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Title: The Impact of Vaso-Occlusive Crises and Disease Severity on Quality of Life and Productivity Among Patients with Sickle Cell Disease in the US

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ABSTRACT

Sickle cell disease (SCD) is a lifelong blood disorder affecting approximately 100,000 individuals in the United States (US). A number of new treatments have recently become available to improve SCD clinical outcomes, but it is unclear how treatment innovations that reduce disease severity could affect patients' humanistic and economic outcomes. To answer this question, an online survey of US adult residents with a self-reported SCD diagnosis was conducted. Humanistic outcomes based on health-related quality of life (HRQoL)) were assessed during and outside of vaso-occlusive crises (VOCs). Economic outcomes were measured by annual household income and whether the respondent received disability insurance. Among the 301 respondents completing the survey, average age was 34.4 years and 73.4% were female. Average HRQoL, measured using health utilities, were 0.311 (95% CI: 0.286, 0.337) during a VOC and 0.738 (0.720, 0.756) not during a VOC. The likelihood of claiming disability insurance was correlated with more frequent VOCs (0 VOCs: 12% vs. ≥4 VOCs: 47%, p=0.002) and disease severity (Severity Class II: 16% vs. Severity Class III: 39%, p=0.03). There was a weak relationship between VOC frequency and household income (0 VOCs: $47,488 vs. ≥4 VOCs: $34,569, p=0.06) and no evidence of a relationship between disease severity class and income (Severity Class II: $42,443 vs. Severity Class III: $36,842, p=0.29). In conclusion, disease severity, strongly predicted worse self-reported HRQoL, moderately predicted increased likelihood of collecting disability insurance, and weakly predicted lower household income levels.

INTRODUCTION

Sickle cell disease (SCD) is a lifelong chronic blood disorder affecting approximately 100,000 people in the United States (US).[1] SCD is a complex genetic disease with a multifactorial pathophysiology including multi-cell adhesion between red blood cells, white blood cells, platelets and endothelial cells, ultimately resulting in vaso-occlusive crises (VOCs).[2] VOCs are the hallmark of SCD and are the primary cause for hospitalization.[3] These recurrent episodes induce severe pain, can cause life-threatening complications, and are associated with increased risk of organ damage and mortality, and as such, affect a patient's health related quality of life (HRQoL).[4,5] The clinical and economic burden of SCD is well-documented [6,7] and some SCD treatments have demonstrated the potential to reduce acute care and hospitalization costs.[8-12] However, limited evidence exists surrounding how the severity of SCD affects patients' HRQoL, income, and productivity. In particular, there is limited evidence on the impact of a VOC on HRQoL and it is thus of interest to compare HRQoL during and outside of a VOC. The present study aims to shed greater light on these impacts.

Although a number of studies[7,13] have evaluated HRQoL among patients with SCD compared to those without SCD, little is known about health utilities in patients with SCD during and outside the experience of a VOC, particularly in the US. Many of the seminal studies on HRQoL and disease severity have occurred outside the U.S. or were limited to the inpatient setting. [13,14] Further, due to the frequency of VOCs and other causes of hospitalization, patients with SCD frequently lose educational and job opportunities, earn lower average income, have lower income growth, and are more likely to claim government disability insurance due to reduced income and physical impairments.[15-19] For instance, nearly three out of every four SCD patients reported that SCD symptoms affected them psychologically or physically at work. [20]

This impact may expand beyond simply missing days of work, and may extend to reduced promotion prospects, missed interviews, difficulties relocating for work, unwillingness to take on greater responsibilities, or reduced educational attainment.[16,19,20] In fact, lifetime earnings for patients with SCD were 36% lower than for patients without SCD. [21] While these studies demonstrate the impact of SCD as a whole, information on how SCD disease severity affects these outcomes is not well-understood.

The objective of this study was to evaluate the impact of SCD disease severity on patient HRQoL, income, and likelihood of receiving disability insurance among adults in the United States.

