.0)	186 (41.1)
	No insurance	12 (4.2)	8 (4.8)	20 (4.4)
Employed*	Yes	124 (43.4)	107 (65.6)	
	No	162 (56.6)	56 (34.4)	

* Employment variable represents employment status for the patient and caregiver.

Patients reported significant health and activity impairments due to SCD. Chronic pain (70%) and fatigue or sleep disturbance (65.5%) were the most cited health effects of SCD followed by acute patient crises (41.8%), other effects (31.7%), and cognitive impairment (13.6%). More than 42% of patients reported that pain crises last more than four days. To manage the symptoms of SCD patients used a combination of treatment, including prescription pain medication (57.8%), over the counter pain medication (43.6%), and hydroxyurea (35.2%).

Table 2. Health effects of sickle cell disease.

		Patient Respondents s (N=287)	Patient Characteristics Reported by Caregiver Respondents (N=165)	Total (452)
		N (%)	N (%)	N (%)
Health effects of SCD on patients' life	Acute pain crises	120 (41.8)	71 (43.0)	191 (42.3)
	Chronic pain	201 (70.0)	85 (51.5)	286 (63.3)
	Fatigue or sleep disturbance	188 (65.5)	75 (45.5)	263 (58.2)
	Cognitive impairment	39 (13.6)	25 (15.2)	64 (14.2)
	Other	91 (31.7)	57 (34.5)	148 (32.7)
# of days pain crises lasted	Less than 1 day	20 (8.3)	8 (6.3)	28 (7.6)
	1-2 days	47 (19.4)	25 (19.7)	72 (19.5)
	3-4 days	73 (30.2)	24 (18.9)	97 (26.3)
	More than 4 days	102 (42.2)	70 (55.1)	172 (46.6)
Types of treatment to manage SCD	Hydroxyurea	101 (35.2)	64 (38.8)	165 (36.5)
	Simple blood transfusion/exchange	80 (27.9)	44 (26.7)	124 (27.4)
	Pain medicine: Over the counter	125 (43.6)	75 (45.5)	200 (44.2)
	Pain medicine: Prescription	166 (57.8)	70 (42.4)	236 (52.2)
	Other	112 (39.0)	46 (27.9)	158 (35.0)

Table 3 shows past seven-day patient and caregiver work and activity impairments among individuals who were employed. Patients and caregivers reported 9.6 and 10 average hours of work missed, respectively, in last seven days due to SCD. Interestingly average hours of work missed caregivers (29.6 hours) reported a higher average number of hours worked in the last seven days as compared to patients (28.8 hours). We measured work and activity impairment using a scale of zero impairment to 10 – severe impairment. There was no statistically significant difference in productivity loss due to SCD between caregivers and patients. However, there was a statistically significant difference in activity impairment between patients and caregivers (patients: 5.7 scores; caregivers: 5.4; p=0.01).

Employed patients and caregivers respectively reported 23.3% and 22.2% of work time missed the last seven-days due to SCD. However, caregivers reported more work impairment (46.3%) than patients (43.3%). Table 4.

Table 3. Employed patient and caregiver work and activity impairments.

	Patients (n=124)	**Caregivers (n=107)**	
	Average (Std. Dev)	Average (Std. Dev)	t-value (p-values)
Number of missed work hours due to SCD in last 7 days (Question 9)	9.6 (17.8)	10 (19.3)	0.37 (0.71)
Number of missed work hours due to other reason in last 7 days (Question 10)	2.7 (9.1)	2.9 (6.5)	0.17 (0.86)

Number of hours worked in last 7 days (Question 11)	28.8 (17.1)	29.6 (16.1)	0.81 (0.43)
Productivity loss due to SCD in last 7 days (Scale 0 to 10) (Question 12)	4.3 (2.8)	4.6 (2.7)	0.71 (0.48)
Activity impairment in last 7 days (Scale: 0 to 10) (Question 13)	4.4 (2.8)	4.6(3)	0.56 (0.57)

*5% level of significance.

Table 4. Employed patient and caregiver Work, Productivity, and Activity Impairment (WPAI).

