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Predictors of Health-Related Quality of Life over Time Among Adolescents and Young Adults with Sickle Cell Disease

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Abstract Little is known about what factors affect the health-related quality of life (HRQoL) of adolescents and young adults (AYAs) with sickle cell disease (SCD), and how their HRQoL changes over time. This retrospective study included 87 AYAs attending a SCD Adolescent Clinic who completed a measure of HRQoL at each visit over the course of approximately 1.3 years. Results suggested that the following were associated with poorer physical HRQoL: being female, more healthcare utilization events, and presence of internalizing symptoms. Internalizing and externalizing symptoms were the only factors correlated with poorer psychosocial HRQoL. Generalized linear mixed models indicated that physical and psychosocial HRQoL improved among all participants during the assessment period, and those with externalizing behaviors reported faster improvement in physical HRQoL over time. AYAs with SCD may benefit from early mental health screening and intervention to optimize clinical care.

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Introduction

Sickle cell disease (SCD) is a chronic hereditary disease affecting more than 90,000 individuals in the United States (Brousseau, Panepinto, Nimmer, & Hoffmann, 2010), most of who are of African ancestry. Individuals with SCD experience painful vaso-occlusive events, resulting in frequent emergency room visits and hospitalizations. SCD also places individuals at risk for significant medical complications, including stroke, renal dysfunction, and pulmonary disease. The physical consequences of the disease result in a loss of social and academic opportunities during critical periods of cognitive, emotional, and social development (Wison Schaeffer et al., 1999). One such critical period may be adolescence and young adulthood (AYA), when individuals are forming romantic relationships, assuming more responsibilities (e.g., working, driving, and disease self-management), and eventually leaving the home (Arnett, 2000). These challenges faced during AYA are further exacerbated by factors associated with having a chronic illness (DeBaun & Telfair, 2012; de Montalembert, Guitton, & the French Reference Centre for Sickle Cell, 2014), including the stress of increased healthcare costs and less coverage by private insurance (Dickerson, Klima, Rhodes, & O'Brien, 2012) while navigating the transition to an adult medical setting.

SCD, like many chronic conditions, affects both physical and psychosocial areas of functioning. Therefore, to better understand the impact of SCD, research has incorporated the assessment of health-related quality of life (HRQoL). HRQoL is a multidimensional construct that encompasses physical symptoms and burden, as well as psychosocial well-being. Studies on individuals with SCD have predominantly focused on HRQoL among children and adults, suggesting these individuals have physical and psychosocial functioning comparable to or worse than other chronic diseases (Panepinto & Bonner, 2012). However, less is known about the HRQoL among AYAs with SCD, including what factors may predict change in HRQoL over time. This lack of understanding about HRQoL among AYAs is an especially important consideration for AYAs given the rapid psychosocial development that occurs during this period. Furthermore, the process of transitioning to adult-focused medical care takes years to complete and has been suggested to start as early as 12 years of age (DeBaun & Telfair, 2012), which indicates a need for better understanding of factors that influence health-related and psychosocial outcomes over time.

Patient and family demographics have been examined as predictors of HRQoL among children and adults with SCD, including gender and age of the patient, parental education, and socioeconomic status (Palermo, Riley, & Mitchell, 2008; Palermo, Schwartz, Drotar, & McGowan, 2002; Panepinto, O'Mahar, DeBaun, Loberiza, & Scott, 2005; Panepinto, Pajewski, Foerster, Sabnis, & Hoffmann, 2009; Robinson, Daniel, O'Hara, Szabo, & Barakat, 2014). While equivocal findings have been reported about whether several of these factors are significant predictors of physical HRQoL among individuals with SCD, female gender has been associated with poorer self-reported physical HRQoL among both children and adults with SCD (Palermo et al., 2002; Dampier et al., 2010). Age is one of the few demographic variables consistently associated with psychosocial HRQoL. (Panepinto et al., 2009) reported that older children and adolescents had increased odds of poorer psychosocial HRQoL as reported by parents. This relationship was not significant for child-report of psychosocial HRQoL. How these factors may be related to patient-reported HRQoL among AYAs is yet to be determined.