MATERIALS AND METHODS

Study design and data sources

This study was a non-interventional, cross-sectional, online survey study of patients with SCD. The aims of the study were to measure the impact of disease severity (measured by either disease class or number of VOCs) on three outcomes: utility, likelihood of claiming disability, and household income. Individuals were recruited through SCD patient advocacy groups and a market research group. The survey—which was part of a larger study described in more detail in Rizio et al.[22]—evaluated SCD patient HRQoL and life and work productivity, focused on collecting information around respondent history of complications and organ damage, home-managed VOCs, and retrospective EQ-5D responses during previous VOCs. Prior to the initiation of participant recruitment, the study protocol and all associated study materials (e.g., participant recruitment materials, informed consent, survey items) were approved by the New England Independent Review Board (IRB number 120180240).

Study population

Individuals recruited for this study were required to: be ≥18 years of age, have a self-reported SCD diagnosis, be a US resident, be able to provide informed consent, and be able to complete the survey in English. The survey was deployed between November 2018 and January 2019. Individuals were compensated for their participation. Some received a gift card in exchange for completing the survey; others received an equivalent number of points, which could be redeemed for items such as gift cards. The target recruitment goal was 325 patients.

Outcome measures

There were three outcome metrics of interest. The first outcome of interest of this study was health utility values. Utility is a continuous measure of health status or HRQoL, where a utility of 1 represents perfect health, and a utility of 0 represents death. A utility of 0.5 indicates that a person would be indifferent between living two years in that health state and 1 year in perfect health (sine 2 years x 0.5 utility = 1). Health state utilities were used as a measure in this study due to their relevance in clinical settings. They measure outcomes through a singular value, and as such, can be used as a common denominator for comparison across interventions, or within a disease area. The utility measures were derived from the EuroQoL Five Dimension 5 level (EQ-5D) scale. The EQ-5D survey responses were converted to EQ-5D health utilities using the United States EuroQoL value set.[13] Respondents completed the EQ-5D questions twice: once in reference to their health status when they were not experiencing a VOC, presented to respondents as a "pain attack (crisis)," and once in reference to their health status when experiencing a VOC. The responses were used to estimate EQ-5D health utilities not during VOC and during VOC.

The second outcome measures of interest were self-reported total household annual income in 2017, and the third outcome was whether the patient received disability insurance (i.e., Supplemental Security Income [SSI]). SSI provides income support for individuals who are blind, disabled or aged with little or no income. In 2018, the US federal government paid out $54.8 billion to the 8.1 million Americans who qualified for SSI.[23]

Disease severity definitions and patient characteristics

The study assessed how the self-reported outcomes of interest varied by SCD disease severity. The first measure of disease severity was the number of self-reported VOCs prior to the survey.

The second measure of disease severity was SCD severity class. These severity classes were developed through clinical expert opinion and relied on an algorithm for dividing patients into 4 disease severity classes, ranging from asymptomatic to Class I as the least severe, and Class III as the most severe. Individuals were assigned to the Asymptomatic Class if they self-reported no health problems due to SCD. Severity Class I was defined as symptomatic, but had no emergency department or hospital admissions in the past year; Severity Class II was defined as individuals who reported ≥1 emergency department visit or hospital admission for a VOC, or an SCD-related acute complication, but with no organ damage; and Severity Class III included individuals who self-reported having SCD-related organ damage. SCD-related complications were defined as the patient experiencing any of the following health conditions due to sickle cell disease: acute chest syndrome (ACS), cerebrovascular accidents, cerebrovascular disease, hepatic sequestration, hypersplenism, priapism, splenic sequestration, and stroke. SCD-related organ damage was defined as having avascular necrosis, erectile dysfunction, gall bladder disease, hearing loss, leg ulcer, microalbuminuria, pulmonary hypertension, renal failure, retinopathy,

sickle chronic lung disease, sickled hepatopathy, thromboembolic diagnosis, and thrombophilia, or venous thromboembolism. This disease severity classification was similar to one developed by a Delphi Panel of clinicians where the results were presented at the 2019 American Society of Hematology annual meeting.[24]

