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Health-related Quality of Life Predictors in Children and Adolescents with Sickle Cell Disease: A Systematic Review

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Authors' contributions

This work was carried out in collaboration between all authors. All the authors participated in the design of the study. Author AOO conceived the study, performed the literature searches, synthesis and analysis, and wrote the draft manuscript. Author YG advised on acquisition of data and analysis. Author JL participated in the sequence alignment of data, and coordination of the study. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of this systematic review is to examine the predictors of HRQL(health-related quality of life) in children and adolescents (aged 18 years and under) with SCD(Sickle Cell Disease).
Methodology: A systematic review was conducted to identify published articles meeting defined inclusion criteria to identify determinants of HRQL in children and adolescents with SCD.
Results: Children and adolescents with SCD have poor HRQL compared with healthy peers, normative populations or siblings. A number of socio-demographic variables, socioeconomic markers and psychosocial factors along with clinical measures predict HRQL in the study population. These include child demographics, family income, parental support, depression, comorbidities and frequency of hospitalisation.
Conclusion: In managing SCD in children and adolescents, healthcare providers should pay attention to psychosocial variables along with clinical measures. This holistic approach to disease management may help to mitigate the adverse impact of the disease on people with SCD.

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Keywords: Health-related quality of life; sickle cell disease; predictors; children and adolescents; measures.

1. INTRODUCTION

Sickle Cell Disease (SCD) is a hereditary haematological disorder with severe physical, psychological and social consequences for both those affected and their families [1]. The World Health Organisation has adopted a management and prevention agenda for the disease as a global public health priority [2,3]. The disease is particularly prevalent in sub-Saharan Africa; Spanish-speaking regions in South and Central America, the Caribbean and India but has a global spread through migration and affects millions of people [4].

SCD affects 10,000-15000 people in both the United Kingdom and France [5]. The incidence of those having the sickle cell trait (SCT) of the most common and severe form of SCD - homozygous (HbSS) was 15.5 per 1000 births in the United States [6]. In the Eastern province of Saudi Arabia, the prevalence was 21% SCT and 2.6% SCD [7]. SCT prevalence ranges between 10% and 40% across equatorial Africa and 15% to 30% in West Africa [8]. SCD is responsible for the equivalent of 5% of under-five deaths in Africa with up to 16% in West Africa [8]. Nigeria, India and the Democratic Republic of Congo are the most affected countries and combined are responsible for 77.6% of new-borns with SCD globally [9,10]. The disease is estimated to affect 0.5% of people in Nigeria, with 24% SCT prevalence [2,11]. Annual new-borns with SCD has been projected to reach 140,000 in Nigeria by 2050 [9]. SCD also places huge economic burden on healthcare systems, for example during 2005, medical expenditure on SCD in USA averaged $11,702 for children with medical coverage [12].

Medical intervention through the use of antibiotic prophylaxis, neonatal screening, analgesics and vaccines has significantly increased the median survival age of SCD patients to 58 years in the USA [13], this was 14.3 years four decades ago [14]. For example, in the USA, SCD-related deaths of children below four years fell by 42% between 1999 and 2012 as a result of vaccination [4,15]. The increase in survival rate and the consequent burden of the disease has led to the need to investigate the quality of life (QoL) of the patients and associated factors for better management of the disease.

The concept of health-related quality of life (HRQL) emerged in the 1970s as a construct to define QoL with respect to how an illness, its complications and treatments affect the patient [16,17]. Advantageously, QoL evaluation puts patients at the centre of inquiry and gives weight to their opinions [18].

The HRQL of chronic disease patients is generally low and for SCD, studies have shown that patients generally have impaired HRQL compared to those without SCD [19-21]. Various instruments have been developed to measure the impact of chronic diseases on HRQL. Efforts have also been directed at investigating the factors that affect HRQL in order to minimise the negative impact of the disease. This study aims to systematically review work exploring HRQL in children and adolescents living with SCD (CALSCD) and to identify the determinants.

2. METHODS

This study followed the format of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [22]. The electronic databases searched included Science Direct, MEDLINE, CINAHL and PsyARTICLES. Search terms consisted of (Health-related quality of life OR HRQL OR HRQL OR quality of life OR QOL OR health status OR patient-reported outcome OR Well-being) AND (Sickle cell anaemia OR sickle cell disease OR haemoglobinopathies OR HbSS OR HbSC OR SCD OR SCA OR sickle cell disorder).AND (predictors OR factors OR determinants).

2.1 Inclusion Criteria

- Articles published in English language.
- Children and adolescents (aged ≤18) with SCD.
- HRQL measured with a validated instrument.
- Any reported variable associated with HRQL.
- Articles published between January 2000 and December 2015.

- Peer-reviewed articles with full-text available online.

2.2 Exclusion Criteria

- Articles that did not measure HRQL as outcome variable.
- Articles that focused on adult populations (≥ 18 years of age).
- Studies which were not written in English.

3. RESULTS

The initial search yielded a total of 13,414 articles (see Fig. 1). A filter 'quality of life' reduced the articles to 91. These were screened on titles and abstracts. Duplicates and articles that did not meet the inclusion criteria were removed leaving 14 articles for review. Two additional articles were added through searching of reference lists.