Disease severity, including the occurrence of disease-related complications, comorbid conditions (e.g., vaso-occlusive events, acute chest syndrome, priapism), and treatment modalities (e.g., use of hydroxyurea), as well as healthcare utilization (e.g., hospitalizations, emergency department visits.), have also been explored as predictors of HRQoL. More severe disease and greater healthcare utilization are associated with worse physical HRQoL of children and adolescents as reported by parents (Dampier et al., 2010; Palermo et al., 2002; Panepinto et al., 2009) and of adults with SCD (Dampier et al., 2011). Dampier et al. (2010) also found this relationship when using indicators of disease severity and healthcare utilization within 1 year prior to HRQoL assessment, suggesting that these factors may have a lingering effect on HRQoL over time. One disease severity indicator that has been associated with improved parent-reported HRQoL among children and adolescents is the use of hydroxyurea, a medication typically prescribed to individuals who have been diagnosed with acute chest syndrome or who have had more vaso-occlusive pain crises (Thornburg, Calatroni, & Panepinto, 2011).

Another predictor of HRQoL is mental health status. Psychological symptoms or neurobehavioral comorbidities have been associated with poorer parent-reported psychosocial HRQoL among children and adolescents with SCD (Panepinto et al., 2005, 2009), though this relationship has not been universally identified (Palermo et al., 2008). Among adults with SCD, symptoms of psychological distress have also been predictive of poor HRQoL in both the physical and emotional domains (Levenson et al., 2008). Symptoms of psychological distress have yet to be assessed among AYAs with SCD in relation to physical and psychosocial HRQoL, nor has the impact of symptoms of psychological distress on HRQoL over time been explored.

The aims of the current study were to (1) determine the relationship among demographics, disease severity, healthcare utilization, symptoms of psychological distress, and baseline HRQoL among AYAs with SCD; and (2) explore which variables predict change in HRQoL over time. It was hypothesized that the following would be associated with poorer physical HRQoL: being female; older age; a lower socioeconomic status (i.e., public insurance coverage); a more severe disease genotype; greater number of comorbid medical conditions; more unscheduled healthcare (e.g., emergency department visits [ED]). Furthermore, the presence of symptoms of psychological distress was predicted to be associated with poorer psychosocial HRQoL.

Method

Participants

This retrospective study used information collected from January, 2009, through December, 2011, and was approved by the institutional review board. As seen in Table 1, participants included 87 AYAs between the ages of 13 and 22 (M = 16.6 ± 2.1 years). The sample was 99 % African American, with one participant self-identifying as Hispanic. Approximately half of participants were diagnosed with more severe genotypes of SCD (Hb SS or Hb Sβ0Thal), with the remaining individuals having Hb SC or Hb Sβ + Thal. Participants were patients attending a SCD Adolescent Clinic at a pediatric hospital located in a Midwestern metropolitan city, which serves approximately

Table 1 Means and standard deviations for demographics, disease severity, healthcare utilization, mental health status, and health-related quality of life

n = 87	Mean (SD)	Range
Demographics		
Age (years)	16.6 (2.1)	13–22
Age distribution[a]		
Adolescents: 13–18 years (*n* = 62)	15.7 (1.4)	
Young adults: 18–22 years (*n* = 25)	19.2 (1.2)	
Ethnicity (% African American)	98.9 %	
Gender (% male)	51.7 %	
Private insurance	39.1 %	
Medicaid, medicare, none	60.9 %	
Disease severity		
Genotype		
Hb SS/Hb Sβ0Thal	52.8 %	
Hb SC/Hb Sβ + Thal	47.2 %	
SCD-related comorbid conditions (number of)	0.62 (0.67)	0–2
Received hydroxyurea (% yes)	18 %	
Healthcare utilization		
Hospital admissions	1.11 (2.13)	0–12
Duration of hospital admissions (days)	4.83 (10.96)	0–66
Emergency room visits	1.02 (1.68)	0–9
Mental health status		
Psychiatric symptoms (% yes)		
Internalizing disorder	25 %	
Externalizing disorder	13 %	
Health-related quality of life (PedsQL)		
Physical	72.70 (16.32)	34.38–100.00
Psychosocial	72.48 (14.72)	35–100.00

PedsQL pediatric quality of life inventory, *SCD* sickle cell disease

[a] Participants who were in high school at baseline completed the Adolescent Version of the PedsQL, while those who had graduated high school completed the Young Adult Version

110 AYAs annually. Patients in the SCD Adolescent Clinic are followed every 6 months and are seen by a physician, nurse practitioner, nurse clinician, social worker, psychologist, and a genetic counselor to address both medical and psychosocial concerns.