2.5 Statistical analysis

An initial analysis was performed to describe the characteristics of respondents. Continuous variables (i.e., age, utility not during VOC, utility during VOC) were summarized by their mean and 95% reference ranges. Binary or discrete variables (i.e., male; Black or African-American, household income level; married, living as married, or in a civil partnership; higher education level; currently receiving public disability assistance; receiving private insurance; counts of VOC; disease class) were reported as proportions of those who responded to the query. Summary statistics for each continuous or binary variable excluded patients who indicated they did not know or preferred not to say in response to the query generating that variable; a patient excluded from one variable was not necessarily excluded from all. Patients counted as having higher education were those reporting a 4-year college degree (e.g., BA, BS), an associate's degree (2-year college degree), graduate or professional degree (e.g., MBA, MS, MD, PhD), or some graduate education but no degree. Household income was recorded as one of 7 categories: Less than $25,000; $25,000-$49,999; $50,000-$74,999; $75,000-$99,999; $100,000-$149,999; $150,000-$199,999; $200,000 or more. To analyze as a continuous variable for linear regression and calculation of means, we used the mid-points of these categories: $12,500 for less than $25,000; $37,500 for $25,000-$49,999; $62,500 for $50,000-$74,999; $87,200 for $75,000-$99,999; $125,000 for $100,000-$149,999; $175,000 for $150,000-$199,999; and $225,000 for $200,000 or more.

To answer our first research aims, the study measured the relationship between disease severity and utility. Mean and 95% CI for EQ-5D utility not during crisis and EQ-5D utility during crisis, stratified by SCD disease class, were estimated. Pairwise comparisons were made using a t-test, and testing for joint differences across disease state levels were tested using an analysis of variance (ANOVA) evaluation tested using an F-distribution.

To understand the influence of patient characteristics on health state utility during and not during VOC, multivariate linear regression analyses were conducted. The variables explored were presence of organ damage (split into those recorded: avascular necrosis, gall bladder disease, hearing loss, hypersplenism/splenic sequestration, leg ulcer, pulmonary hypertension, renal failure), whether patients have complications (again split into those recorded: ACS, hepatic sequestration, priapism, stroke), whether VOCs were managed at home, and whether patients have no health-related problems with SCD. For regression models employed, estimates, standard errors (SE), and (students' *t*-test) *p*-values were reported for the intercept and slope (regression coefficient) of each covariate.

The analysis to evaluate the second aim—estimation of the relationship between disease severity and receipt of public disability insurance—involved calculating correlations as well as implementing unadjusted and adjusted logistic regression models. The association between the number of VOCs and receipt of public disability insurance was first measured using the Pearson's correlation. Next, both an adjusted and unadjusted logistic regression of current receipt of disability insurance by number of VOCs was conducted for age and income. Education was also investigated as a covariate but the ANOVA model found no evidence in favor of its inclusion ($p=0.3435$). There were only 18 patients (6.8% of a total 264) in the higher household income (>$100,000 per year) categories, which caused difficulty fitting an adjusted regression model. For

this reason, the income categories above $100,000 per year were merged when including a confounder in the disability assistance regressions. Predicted probability of receiving disability insurance with 95% CI based on regression models was also reported. These analyses were repeated to evaluate the association between SCD severity classes and current receipt of disability insurance. Household income categories above $100,000 were again merged when conducting adjusted analyses.

Two different approaches were used to measure the third aim: the relationship between disease severity and household income. Initially, a Somers' Delta test was carried out to evaluate the relationship between SCD disease severity (as measured by frequency of VOC and severity classes) and household income. To explore these associations further, a linear regression model was used to analyze the relationship between number of VOCs and income as a continuous outcome, while an ordered logistic regression model was used to analyze the relationship between SCD disease severity classes and income. Both regression analyses were conducted—firstly unadjusted, and then adjusted by age, gender and educational attainment. Predicted mean household income with 95% CI based on regression models was reported.

For interpretation of the *p*-values from regression analyses or statistical tests, American Statistical Association guidelines were followed and avoided the use of a strict significance threshold when interpreting p-values. [25] We instead assessed strength of evidence as weak (~0.1), moderate (0.01 to 0.001), or strong (<0.001). [26]

Sensitivity analysis

The utility during crisis was recalculated using alternative definition of SCD severity class III which removed damage to kidney and liver. As the survey defined kidney and liver damage

broadly, these definitions may apply to non-SCD related organ damage and thus individuals were re-classified to different disease severity classes ignoring these two indicators of organ damage.