3.1 Characteristics of Studies Reviewed

Ten of the studies originated from the USA, two from Saudi Arabia and one each from Brazil, India, Netherlands and Nigeria (Table 1). The mean ages of participants ranged from 8.97±5.28 to 16.9±1.7. Three of the studies focused specifically on adolescents while others combined children and adolescents together. Two of the studies were longitudinal, one a prospective study, nine cross-sectional and four case-control studies. The proportion of HbSS phenotype ranged between 62.5% and 95.2% among the participants.

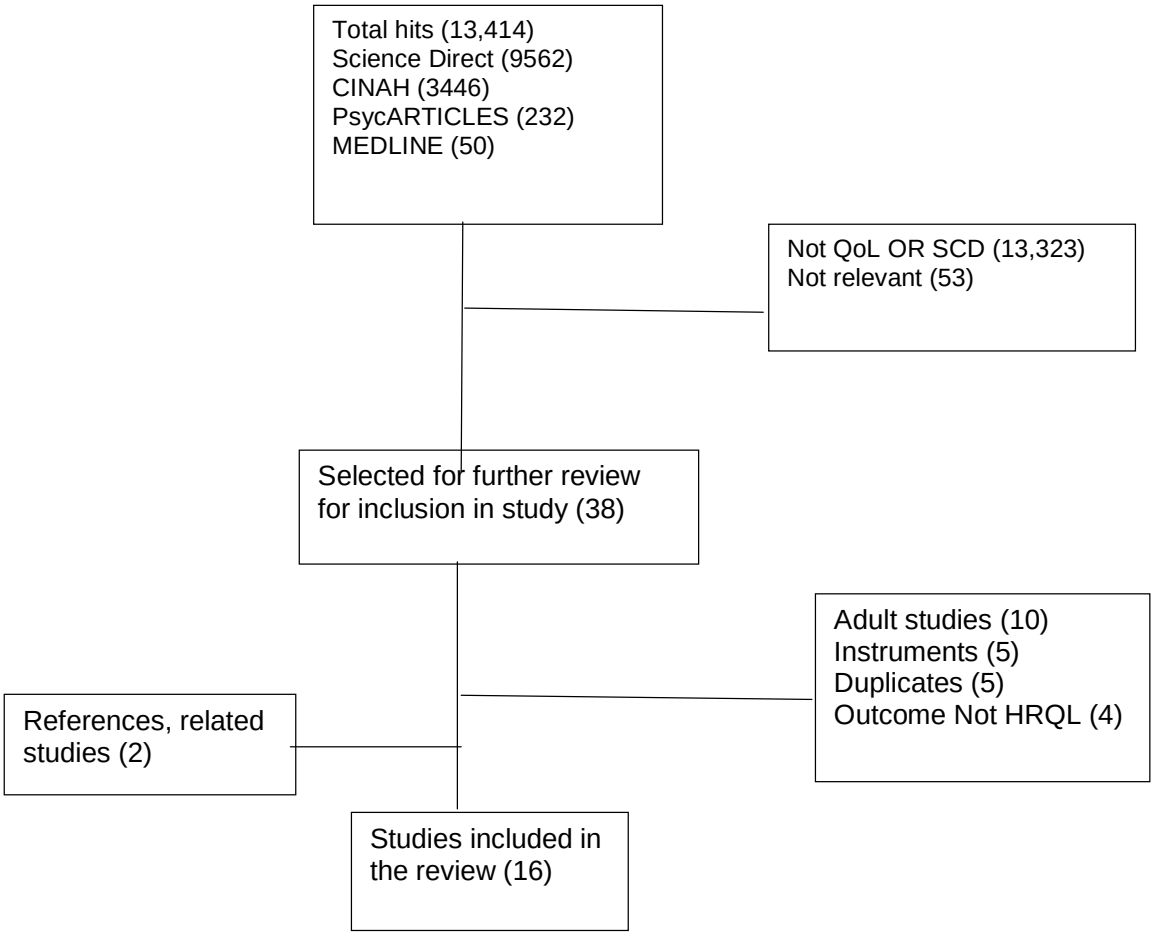

Fig. 1. Flow chart of study selection procedure

Table 1. Characteristics of included studies

Authors year	Country	Design	Population	Sample size		Mean age with SD	Female (SCD) %	HbSS %	Setting	Outcome Variables	Measures		Rater
				SCD	Non-SCD						HRQL	Others	
Palermo et al. 2002	USA	Case-control	Children/Adolescents	58	120	10.97±3.41	44.9	79.3	Outpatient Sickle Cell Anaemia clinic and ambulatory paediatric clinic	HRQL	CHQ-PF50	Questionnaire, medical chart	Caregivers
Barakat et al., 2005	USA	Cross sectional	Children age ≥8 Caregivers (age≥5)	21	43	10.5±4.55.	40.4	76.6	Haematology Acute Care Unit Sickle Cell Centre	HRQL	Miami Paediatric QOL	Information form Medical review	Self Caregivers
Barakat et al. 2008	USA	Cross sectional	Adolescents	42	42	15±1.82 44.1±10.19 (caregiver)	50		Urban Comprehensive Sickle Cell Centre	HRQL	CHQ-50	Information form, Risk Index PPQ, BASC, PIP, Medical review	Self caregivers
Palermo et al. 2008	USA	Cross sectional	Children/Adolescents	56	n/a	12±2.5	43	83.9	Sickle cell centre clinic	HRQL	CHQ-P50	Questionnaire, Faces scale, 10-cm visual analogue scale, RCADS, FDI	Self Parents
Panepinto et al. 2008	USA	Cross sectional	Children/Adolescents	104	74	Range: 2-18	50	63.5	Outpatient haematology clinic	HRQL	PedsQL	Census Bureau Factfinder	Self Proxy
Dale et al. 2009	USA		Children/Adolescents	124	143	13+3.3	51.6	95.2	Sickle cell clinic	HRQL	PedsQL4.0	Published scores for healthy children, Questionnaire	Self, Parents, Published scores for healthy children
Hijmans et al. 2010	Netherlands	Case Control	Children/Adolescents	40	36	11.7±3.1 11.6±3.4	50	81.1	Comprehensive Sickle Cell centre clinic	HRQL	KIDSCREEN-52	Questionnaire, Dutch norm population data	Self
Amr et al. 2011	Saudi Arabia	Cross sectional	Adolescents	180	202	16.8±3.6 16.9±1.7	75.6		2No General hospitals	HRQL	SF-36	Demographic form, Medical records	Self
Fisak et al. 2011	USA	Cross sectional	Children/Adolescents	78	n/a	11.38±3.92	44.9	62.8	Paediatric sickle cell clinic	HRQL	PedsQL4.0	ASCI, BHCS, MCR	Parent