Procedures

Participants completed a self-report questionnaire of HRQoL during consecutive routinely scheduled SCD Clinic visits (M = 2, max = 5), averaging 490 days between the initial completion of the self-report questionnaire (baseline) and the most recent (final follow-up). The questionnaire is given as part of patients' healthcare and is reviewed by the psychologist with the patient during a routine clinic visit. Areas identified as concerning are discussed with the patients, as well as the medical team, to facilitate discussion on coping skills and problem-solving.

Measures

Demographics

The following demographic variables were gathered from participants' electronic medical chart: age; gender; insurance coverage (private vs. public or uninsured).

Disease Severity

Indications of disease-severity included SCD genotype, the number of SCD-related comorbid medical conditions and the use of hydroxyurea, all of which were collected from participants' medical chart. SCD-related comorbid medical conditions were defined as being medical conditions that result from having SCD and were present within the 6 months prior to the first HRQoL assessment (baseline). For the purposes of this study, the following conditions were considered SCD-related: stroke, pulmonary hypertension, kidney disease, cholecystectomy, splenectomy/splenic sequestration, acute chest syndrome, priapism, avascular necrosis, leg ulcers, nocturnal enuresis, delayed growth or puberty, and sleep apnea related to enlarged tonsils. SCD can affect multiple organ systems, and patients may experience none, some, or all of these conditions. Therefore, the number of SCD-related comorbid conditions experienced by each participant was totaled. Whether patients received hydroxyurea was recorded as a dichotomous variable (no/yes).

Healthcare Utilization

The following healthcare utilization variables that occurred within the 6 months prior to the first HRQoL assessment were included: number of hospitalizations; duration of hospitalizations; number of ED visits.

Symptoms of Psychological Distress

Participants attending the SCD adolescent clinic were seen by a psychologist and social worker, who conducted interviews pertaining to psychosocial functioning. When symptoms of psychological distress were present, the symptoms were noted in the online medical chart. Furthermore, if a participant had been seen by a mental healthcare professional and notes were available to the clinic team, the symptoms were also added to the medical chart. Symptoms of psychological distress were categorized as either internalizing (e.g., depressive and/or anxiety symptoms) or externalizing (e.g., inattentiveness, hyperactivity and/or oppositional behavior). Both categories of psychological distress were dichotomized (no/yes).

HRQoL

The pediatric quality of life inventory (PedsQL) generic core scales (Varni, Seid, & Kurtin, 2001) is a 23-item self-report (for ages ≥5) measure of general HRQoL that yields information on the physical, emotional, social, and school functioning of children, adolescents, and young adults during the past 4 weeks. Mean scores are based upon a 5-point Likert scale and then transformed into a 0–100 scale, with higher scores suggesting better functioning. This study used the physical psychosocial summary scores. Participants between the ages of 13 and 17 completed the Adolescent Version of the PedsQL, while those between the ages of 19 and 22 were given the Young Adult Version (Varni & Limbers, 2009). Participants who were 18 years of age were given the Adolescent Version if they were still in high school or continuing to live with parents. Otherwise, 18-year-old participants were given the Young Adult Version. Means for the study sample can been seen in Table 1. Because the Adolescent and Young Adult Versions only vary slightly in wording, the responses were combined for analyses. For example, the Adolescent Version reads "I have trouble getting along with other teens," whereas the Young Adult Version states "I have trouble getting along with other young adults." Similarly, references are made to school in the Adolescent Version ("It is hard to pay attention at school"), while the Young Adult Version incorporates work as well ("It is hard for me to pay attention at work or school").

The PedsQL has been used extensively in studies with healthy, chronically ill, and individuals with SCD of various age groups (McClellan, Schatz, Sanchez, & Roberts, 2008; Panepinto, Pajewski, Foerster, & Hoffmann, 2008; Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002; Varni, Burwinkle, Rapoff, Kamps, & Olson, 2004; Varni, Limbers, & Burwinkle, 2007). In this study, the internal consistency for the Adolescent Version was excellent: 0.79 (physical health score) and 0.85 (psychosocial score). For the Young Adult Version, internal consistency measures were also favorable: 0.79 (physical health score) and 0.78 (psychosocial score).

Statistical Analyses

Study Aim 1

Pearson and point-biserial correlations were used to examine the relationship between predictor variables, including demographic (age, gender, insurance coverage), disease severity (genotype, number of SCD-related comorbid conditions, use of hydroxyurea), healthcare utilization (number of hospitalizations, duration of hospitalizations, number of ED visits), and psychological distress (presence of an internalizing or externalizing symptoms), and baseline levels of physical and psychosocial HRQoL.