RESULTS

Respondent characteristics

After posting the recruitment on patient advocates social media pages, 1,205 individuals submitted the screener. Of these, 708 did not meet the inclusion for the survey overall and 119 were over quota. Another 52 individuals were removed for being duplicate admissions or beginning the survey but not completing it, which left 326 individuals completing the survey. Of these, 25 individuals either failed quality checks, or did not answer key questions, ultimately leaving 301 individuals in the final analytic sample. A summary of these patients is provided in Table 1. Among these individuals, the average age was 34.4 years (95% reference range 18 – 56); 221 (73.4%) were female and 1 (0.3%) was non-binary. Mean household income was $38,021 (12,500 - 140,938) among the 264 individuals who responded to this question, and 52.5% of patients reported having higher-level education. The proportion of respondents covered by private insurance was 34.9% (105/301), while the proportion receiving public disability assistance was 37.5% (107/285). The survey included respondents from 34 states. Further, the share of respondents by Census Region was similar to the distribution of African-Americans across the US based on data 2018 Census data.

Based on self-report of VOC, as well as presence of complications and organ damage of individuals, 79.4% (239/301) were classified as Severity Class III, 12.3% (37/301) were Severity Class II, 7.3% (22/301) Severity Class I, and 1% (3/301) were asymptomatic. Responses from the questionnaire indicated that in the 12 months prior, 8.4% (25/301) experienced 0 VOCs, 9.4% (28/301) experienced 1 VOC, 14.7% (44/301) experienced 2 VOCs, 19.7% (59/301) experienced

3 VOCs, and 47.8% (143/301) experienced ≥4 VOCs. Respondents typically received care for their pain crisis (multiple responses allowed) either at home 49.8% (150/301) or in a hospital inpatient setting 39.2% (118/301).

Aim 1: Association between disease severity and health utilities

HRQoL, as measured using health utilities, varied across disease severity levels, and was lower when patients were experiencing a VOC compared to when they were not. (Table 1). The EQ-5D questions were not completed by all patients; 299 completed the EQ-5D when not experiencing VOC queries, and 292 completed the EQ-5D during VOC queries, with 2 patients reporting the former but not the latter. The estimated health utility value derived from EQ-5D when not experiencing VOC was 0.738 (95% CI: 0.720, 0.756) and during VOC was 0.311 (95% CI: 0.286, 0.337), indicating strong evidence of a difference ($p<0.001$).

The estimated health utility values not during a VOC derived from EQ-5D was 0.733 (95% CI: 0.713, 0.753) for Severity Class III and 0.775 (95% CI: 0.725, 0.826) for Severity Class II (Table 2). This result suggests >5% worse health status utility in Severity Class III than Severity Class II disease severity, although the ANOVA F-test p-value of 0.312 did not suggest evidence of a difference in utility across SCD severity classes while not in a VOC. The estimated health utility during VOC derived from EQ-5D was 0.286 (95% CI: 0.259, 0.313) for Severity Class III and 0.436 (95% CI: 0.360, 0.513) for Severity Class II (Table 1). Patients with SCD Severity Class III had 34% worse HRQoL than those with SCD Severity Class II. An ANOVA F-test for joint differences showed strong evidence of association between SCD severity class and utility during VOC ($p < 0.001$).

Patient characteristics did not have a major impact on HRQoL after accounting for overall disease severity. The results of the multivariate linear regression exploring impact of patient characteristics on utility during VOC and not during VOC are presented in Appendix 1. There is weak evidence that damage to spleen (hypersplenism/splenic sequestration), history of ACS, whether VOCs are managed at home, and whether they have no health problems related to SCD was associated with utility during crisis. There was no evidence of association with any other characteristics. There was only weak evidence that avascular necrosis, pulmonary hypertension, priapism, whether VOC was managed at home, and whether patients have no health-related problems with SCD are associated with utilities not during VOC. There was no evidence of association with any other characteristics.

Aim 2: Association of disease severity and receipt of disability insurance

The unadjusted logistic regression model of number of VOCs (0, 1, 2, 3, ≥4) on disability insurance (currently receiving or not) showed that the probability of receiving disability insurance among patients with SCD varied across VOC frequency in the previous year (Figure 1). The probability of receiving disability insurance for patients having 0 and ≥4 VOCs in the past year was 8% (95% confidence interval (CI: 2% to 28%) and 53% (45% to 62%), respectively. The Pearson's chi-squared p-value of <0.001 indicated strong evidence of an association between a greater number of VOCs, and probability of receiving disability insurance.