Authors year	Country	Design	Population	Sample size		Mean age with SD	Female (SCD) %	HbSS %	Setting	Outcome Variables	Measures		Rater
				SCD	Non-SCD						HRQL	Others	
Wrotniak et al. 2012	USA	Longitudinal, randomised, controlled trial	Children	47	66	8.6±2.4	43		5 study centres	HRQL	CHQ-PF-50	Anthropometric measurements, HPLC	Parent
Menezes, 2012	Brazil	Cross sectional	Children/Adolescents	100	50	n/s			Tertiary hospital	HRQL	PedsQL4.0 SF-36	Questionnaire	Self
Schlenz et al. 2012	USA	Prospective	Children/Adolescents	90	n/a	11.04±4.34	51.1	71.1	Paediatric Haematology/Oncology outpatient clinic	HRQL	PedsQL4.0	Medical Chart Review, Demographic information	Self
Bhagat et al. 2014	India	Case – Control	Children/Adolescents	105	105	11.78±2.67 10.98±4.23	55.2		Sickle Cell COPD (Paediatrics Department)	HRQL	WHO SF-36	Information proforma, physical examination	Self
Adeyemo et al. 2015	Nigeria	Cross sectional	Adolescents	80	80	16.0±1.5 16.6±1.4	43.75		3 Sickle cell clinics	HRQL	SF-36	Questionnaire, Adapted measure for stigma	Self
Bhatia et al. 2015 USA	USA	Mixed Longitudinal	Children	17	23	8.97±5.28	n/s	65		HRQL	PedsQL4.0	Questionnaire, Standard scoring scales	Self, Proxy
Sehlo & Kamfar 2015	Saudi Arabia	Cross sectional study (case control)	Children/Adolescents	60	60	11.93±1.72 11.77±1.96	60	70	General Hospital	HRQL.	PedsQL4.0	CDI, CDI-P, DISC, CASS.	Self, Parent

Abbreviations: PedsQL 4.0 – Paediatric Quality of Life Inventory (fourth version). CHQ– Child Health Questionnaire. CHQ-PF-50 (CHQ Parent proxy version). SF-36: Medical outcomes short form-36. BHCS – Barriers to Health Care Scale. ASCI – Adherence and Self-Care Inventory. MCR – Medical Chart Reviews. CDI – Children Depression Inventory. CDI-P – Children Depression Inventory. DISC – Diagnostic Interview Schedule for Children. RCADS- Revised child anxiety and depression scale. n/a-not applicable, n/s-not stated

3.2 Measures of HRQL in Children and Adolescents with SCD

Two types of ratings were employed in all included studies: Self-reported measures for children over 8 years who were literate and could understand, and caregiver proxy-reports, for children ages 0 to 8 years, or for older children for purpose of comparison. HRQL instruments are broadly categorised in the literature as either generic or disease-specific. Generic HRQL instruments are useful for comparison across populations with chronic diseases or healthy populations in order to facilitate broader understanding about the burden of the SCD. Disease-specific instruments enhance the specificity in measuring HRQL to sensitively discriminate within patients ([23]. All papers included in the review employed generic HRQL instruments.

3.3 Paediatric Quality of Life Inventory Fourth Edition (PedsQL 4.0)

Seven of the studies employed the PedsQL 4.0 [24] generic core scales to investigate HRQL in CALSCD. PedsQL comprises 23 items that assess the child's functioning in four domains, physical, emotional, social and school (role) functioning. PedsQL4.0 has been translated into multiple languages [25,26]. The patient-proxy version has also demonstrated criterion validity with the ability to differentiate between specific subgroups of children and distinguish disease severity within a chronic condition and in children with SCD (e.g. children with or without pain, or neurobehavioral complications) [27,28]. The use of the instrument has been endorsed in the study of paediatric SCD population and has been found to have internal consistency for caregivers for SCD patients [27,29,30].