		Patients (n=124)	**Caregivers (n=107**
		Percentage (Std. Dev)	Percentage (Std. Dev)
Work, Productivity, and Activity Impairment	Work time missed due to SCD in the last 7 days (absenteeism)	23.3 (32.0)	22.2 (29.1)
	Impaired while working due to SCD in the last 7 days (presenteeism)	43.3 (28.9)	46.3 (27.4)
	Overall work impairment score due to SCD (work productivity loss)	50.5 (31.9)	56.2 (30.2)
	Overall activity impairment score due to SCD (activity impairment)	55.8 (29.9)	47.9 (30.4)

Table 5 shows that patients and caregiver's average monthly OOPCs and estimated lost wages due to SCD. On average, patients spent $388.10, and caregivers spent $226 per month in out-of-pocket expenses with medical appointment and hospitalization costs being the largest expense for patients ($202.60), followed by caregiver support ($60.40), and medication ($53.70). Patients and caregivers lost an average of $1,659.80 and $1,496.90 per month, respectively, in estimated wages due to the overall impairment caused by SCD.

Table 5. Patient and caregiver OOPC and estimated lost wages.

		Patients	**Caregivers**
		$ Average (Std. Dev)	$ Average (Std. Dev)
Monthly out-of-pocket costs in U.S. dollars	Medical appointments and hospitalizations	202.6 (867.5)	54.2 (99.2)
	Medication	55.8 (86.2)	49.8 (83.7)
	Vitamins and nutritional supplements	43.4 (63.7)	29.5 (39.4)
	Caregivers/support	60.4 (295.0)	29.4 (102.3)
	Medical supplies	38.2 (134.8)	14.4 (48.1)
	Transportation	54.6 (144.4)	57.2 (94.1)
	Pain management	55.7 (119.7)	34.7 (151.5)
	Mental health services	39.4 (159.6)	18.2 (77.8)

	Other	15.2 (50.8)	20.8 (60.6)
	Overall OOPCs	388.1 (1003.6)	226.0 (316.9)
Estimated lost monthly income/wages in U.S. dollars due to SCD impairment		1659.8 (886.4)	1496.9 (902.7)

We explored if caregiver's and patient's estimated lost wages were associated with the number of pain crises in the last year and duration of recent pain crises. In the regression analyses reported in tables 6 and 7, the beta estimate represents the change in the dependent variables, lost wages and work impairment score, for a unit change in the independent variables. The beta estimate quantifies the magnitude of the effect of the dependent and independent variables. Table 6. Patient estimated lost wages were associated with the number of patient pain crises in the last year (β=9.5; p=0.00); the more pain crises, the more estimated lost wages among patients. Estimated lost wages for both patients and caregivers were statistically significantly associated with the duration of recent patient pain crises (patient: β=245.5; p=0.00; caregivers: β=241.4; p=0.00), indicating increased estimated lost wages for both patients and caregivers with longer durations of patient pain crises. Given the overrepresentation of females in the sample, we performed sensitivity analyses by randomly eliminating some females from the sample to determine whether the larger female sample affected the regression estimates. The sensitivity analyses showed no significant change in the study results. The regression analysis showed a statistically significant relationship between patient age as reported by caregivers and lost wages. We further investigated this result by performing a correlation analysis between patient age and estimated lost wages and found no statistically significant difference but did see a significant difference between patient age as reported by caregivers and estimated lost wages. We attribute these results to the difference in the age variation between patient age and patient age as reported by caregivers shown in Table 1. We also performed additional sensitivity analyses by removing respondents under 18 years old from the sample and found no differences in the results. In Table 7, we show that patient work impairment score was statistically significantly associated with the number of patient pain crises per year (β=0.48; p=0.04). Patient and caregiver work impairment scores were associated with the duration of patient pain crises (patient: β=14.8; p=0.00; caregiver: β=8.3; p=0.02). The higher the work impairment scores, the longer the duration of patient pain crises. OOPC was not statistically significantly associated with the number or duration of pain crises (results not shown).

Table 6. Regression analysis shows the association between estimated lost wages due to SCD and patient pain crises.