The adjusted logistic regression model (controlled for age and household income using 255 patients who reported required data) of number of VOCs (0, 1, 2, 3, ≥4) on disability insurance (currently receiving or not) showed that the highest probability of receiving disability insurance was among patients who experienced the highest number of VOCs (≥4) (Figure 1). The probability

of receiving disability insurance for patients having 0 and ≥4 VOCs in the past year, was 11% (95% CI: 5%, 21%) and 47% (95% CI: 38%, 56%), respectively.

Patients assigned to a more severe disease class were also more likely to receive disability insurance. The unadjusted logistic regression model of SCD class on disability insurance (currently receiving or not) showed that the probability of receiving disability insurance among SCD patients with Severity Class asymptomatic/Class I, Severity Class II and Severity Class III SCD was 33% (95% CI: 18%, 54%), 19% (95% CI: 9%, 36%), and 41% (95% CI: 34%, 47%), respectively. The Pearson's chi-squared p-value of 0.05 indicated moderate evidence of an association between SCD disease severity class and probability of receiving disability insurance.

Based on the results of a logistic regression model, adjusted for age and household income, of SCD class on disability insurance (currently receiving or not), the probability of receiving disability insurance among SCD patients with Severity Class asymptomatic/Class I, Severity Class II and Severity Class III SCD was 24% (95% CI: 10%, 48%), 18%)8% (95% CI: 8%, 36%) and 388% (95% CI: 32%, 46%) respectively. In other words, the probability of receiving disability insurance was highest for patients with greatest SCD severity.

Aim 3: Association of VOC frequency or disease severity with household income

VOC frequency was weakly associated with a respondent's household income. Among 264 patients who reported both income category and history of VOC, the unadjusted predicted mean income for patients with SCD experiencing 0 and ≥4 VOCs in the past year was $46,194 and $35,284 respectively (Figure 2). The Somers' Delta test showed that there was a negative association between increasing number of VOCs and income level (-0.11, with 95% confidence interval -0.21 to -0.01). A linear association test p-value of 0.1 indicated weak evidence of a lower mean household income in relation to number of VOCs experienced.

Although average household income was lower for patients in a more severe disease class, there was no statistical evidence of this relationship ($p = 0.4$). The unadjusted predicted mean income among patients with asymptomatic/ Severity Class I, Severity Class II and Severity Class III SCD was $44,282, $40,846 and $37,364 respectively. When adjusted for age, gender and education, the predicted mean income among patients with asymptomatic/Severity Class I, Severity Class II, and Severity Class III SCD was $38,260, $37,280 and $33,138 respectively. The Somers' Delta test showed evidence that there could be some negative association between increasing SCD class and household income level (-0.072, with 95% confidence interval -0.234 to 0.090).

Sensitivity analysis

The estimated health state utilities of the sensitivity analysis removing damage to kidney and liver from Severity Class III SCD are presented in Appendix 2. Comparing with the base case definition of Severity Class III there is no impact on utilities.

DISCUSSION

This study is one of the first we are aware of that measures HRQoL of adult patients with SCD in the US population. Further, while a number of new treatments (l-glutamine, crizanlizumab, and voxelotor) have recently become available to improve SCD clinical outcomes, it is unclear how treatment innovations that reduce disease severity could affect patients' humanistic and economic outcomes. Findings from this survey contribute largely to the existing evidence base surrounding SCD by quantifying the true impact of VOCs/disease severity in economic terms. We found the magnitude of this HRQoL impact was larger than previous studies. A previous study on SCD patients in the United Kingdom demonstrated that higher pain scores on Visual Analog Scale (VAS) were associated with lower health utilities

among patients with SCD, but the study's estimated utility levels during VOC (0.39)[13] were higher (i.e., not as severe) than those found in this study (0.311). Both studies support the notion that VOC frequency meaningfully impacts HRQoL among patients with SCD. Among patients reporting HRQoL not during a VOC, this study did not observe a monotonic trend across the disease classes (i.e., asymptomatic to Severity Class I to Severity Class II), likely in part as there were small sample sizes for asymptomatic and Severity Class I respondents.

The study also found that SCD disease severity was correlated with patient productivity. There was strong evidence of an association between number of VOCs and receipt of disability insurance, but the trend was not fully monotonic. This finding may have occurred as we have limited confounding variables to adjust this model, or that the relationship between income and disability insurance is non-linear due to income-level cutoffs for receipt of disability insurance. Although this study provides moderate support for an association between receipt of disability insurance and SCD class, the trend did not always indicate that a worsening in SCD severity class resulted in an increase in probability of receiving disability insurance.