3.4 Child Health Questionnaire (CHQ) and CHQ-PF50)

Four of the studies (Table 1) used the CHQ [31] which was the first comprehensive and multidimensional tool developed to measure HRQL in children aged 5-18 along with a parent proxy CHQ-PF50. Widely used, the tool has been useful in comparing HRQL of children with chronic health conditions (eg. asthma, epilepsy, survivors of cancer) and healthy control groups, and has been found to be a valid predictor of psychosocial and physical health [32,33]. Individual scores of the 14 subscales were aggregated into two summary scores, the physical health summary and the psychosocial health summary. The instrument also has been shown to have good discriminant validity when compared with other chronic illness and scores in normative samples [32,33] and was first used to measure HRQL in children with SCD in 2002 [31].

3.5 Medical Outcome Study (MOS) Short Form-36 (SF-36)

The SF-36 [34] contains 36 items that measure quality of life across 8 domains and has been widely accepted and used in general and specific populations to compare relative burden of diseases in more than 200 diseases and conditions. The instrument has been translated into over 50 languages while the psychometric properties have been validated in many studies. Four studies used the SF-36 as a measure of HRQL either as self-reported by adolescents or caregiver proxy-report (Table 1).

3.6 HRQL in SCD Patients Compared with Other Groups

Studies consistently showed that the HRQL is affected in CALSCD (Table 2). CALSCD showed more limitations in physical, social and psychological functioning compared with a healthy group. In a study of 58 CALSCD and 120 healthy peers, they found that CALSCD had significant impairment in 13 of the 14 health dimensions of the CHQ-PF50 subscales [31]. Between 53% and 63% of CALSCD would be 'at risk' for impaired overall HRQL and physical HRQL respectively [25].

In a group comparisons, Palermo et al. [31] found that CALSCD had physical health summary scores comparable to those of a juvenile rheumatoid arthritis (JRA) group but more impaired than an epilepsy group ($t(57)=-4.98$, $p<0.0001$). However, the psychosocial health summary scores of CALSCD were significantly more impaired than the JRA group ($t(57)= -6.43$, $p<0.0001$) but comparable to the epilepsy group [31]. Another study showed that HRQL was lower in CALSCD compared with other chronic non-communicable diseases except in the domain of social functions [35]. Also, the literacy, socio-economic status and duration of disease, of CALSCD were found to be comparable with other chronic diseases including congenital heart disease, nephrotic syndrome and diabetes. Seeking for medical consultations was higher among SCD patients than in the aforementioned illnesses [35].

CALSCD also had lower HRQL scores compared to their healthy siblings on physical well-being and scored significantly lower in 5 domains compared to a normative population [36]. Also, comparing both children and parents HRQL ratings with a healthy group using the published data, CALSCD had significantly lower HRQL than the published normative HRQL score [25]. Furthermore, the socio-demographic profiles (education and income) of parents of adolescents with SCD were lower compared to those without SCD, and educational delay (excessive failing and school retention) and absenteeism were more common among CALSCD than non-SCD peers [37]. Poorer behaviour, worse mental health, and lower self-esteem were reported among CALSCD [31]. Another study [38], also confirmed that children with SCD had significantly poorer academic performance compared to a control group of healthy children.

SCD also had negative effect on caregivers who were more impacted emotionally, in personal time and family activities [31]. Thus, SCD in children and adolescents was associated with limitations in most aspects of HRQL [39].

3.7 Predictors of Health-Related Quality of Life (HRQL) in Children and Adolescents with SCD

3.7.1 Disease severity/complications

Disease severity and complications in SCD are indicated when there is history of hydroxyurea therapy, chronic transfusion, acute chest syndrome (ACS), stroke, number of acute pain episodes, vaso occlusive crisis or hospitalisation in the last two years [29,31,38]. Disease severity was also associated with a history of pneumonia and asthma [31], recurrent priapism [29], and disease genotype [38]. Seven of the papers reviewed (Table 2) identified disease severity/complications as a predictor of HRQL in CALSCD [29-31,37-40] while one did not [41]. Total number of disease-related complications was associated with worse physical health (r=-0.91) [31]. In another study [40], disease severity was a predictor of psychosocial HRQL (β= -0.5, p≤0.01). Also, the presence of SCD was associated with 4 times higher odds of having worse HRQL [29].

In a Saudi Arabian population, disease complications was an independent predictor of the physical functioning, physical role limitation, emotional role limitation, emotional well-being and general health of the SF-36 HRQL subscales ([37]. Disease severity was also a predictor of poor HRQL in CALSCD [30,38]. In a Nigerian population, disease complications influenced 7 out of the 8 subscales of the SF-36 measure of HRQL except the mental/emotional well-being subscale [39]. Disease severity also had individual and joint effects with social support and depression on the HRQL of CALSCD [38].

3.7.2 Comorbidities

Medical co-morbidity and neurobehavioral co-morbidity were both associated with worse HRQL [40] while behavioural comorbidity predicted physical health of the HRQL [33].

3.7.3 Hospitalisation

The frequency of hospitalisation predicted lower overall HRQL [25,37], physical health summary and mental health of the HRQL [33] and school functioning scores and the psychosocial domain [25]. The frequency of hospitalisation actually predicted worse HRQL in CALSCD in all the 8 domains of SF-36 HRQL subscales [39]. Increased emergency department visits were associated with higher scores on the emotional role dimension of the HRQL subscales [25].

3.7.4 Pain episodes

Frequency of pain was a predictor of change in HRQL [28], physical functioning and self-esteem [42]. Pain also predicted low HRQL in CALSCD [43].