	Patient		**Caregivers**	
Patient independent variables	β Estimate (Std_err)	P-values	β Estimate (Std_err)	P-values
Female vs. male gender	271.3 (124.7)	0.02*	-64.8 (143.7)	0.65
Patient age	5.9 (4.3)	0.17	-11.7 (4.9)	0.01*
Black/African American race vs. all other races	-482.6 (232.1)	0.03*	33.3 (290.1)	0.91
Number of past year pain crises	9.5 (2.5)	0.00*	6.2 (3.3)	0.06
Duration of last 7 days pain crises	245.5 (53.3)	0.00*	241.4 (76.7)	0.00*

*5% level of significance.

Table 7. Regression analysis shows the association between the work impairment score and patient pain crises.

	Patient		Caregivers	
Patient independent variables	**β Estimate (Std_err)**	P-values	β Estimate (Std_err)	P-values
Female vs male gender	-7.1 (6.6)	0.28	-0.98 (7.1)	0.88
Patient age	-0.25 (0.27)	0.36	-0.42 (0.24)	0.08
Black/African American race vs. all other races	0.49 (19.3)	0.97	-17.1 (13.3)	0.20
Number of past year pain crises	0.48 (0.24)	0.04*	0.15 (0.31)	0.63
Duration of last 7 days pain crises	14.8 (2.8)	0.00*	8.3 (3.6)	0.02*

*5% level of significance.

4. Discussion

The ICER review of newer SCD medications contributes to the cost effectiveness literature but is limited by not incorporating patient and caregiver perspectives into the review, other than to provide limited contextual information. The impact of SCD on quality of life (QOL) is complex and affects both patients and their caregivers. In addition to the health-related burden of disease, many other factors further diminish QOL. Discrimination, stigma, lack of quality care, and disruption of family and social activities all combine to make a living with SCD very difficult.

The ICER cost effectiveness review relies on quality adjusted life years (QALYs) as a primary outcome. The lack of patient's perspectives on the value of health status in QALY are well known [30-32] but not addressed in the ICER SCD review. Patients with painful, chronic conditions often need caregiver support. Therefore, caregiver's experiences of supporting patients and the impact of the disease on the caregiver's life are just as important. However, the caregiver perspective was missing without additional data collection efforts. The current study attempts to address this concern by including the caregivers' perspective and questions represented in health-related quality of life (HRQL) measures, such as assessments of bodily pain and how SCD affected one's life, which has been used for SCD patient self-assessments of wellbeing [33-35].

Patients reported considerable health effects of SCD, which is unsurprising given the debilitating nature of the disease. For patients and their caregivers, patient fatigue, chronic pain, and consecutive days in pain affect more than quality of life. These symptoms effect the ability to engage in daily activities, work, and go to school [36]. Pain is a primary concern for patients. In the current study, 81% of patients reported a past year pain crisis, of which 88% sought medical attention to ease pain (data not presented). It is likely that the remaining 12% treated their pain at home, although the survey did not capture additional settings for treating pain. Pain treated at home would not appear in claims data..

While not statistically significant, both patients and caregivers missed more than one workday a week due to SCD, which is much higher than patients with other chronic diseases such as rheumatoid arthritis [37] but consistent with Crohn's disease [38]. However, patients with cystic fibrosis, a rare, chronic disease, reported similar challenges of their disease affecting employment [39-41]. Like SCD, cystic fibrosis patients and caregivers forgo employment opportunities and/or are impaired at work due to the disease [41]. The detrimental impact of SCD on time missed from work is further confirmed by recent data from a multi-country study where patients missed an average of seven hours (SD=14.8) of work in the seven days prior to the survey due to SCD [42]. Research by Holdford and colleagues surveyed patients on the impact of SCD on work-related productivity [24]. Approximately 30% of the patients in the Holdford study were employed as compared to 43% in the present study. Both the current study and Holdford studies limited work-related analyses to those who were employed. However, patients in the Holdford and the current study reported missing about one workday per week due to their SCD symptoms

and lost more than $1250 in estimated wages per month due to time missed from work and SCD activity impairments. The current study shows patients lost an estimated $1600 in wages per month due to overall SCD impairments. Of note, the Holdford quantified the economic burden of SCD on unpaid work, labor provided that is not directly compensated. Patients and caregivers lost an estimated $1795 and $1638 in unpaid work per month, respectively, due to SCD. For patients and caregivers, lost productivity is more than paid employment, as acknowledged by Holdford and colleagues.