Table 2 Pearson and point-biserial correlations between predictors and health-related quality of life

	r	
	Physical HRQoL	Psychosocial HRQoL
Demographics		
Age (years)	.05	.21
Gender (male vs. female)	−.27*	−.09
Insurance status (private vs. public/none)	−.09	−.01
Disease severity		
Genotype (Hb SS/Hb Sβ0Thal vs. Hb SC/Hb Sβ + Thal) + Thal)	.05	−.12
SCD-related conditions (total number)	−.01	.04
Hydroxyurea (no vs. yes)	−.06	.14
Healthcare utilization		
Hospitalizations (total number)	−.25*	−.16
Duration of hospitalizations (days)	−.23*	−.13
Emergency room visits (total number)	−.24*	−.16
Mental health status		
Internalizing symptoms (no vs. yes)	−.30**	−.29**
Externalizing symptoms (no vs. yes)	−.10	−.26*

HRQoL health-related quality of life, *SCD* sickle cell disease

* $p \geq .05$: ** $p \geq .01$

Study Aim 2

To explore what predictors influence HRQoL over time, generalized linear mixed models (GLMM) with random intercept effects were employed. First, change in physical and psychosocial HRQoL over time without the inclusion of predictors was analyzed. Next, interaction terms were created using the predictors that were significantly associated with physical or psychosocial HRQoL at baseline and time (days between administrations) to determine whether predictors affected the trajectory of HRQoL.

Results

Study Aim 1

Associations between predictors and HRQoL can be seen in Table 2. Being female was correlated with poorer physical HRQoL, as well as a greater number of hospital admissions, longer hospital stays, and a greater number of ED visits. Internalizing symptoms were also associated with poorer physical HRQoL.

Psychosocial HRQoL was only significantly correlated with the presence of psychological distress such that experiencing symptoms of an internalizing or externalizing disorder was associated with poorer psychosocial HRQoL.

Study Aim 2

GLMM analyses indicated that, in general, participants reported improved physical and psychosocial HRQoL over time (physical: $\beta = .01$, $SE = .00$, $p = .027$; psychosocial: $\beta = .01$, $SE = .00$, $p = .024$). Interaction terms between the predictor variables (gender, number of hospital admissions, duration of hospital stays number of ED visits, and psychological distress) and time were then added to the model. A significant symptoms of psychological distress x time interaction suggested that participants with externalizing symptoms reported faster improvement in physical HRQoL over time than those without such symptoms ($\beta = .04$, $SE = .02$, $p = .039$). No other significant interactions between predictors and time were identified.

Discussion

This is the first study to examine demographic, disease severity, and psychological distress variables as predictors of self-reported HRQoL among a clinic sample of AYAs with SCD. In addition, this is the first investigation to explore which factors may predict HRQoL over time. Lower baseline levels of physical HRQoL were associated with being female, a greater number of hospitalizations, longer hospital admissions, a greater number of emergency room visits, and the presence of internalizing symptoms. The presence of internalizing or externalizing symptoms was the only factor associated with psychosocial HRQoL at baseline. Longitudinal analyses suggested that, in general, physical and psychosocial HRQoL improved over time, though physical HRQoL improved more quickly among those with externalizing symptoms.

The association between being female, utilizing more healthcare, and poorer physical HRQoL is consistent with previous studies on children and adults with SCD (Dampier et al., 2010, 2011; Palermo et al., 2002; Panepinto et al., 2009). Women report greater deep tissue pain sensitivity than men across multiple chronic pain conditions, which may be modulated by hormonal differences (Traub & Ji, 2013). More trips to the hospital and/or ED, and longer hospital stays would suggest greater physical impact of the disease. However, these variables did not predict physical HRQoL over time. Both physical, as well as psychosocial, HRQoL significantly improved as time progressed, suggesting that gender and healthcare utilization events may not have a long-term influence on physical functioning. Another important factor to consider is the presence of a psychologist in clinic as a member of the multidisciplinary treatment team. The more clinic visits patients attend, the more exposure they have to a psychologist who is providing brief psychosocial interventions and support. This likely helps patients cope with hospitalizations and other negative aspects of their disease, though further research is needed to determine if interactions with a psychologist explains the improvement in HRQoL over time. Additionally, individuals are served both as inpatients and outpatients by a multidisciplinary medical team with a focus on early intervention for medical, as well as psychosocial needs. This system for fast and aggressive responses to burdensome symptoms may have also mitigated whether medical variables predicted change in HRQoL over time.