3.7.5 Depression

Depression was a predictor ($\beta = 0.77$, $p < 0.001$) of the psychosocial HRQL domain [40] and associated with poor quality of life [38]. Mediator variables consisting of internalizing symptoms and disease-related parenting stress correlated with HRQL domains [42]. Moreover, depression predicted self-esteem while anxiety predicted physical functioning [42].

3.7.6 Stigma

Health-related stigma is characterised by discrediting of individuals and populations as a result of a health condition resulting in adverse effects on health [44]. Stigma was associated with worse HRQL in all domains of the SF-36 HRQL measure [39].

Table 2. HRQL of SCD in children and adolescents

Author Year	Designs	Main focus	investigated Determinants	Outcomes	Predictors/ Correlates
Palermo et al. 2002	Case-control	To provide information on HRQL and parental burden of children with SCD and describe relationships between demographic and disease related factors and children HRQL	Demographic factors, Disease related factors	Caregivers of CALSCD were significantly more impacted by the child's health emotionally, personal time and family activities than those of healthy children. Also CALSCD demonstrated more limitations across the physical, psychological and social functioning domains of the HRQL compared to their healthy counterpart.	Disease complications, age, female gender
Barakat et al. 2005	Cross sectional	To investigate the association of treatment adherence with QOL in children with SCD	Treatment adherence Disease complications	Treatment adherence associated with poorer quality of life in the children.	Treatment adherence
Barakat et al. 2008	Cross sectional	To examine association between pain, psychological adjustment and family functioning with HRQL	Pain frequency, anxiety, depression, family functioning difficulty	Pain was associated with HRQL along some potentially modifiable concomitant variables (eg anxiety & depression).	Anxiety, pain, depression, disease-related parenting stress.
Panepinto et al. 2008	Cross sectional	To determine the impact of family income and SCD on HROL	Family income Disease severity, comorbidities	CALSCD reported worse HRQL than non-SCD peers. Furthermore, CALSCD had a 4.0 (parent-report) and 3.33 child report) times higher odds of having worse overall HRQL than healthy counterpart as result of disease severity and 2.88 as a result of low family income.	Disease severity Age medical or neurobehavioral commodities
Palermo et al. 2008	Cross sectional	To investigate if individual distress and residence in neighbourhood of economic distress would predict children level of pain-related functional disability and health-related quality of life .	Depression, diseases severity, individual/ family SES parent education	Greater depression was associated with greater pain and disability while higher family income was associated with low child-reported disability and higher physical HRQL	Depression disease severity individual/family SES parent education distressed neighbourhood
Dale et al. 2009		To assess HRQL in in children and adolescents with SCD compared with healthy children and adolescents	Hospitalization, Emergency visits	CALSCD had lower overall HRQL in all the subdomains except emotional functioning when compared with healthy peers.	No of hospitalisations, ED visits
Hijmans et al. 2010	Case-Control	To examine whether reduced HRQL in children with SCD is related to consequences of the disease or to the low SES of most patients.	Parents SES	Children with SCD had significantly lower HRQL compared to healthy siblings on physical well-being domain but scored significantly lower in 5 domains compared to the normative population.	SES
Amr et al. 2011	Cross sectional	To assess the impairment of the different domains of HRQL among adolescents with SCD compared to healthy peers.	Socio-demographic factors, disease-related factors, family income	Domains of HRQL were significantly deteriorated in adolescents with SCD compared to peers. Increasing age, was negatively associated with HRQL	Rural residence, Female gender, Family income, Disease-related complications
Fisak et al. 2011	Cross sectional	To evaluate factors associated with HRQL in a paediatric SCD sample	Barriers to treatment adherence	Pain episodes and barriers to treatment adherence were robust predictors of HRQL in the paediatric SCD sample	Disease type, Frequency of pain and Barriers to treatment adherence

Author Year	Designs	Main focus	investigated Determinants	Outcomes	Predictors/ Correlates
Wrotniak et al. 2012	Longitudinal, randomised, controlled trial	To examine the impact of a 12-month nutritional intervention on the HRQL of children having SCD compared with their non-SCD counterparts in a non-white US population.	Hospitalisation, comorbidity, age, gender, haematocrit status	Children with SCD had lower HRQL, compared to healthy counterpart in general health, overall physical health and parental emotional stress but higher mental health. Hospitalisation predicted physical health and mental health. Behavioural comorbidity predicted psychosocial health, mental health, general health, parental emotional stress, role functioning and parental time. while gender predicted general health.	Hospitalisation, Behavioural comorbidity, female gender
Menezes et al. 2012	Cross sectional	To assess the quality of life in children and adolescents with SCD and those of their relatives	Pain, care overload	SCD associated with the physical, social, emotional and school domains of HRQL. The HRQL of parents were also impaired compared with parents of healthy peers due to overload of care.	Pain, Care overload
Schlenz et al. 2012	Prospective	To examine the responsiveness of caregiver report of PedsQL4.0 to pain-related changes in HRQL	Frequency of pain episodes	Caregiver proxy reports were responsive to pain-related changes in physical, psychosocial and overall HRQL	Pain episode frequency between Time1 and Time2
Bhagat et al. 2014	Case – Control	To determine HQROL in SCD patients and compare same with those of other chronic non-communicable diseases	emotional problems chronic fatigue small physical size	The overall HRQL of patients with SCD was significantly lower than matched patients with chronic illness.	Indirect influence of emotional problems/ physical size suggested
Adeyemo et al. 2015	Cross sectional	To identify sociodemographic and clinical factors impacting on HRQL of adolescents with SCD and effects of SCD-related stigma on quality of life	Child demographics, stigma	Adolescents with SCD have significantly impaired HRQL in all the subscales of the SF-36 compared with healthy group. The HRQL was affected by Stigma.	Disease complications, Stigma hospitalisation, education status, age
Bhatia et al. 2015	Mixed Longitudinal	To investigate physical, psychological and social functioning in SCD subjects before and after Allogeneic Hematopoietic Stem Cell Transplantation (allo-HCT)	Effect of treatment with allo-HCT	Self-reported overall baseline HRQL was below published ‘at risk’ cut off scores for chronically ill children. Also, parent-proxy report indicated overall HRQL was lower than the population mean for chronically ill children. Overall HRQL score significantly increased at 1 year of allo-HCT in the physical, psychosocial and emotional domains of HRQL.	Treatment with allo-HCT
Sehlo & Kamfar 2015	Cross sectional study (case control); systematic random sampling	To assess the association between social support, disease severity and depression, and their individual or composite effect on HRQL in children with SCD	Social support, Disease severity, Depression	Higher level of parent support was associated with lower depressive state and better ratings of quality of life.	Parent support, Depression, Disease severity