We also found an association between number of VOCs and household income, but no evidence of a relationship between SCD severity class and income. This finding mirrors earlier studies that have shown negative impact of SCD-related VOCs on work productivity. Rizio et al. demonstrated that patients with more frequent and severe VOCs were more likely to have experienced losing a job or having to reduce work hours due to their SCD.[19] Another study of patients from Virginia Commonwealth University's adult sickle cell clinic reported impact of SCD symptoms on absenteeism, presenteeism, and lost work. Researchers reported 75% patients missed an average 36.75 days in the last year due to SCD symptoms, which amounts to an average of approximately $7,506 lost wages each year. An estimated 73% of patients included in

the study reported that SCD symptoms affected them psychologically or physically at work, showing a negative impact on presenteeism.[20] One study found that lifetime income was 36% lower for patients with SCD compared to those without SCD.[21]

The results of the analyses of this study can be used in a variety of contexts. HRQoL impacts are helpful for understanding how disease severity affects patients' lives in a numerical way. Economic outcomes are pertinent as treatments that reduce VOCs or decrease disease severity have additional benefits beyond just medical impacts. While FDA approved treatments for SCD [27,28] have been extremely limited despite the higher prevalence of SCD, the treatment landscape is emerging. Three new therapies—crizanlizumab[11], l-glutamine[29], and voxelotor[30]—have been approved since 2017, and there are several novel therapies targeting new pathways and gene therapies currently in the pipeline.[31] The economic impacts of these treatments are important as treatments that reduce VOCs or decrease disease severity have additional benefits beyond just medical impacts. From a clinical standpoint, findings from this study indicate that mitigating disease severity through a reduction in VOCs as a result of effective emerging therapies have significant impacts on patient HRQoL and productivity. When researchers or health technology assessment agencies measure the value of these new treatments, the results from this study can be used to inform the likely quantitative impact of reduction in VOCs or disease severity on economic and humanistic outcomes.

While 326 individuals completed the survey, 25 failed quality checks or did not answer key questions, which resulted in a sample of 301 responses for analysis. Small numbers of these respondents did not respond to certain questions (e.g. 299 completed the EQ-5D questionnaire; 264 provided information on their mean household income; 255 reported VOC frequency, whether they were on disability insurance, and household income). However, these small

reductions in sample size could result in bias if they were there was a systematic reason for exclusion.

This study had a number of other limitations. First, while this study identified a relationship between disease severity and household income and receipt of disability insurance, the relationship may or may not be causal in nature. Second, the survey was also limited to adults in the United States and the results should not be extrapolated to other countries or pediatric patients. Third, the patients who participated in the study represent a convenience sample. Respondents needed to have access to a device with internet connectivity, and feel comfortable navigating through an online survey. As such, age and computer literacy may have further restricted the generalizability of the results. The sample was also skewed towards patients who were more severely ill (Severity class III) compared to the general SCD population, as current organ damage rates reported in this survey were higher than organ damage rates in the literature.[32] Fourth, while more than 9 of every 10 respondents in this survey had a VOC, one study of commercially-insured individuals found that more than 6 in 10 did not have a VOC.[33] While this sample composition allows us to make conclusions about the gradations of how disease severity affects outcomes of interest, the results are not fully representative of the overall US adult SCD population. Fifth, two self-reported health characteristics inexactly mapped to clinical definitions. Specifically, renal failure does not perfectly correlate to the 'damage to kidneys' question recorded by the survey, nor does hepatic sequestration correspond exactly to the 'damage to liver' question. To address this issue, we excluded damage to liver and damage to kidneys from health state definitions in a sensitivity analysis and found minimal changes to our estimates. Finally, the survey was limited to English speakers only and is not representative of non-English speaking US residents with SCD.

In conclusion, disease severity—as measured by VOC frequency and disease severity class—strongly predicted worse self-reported HRQoL, moderately predicted increased likelihood of collecting disability insurance, and weakly predicted lower household income levels. While previous studies have estimated the economic and clinical burden of SCD compared to patients without the disease, this study explicitly examines how disease severity among patients with SCD affects these outcomes. New treatments for SCD have the potential not only to impact patient clinical outcomes, but overall quality of life, patient productivity, and government costs for disability insurance.

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