In addition to time missed from work, both patients and caregivers reported work and activity impairments. Consistent with research by Rizio and colleagues [43], work impairment score was associated with the number and duration of patient pain crises. Other research shows that SCD patients report difficulty maintaining employment because of absenteeism and impairment due to disease symptoms [24,44] which we hypothesize is the case in our sample given that more than half of patients were unemployed.

Time missed from work and work impairment can exacerbate the cost burden of the disease. Patient and caregiver OOPCs and estimated lost income are notable. Monthly OOPCs total hundreds and estimated lost monthly income far exceeds $1000 for both patients and caregivers. Research from Huo and colleagues [23] estimate patient OOPC to be 5% of the $2.98 billion annual SCD health system economic burden. However, the current study does not include total patient costs to determine the overall cost burden of SCD.

Intuitively, patient estimated lost wages were associated with the number and duration of patient pain crises. Patients unable to work due to disease symptoms or caregivers supporting patients with long duration pain crises are unlikely to receive wages during those times. The current research suggests when accounting for costs to patients and caregivers not captured in claims data, the true costs of SCD exceeds previous high-cost estimates that rely on utilization data [45,46]. If the indirect cost data from the present study were included in the ICER review, ICER could perform additional analyses on the indirect costs per pain episode or hospitalization to further investigate the economic, and QOL benefits of the medications for patients and caregivers. It is also likely that the QALYs would change when including the indirect cost data because of the change in the treatment cost estimates. However, the current study was unable to investigate the potential change in QALYs because we lacked access to the data ICER used to conduct the review. Further, ICER previously used patient and caregiver employment status and rates, and lost productivity data provided by an advocacy organization to estimate cystic fibrosis indirect costs [47] and the effect of unemployment on total costs for rheumatoid arthritis [48] but did not use such data for the SCD review.

The study must be interpreted within the context of several limitations. The study relied on a convenience sample and may not be generalizable to all patients and caregivers. The survey did not collect or differentiate sickle cell disease genotypes. Survey respondents were majority female which is not reflective of all patients with SCD since SCD is an autosomal recessive disorder. Respondents also reported high rates of patient commercial health insurance coverage which may generate different results than studies with higher rates of public health insurance coverage [49,50]. Unlike the Holdford study, the current research did not account for unpaid work activities, have more robust information on employment status, or ask about household size. Nonetheless, the survey results shed light on the burden of SCD on patients and caregivers and the importance of gathering information on patient and caregivers' perspectives.

Estimated lost monthly income was calculated based on the number of hours missed from work among individuals who were employed and daily income rate. The calculation does not include factors such as fringe benefits or employee discounts. Therefore, the estimated lost monthly income is likely an underestimate of the financial burden [51] of SCD on patients and caregivers.

This research was done as part of the 2019-2020 ICER cost effectiveness review of SCD. This ICER review was indefinitely suspended due to the COVID-19 pandemic and did not include ICER's final assessment of the clinical and economic benefits of the newer

medications or the evidence presentation and meeting that includes expert panel and stakeholder comments. Patients and caregivers did not get to share their perspectives during the evidence meeting presentation on the health and economic outcomes of crizanlizumab, voxelotor, and L-glutamine. Regardless, patients' and caregivers' perspectives would not have been incorporated into the ICER economic model and would have been solely contextual. Future cost effectiveness models should incorporate HRQL measures, caregivers' perspectives, and health equity adjustments to fully capture the value of treatments. Measures of health equity are important given the often-small sample sizes of people of color in clinical trials. Sickle cell clinical trials enroll a majority of Black/African-Americans participants due to the demographic of the impacted population. Given this, economists must be mindful of the implications of health economic models on communities that are not often included in the data or consulted on the impact of cost-benefit analyses on their lives.

5. Conclusions

Our findings show the importance of gathering patients' and caregivers' experiences in health economic assessments. Without asking these stakeholders their experiences and indirect costs, the analyses will underestimate the burden of disease. Collecting information on indirect costs will require additional investments by health economists but is important to providing a comprehensive assessment of medications and the disease.

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