3.7.7 Parental support

A high level of parental support significantly reduced depression in CALSCD and predicted better HRQL in CALSCD [38].

3.7.8 Treatment Adherence/barriers to treatment adherence

Treatment adherence predicted poor HRQL in CALSCD though the negative correlation was unexpected [41]. This unexpected direction of the relationship may be due to the measures for adherence. The authors acknowledged that the measures of adherence used were not standard or objective. It is also possible that those people with higher adherence are just more ill, more focused on their health and so more likely to report any problems. However, barriers to treatment adherence (eg transportation problems, financial problems, access to medication) predicted HRQL [20].

3.7.9 Child demographics

Age inversely predicted HRQL in CALSCD [17,31,37,39] and predicted worse psychological HRQL [17]. In fact, all domains of HRQL on the SF-36 were negatively associated with increasing age of CALSCD [37]. Female gender was also associated with worse overall HRQL and general health, physical role functioning and body pain domains of HRQL [31,33,37]. Also, lower BMI was associated with higher scores on the body pain subscale of HRQL [33].

3.7.10 Socio- economic status

Individual/family socioeconomic status were independent predictors of functional disability, physical and psychosocial HRQL in CALSCD [40]. Higher parental education predicted better physical HRQL [37,40]. Neighbourhood socioeconomic distress was an independent predictor of physical HRQL [40]. Furthermore, low family income predisposed CALSCD to 2.88 times higher odds of worse HRQL [17] while low socio-economic status of the patient population was associated with low HRQL [36]. Moreover, rural residence was a negative predictor of vitality and pain of the HRQL subscales [37].

3.7.11 Impact of treatment on HRQL

Two studies examined the HRQL of SCD patients after medical interventions; Allogeneic Hematopoietic Stem Cell Transplantation (allo-HCT) and 12-month daily nutritional supplementation with Vitamin A or Vitamin A plus zinc. Overall HRQL were below the published at risk cut-off scores for chronically ill children at baseline, allo-HCT was a predictor of improved physical, psychosocial and emotional and overall HRQL over time [45]. However, a 12-month Vitamin A supplementation had no effect on the HRQL [33].

4. DISCUSSION

This paper has reviewed publications on the HRQL of children and adolescents living with SCD (CALSCD) from which factors predicting the HRQL have been identified. Understanding these factors will help improve understanding of the burden of the disease and has the potential to influence the development of non-clinical care strategies to complement clinical efforts at reducing the burden of the disease. Furthermore, understanding the predictors and their interrelationships can also reveal information that can help healthcare providers and patients to better manage the disease by focusing on modifiable factors to improve HRQL. While factors like age and gender are not modifiable, they can help to inform healthcare practitioners and caregivers of the need to recognise the differences in their approach to treatment.

Evidence from this review confirmed that HRQL is significantly impaired in CALSCD. HRQL was worse when compared with either healthy peers, a published normative group, their siblings or those with other chronic diseases like asthma, epilepsy, or juvenile rheumatoid arthritis. Also the predictors were multifaceted and impacted significantly on the HRQL either singly or in combination with some others. Hence, it will be necessary to characterise these factors in future work to properly understand interrelationships and possible mediator variables.

The major HRQL measures employed in research with CALSCD have been demonstrated to have acceptable psychometric properties in previous studies [23,24,26]. Observed differences between self-reported and proxy-reported scores suggested that self-rating may be a better measure of HRQL in individuals as the patient can better describe his/her experience than a proxy. However, where patients are too young or too ill, or where available self-report is limited; caregiver/proxy report is acceptable and can be used to broaden the age range of participants and/or increase sample size [23]. This is necessary to effectively

describe risk factors for morbidity and compromised functioning in order to direct necessary interventions at the children at early age. Moreover, HRQL in CALSCD who may have neurocognitive deficits or learning disabilities can best be reported by proxies to reduce the potential risks associated with these conditions which may limit the quality of self-report.