Symptoms of psychological distress were the only predictors to be associated with both physical and psychosocial HRQoL. The correlation between the presence of internalizing symptoms and poorer physical HRQoL has also been found among adults with SCD (Levenson et al., 2008), as well as parent-report of physical HRQoL among children with SCD (Panepinto et al., 2009). Therefore, psychological distress may hinder the well-being of AYAs with SCD more than other types of disease-related burdens and should be considered for screening and early intervention in the clinic setting. One exception to this relationship between psychological distress and HRQoL was the surprising finding that those with externalizing symptoms reported faster improvements in physical HRQoL than those without externalizing symptoms. One explanation may be that oppositional behavior towards authority figures results in limited focus on internal cues. This defiant perspective in conjunction with limited attention paid to internal sensations, such as pain, could help these individuals push past the physical limitations of SCD. Another possibility is that individuals with externalizing symptoms receive more attention and intervention from the treatment team because of their behavior, which could result in improved physical outcomes. Differences in response to both psychosocial interventions and psychotropic medications among those with externalizing versus internalizing symptoms should be considered in future studies.

The current investigation makes several contributions. This study is the first to examine predictors of HRQoL among AYAs attending an adolescent SCD clinic. The importance of providing transition assistance to adolescents as they begin assuming more responsibility for their healthcare has been widely recognized (de Montalembert et al., 2014; Friedman, Holmbeck, DeLucia, Jandasek, & Zebracki, 2009; Henderson, Friedman, & Meadows, 2010; Lyons, Becker, & Helgeson, 2013). Therefore, it is critical to understand what factors are predictive of HRQoL among this unique age group that is now being seen in clinics designed to facilitate the transition to adult medical healthcare, as well as assist physicians and mental healthcare providers in identifying which patients may be at risk for poorer HRQoL. Also, the current investigation is the first to examine change in HRQoL over time as a function of demographic, disease severity, and symptoms of psychological distress. Because HRQoL is not a static construct, it is important to assess how quality of life changes over time for these individuals living with a chronic illness.

Limitations should be noted for this study. First, the study sample was relatively small, which reduces statistical power and limits the ability to detect significant relationships between variables. Despite the small sample, several significant findings emerged that should be considered pilot data for further investigation of predictors of HRQoL over time. Second, the number of follow-ups and duration between follow-ups varied, with the average time between baseline and the final follow-up being a year and 4 months. Because many transition clinics follow adolescents through young adulthood, ideally longitudinal studies of AYAs would measure changes in HRQoL across many years. Third, improvement in HRQoL could be a reflection of regression to the mean as more symptomatic patients may present to clinic and therefore show more improvement over time. Ideally, individuals would be recruited from a roster of all available patients, and not just represent those who attend clinic, to more accurately capture aspects of the larger SCD population. However, the sample represented in the current study had a range in disease severity indicators, suggesting that among those who attend clinic, patients had variability in health status.

Findings from the current study suggest multiple factors are associated with poor physical HRQoL among AYAs with SCD, but only symptoms of psychological distress were correlated with both physical and psychosocial HRQoL. This result highlights the importance of screening and addressing mental health concerns in the clinic setting among AYAs. In general, HRQoL appears to improve over time among AYAs, and the only factor to affect the trajectory of HRQoL was the presence of externalizing symptoms, which warrants further investigation. Future research should also consider examining HRQoL among patients who attend clinics with varying levels of staff support and services to determine whether the clinic environment plays a more prominent role than physical/psychosocial symptom burden. While progress has been made in understanding the experiences of individuals with SCD, questions still remain about how this disease affects HRQoL over time and what factors predict either positive or negative changes. This question is especially important when considering the unique challenges that arise for AYAs, who are in the process of gaining more autonomy in their medical care. Identifying these factors will assist in providing optimal care to individuals with SCD as they transition to adult medical settings.

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Conflict of Interest First (Jackson), second (Lemanek), third (Clough-Paabo), and fourth (Rhodes) authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation of the Institutional Review Board of Nationwide Children's Hospital and with the Helsinki Declaration of 1975, as revised in 2000. The study was approved as Exempt, and so informed consent was not required.

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