The behaviour of the predictors in this study is consistent with findings in the literature. For example, findings that disease severity/ complications significantly predict worse HRQL in CALSCD [30,31,37-40] were in line with the findings of Danckaerts et al. [46] who reported that HRQL grew worse with an increase in severity of the condition in children with ADHD. Factors influencing disease severity include phenotype, Foetal Haemoglobin (HbF) where high level of HbF was associated with decreased morbidity and mortality in those with SCD [23]. Living with a condition can also place stress on patients and caregivers especially when it is believed that there is no immediate cure. The presence of medical comorbidities (e.g. asthma) or neurobehavioral comorbidities (e.g. developmental delay; physical size) were factors responsible for poor HRQL. This should inform decision-making in clinical procedures for managing SCD patients. Child demographics and parent socioeconomic status (SES) were also important predictors of HRQL with low parent SES predicting worse HRQL. Parents of CALSCD were associated with low income and education. Such parents lack the financial ability to prevent or respond to crises rather they engage in self-management and only seek medical attention late on. This has grave implications on management of the disease and clinical outcomes. Not seeking medical help early may aggravate the painful experiences of patients with consequent psychological issues that may affect the self-esteem of the patients, a situation that may lead to anxiety and or depression. Stigma is a hidden burden in chronic health problems [44]. Health professionals should therefore recognise the need to minimise or eliminate stigmatising stereotypes, for example, branding or treating patients with SCD as drug addicts because of their frequent demand for high doses of opioids for pain relief.

The majority of studies were conducted in the USA where the prevalence of SCD is lower; found only in a minority population of African-Americans. Little published research on the HRQL of SCD patients was conducted in Nigeria and India, the two countries with the highest cases of SCD. More studies are needed in these and other developing countries with high prevalence of SCD, to validate instruments, characterise the predictors and influence policies on managing the disease. Greater efforts are needed to initiate and develop plans and policies in line with the declaration of the United Nations [1] to help address the burden of the disease in countries where the relative disease burden is higher.

5. CONCLUSION

This review has established the experience of significant impairment of HRQL in children and adolescents living with SCD and identified factors associated with HRQL in SCD patients. Our analysis will contribute to managing HRQL in CALSCD as priorities are now shifting in the light of medical advancement, from survival to long-term quality of life and, to future research to establish relative importance of predictors of HRQL in CALsCD.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. United Nations General Assembly resolution: A/63/237 December; 2008. Available:http://www.un.org/en/ga/ (Accessed 10 July, 2016)

2. World Health Organization, Fifty-ninth World Health Assembly, Geneva, 22–27 May, Annexes (WHA59/2006/REC/1); 2006.
Available:http://www.who.int/nutrition/topics/WHA59.11
(Accessed 10 July, 2016)
3. World Health Organization Sixty-third World Health Assembly 2010 Resolutions and Decisions.
Available:http://apps.who.int/
(Accessed 10 July, 2016)
4. Centre for Disease Control and Prevention. Available:http://www.cdc.gov/ncbddd/sicklecell/data.html
(Accessed 16 July, 2016)
5. Brousse V, Makani J, Rees DC. Management of sickle cell disease in the community. BMJ. 2014;348:g1765–g1765.
DOI: 10.1136/bmj.g1765
6. Ojodu J, Hulihan MM, Pope SN, Grant AM. Incidence of sickle cell trait--United States, 2010. MMWR Morb Mortal Wkly Rep. 2014;63(49):1155-8.
7. Jastaniah W. Epidemiology of sickle cell disease in Saudi Arabia. Annals of Saudi Medicine. 2011;31(3):289.
DOI: 10.4103/0256-4947.81540
8. Anie KA, Egunjobi FE, Akinyanju OO. Psychosocial impact of sickle cell disorder: Perspectives from a Nigerian setting. Globalization and Health. 2010;6(1):2.
DOI: 10.1186/1744-8603-6-2
9. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin in neonates: A contemporary geostatistical model-based map and population estimates. The Lancet. 2013:381(9861): 142–151.
DOI: 10.1016/s0140-6736(12)61229-x
10. Carey PJ. Addressing the global health burden of sickle cell disease. International Health. 2014;6(4):269–270.
DOI: 10.1093/inthealth/ihu045
11. Akinyanju OO. A profile of sickle cell disease in Nigeria. Annals of the New York Academy of Sciences.1989;565(1 Sickle Cell D):126–136.
DOI: 10.1111/j.1749-6632.1989.tb24159
12. 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. Pediatric Blood & Cancer. 2009;53(4):642-646.
13. Elmariah H, Garrett ME, Castro LM, Jonassaint JC, Ataga KI, Eckman JR, et al. Factors associated with survival in a contemporary adult sickle cell disease cohort. American Journal of Hematology. 2014;89(5):530-535.
14. Diggs LM. Anatomic lesions in sickle cell disease. Sickle Cell Disease: Diagnosis, Management, Education, and Research. 1973;189-229.
15. Yanni E, Grosse SD, Yang Q, Olney RS. Trends in pediatric sickle cell disease-related mortality in the United States, 1983-2002. The Journal of Pediatrics. 2009;154(4):541–545.
DOI: 10.1016/j.jpeds.2008.09.052
16. Ferrans CE, Zerwic JJ, Wilbur JE, Larson JL. Conceptual model of health-related quality of life. Journal of Nursing Scholarship. 2005;37(4):336-342.
17. Panepinto JA. Health-related quality of life in sickle cell disease. Pediatric Blood & Cancer. 2008;51(1):5–9.
DOI: 10.1002/pbc.21557
18. Berlim MT, Fleck MPA. "Quality of life": A brand new concept for research and practice in psychiatry. Revista Brasileira de Psiquiatria. 2003;25(4):249–252.
DOI: 10.1590/s1516-44462003000400013
19. Dampier C, Lieff S, LeBeau P, Rhee S, McMurray M, Rogers Z, et al. Health-related quality of life in children with sickle cell disease: A report from the comprehensive sickle cell centers clinical trial consortium. Pediatric Blood & Cancer. 2010;55(3):485–494.
DOI: 10.1002/pbc.22497
20. McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, et al. Health related quality of life in sickle cell patients: The PiSCES project. Health and Quality of Life Outcomes. 2005;3(1):50.
DOI: 10.1186/1477-7525-3-50
21. Trzepacz AM, Vannatta K, Gerhardt CA, Ramey C, Noll RB. Emotional, social, and behavioral functioning of children with sickle cell disease and comparison peers. Journal of Pediatric Hematology/Oncology. 2004; 26(10):642–648.
DOI:10.1097/01.mph.0000139456.12036.8d
22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ. 2009;339:b2535–b2535.
DOI: 10.1136/bmj.b2535

23. Panepinto JA. Health-related quality of life in patients with hemoglobinopathies. ASH Education Program Book. 2012;2012(1): 284-289.
24. Varni JW, Seid M, Rode CA. The PedsQL™: Measurement model for the pediatric quality of life inventory. Medical Care.1999;37(2):126–139.
DOI: 10.1097/00005650-199902000-00003
25. Dale JC, Cochran CJ, Roy L, Jernigan E, Buchanan GR. Health-related quality of life in children and adolescents with sickle cell disease. Journal of Pediatric Health Care. 2011;25(4):208–215.
DOI: 10.1016/j.pedhc.2009.12.006
26. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL™* 4.0 as a pediatric population health measure: Feasibility, reliability, and validity. Ambulatory Pediatrics. 2003;3(6):329–341.
DOI:10.1367/1539-4409(2003)003<0329:tpaapp>2.0.co;2
27. McClellan CB, Schatz J, Sanchez C, Roberts CW. Validity of the pediatric quality of life inventory for youth with sickle cell disease. Journal of Pediatric Psychology. 2008;33(10):1153–1162.
DOI: 10.1093/jpepsy/jsn036
28. Schlenz AM, Schatz J, McClellan CB, Roberts CW. Responsiveness of the PedsQL to pain-related changes in health-related quality of life in pediatric sickle cell disease. Journal of Pediatric Psychology. 2012;37(7):798–807.
DOI: 10.1093/jpepsy/jss051
29. Panepinto JA, Pajewski NM, Foerster LM, Sabnis S, Hoffmann RG. Impact of family income and sickle cell disease on the health-related quality of life of children. Quality of Life Research. 2008;18(1):5–13.
DOI: 10.1007/s11136-008-9412-8
30. 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 and Development. 2011;38(2):204–210.
DOI: 10.1111/j.1365-2214.2011.01223.x
31. Palermo TM, Schwartz L, Drotar D, McGowan K. Parental report of health-related quality of life in children with sickle cell disease. Journal of Behavioral Medicine. 2002;25(3):269-283.
32. McCullough N, Parkes J. Use of the child health questionnaire in children with cerebral palsy: A systematic review and evaluation of the Psychometric properties. Journal of Pediatric Psychology. 2007; 33(1):80–90.
DOI: 10.1093/jpepsy/jsm070
33. Wrotniak BH, Schall JI, Brault ME, Balmer DF, Stallings VA. Health-related quality of life in children with sickle cell disease using the child health questionnaire. Journal of Pediatric Health Care. 2014;28(1):14–22.
DOI: 10.1016/j.pedhc.2012.09.004
34. Ware JE, Sherbourne CD. Erratum to the MOS 36-item short form health survey (SF-36): I. Conceptual framework. Pharmaco Economics. 1992;2(2):98–98.
DOI: 10.1007/bf03260127
35. Bhagat V, Baviskar S, Mudey A, Goyal R. Poor health related quality of life among patients of sickle cell disease. Indian Journal of Palliative Care. 2014;20(2):107.
DOI: 10.4103/0973-1075.132622
36. Hijmans CT, Fijnvandraat K, Oosterlaan J, Heijboer H, Peters M, Grootenhuis MA. Double disadvantage: A case control study on health-related quality of life in children with sickle cell disease. Health and Quality of Life Outcomes. 2010;8(1):121.
DOI: 10.1186/1477-7525-8-121
37. Amr M, Amin T, Al-Omair O. Health related quality of life among adolescents with sickle cell disease in Saudi Arabia. Pan African Medical Journal. 2011;8(1).
DOI: 10.4314/pamj.v8i1.71057
38. Sehlo MG, Kamfar HZ. Depression and quality of life in children with sickle cell disease: The effect of social support. BMC Psychiatry. 2015;15(1).
DOI: 10.1186/s12888-015-0461-6
39. Adeyemo TA, Ojewunmi OO, Diaku-Akinwumi IN, Ayinde OC, Akanmu AS. Health related quality of life and perception of stigmatisation in adolescents living with sickle cell disease in Nigeria: A cross sectional study. Pediatric Blood & Cancer. 2015;62(7):1245–1251.
DOI: 10.1002/pbc.25503
40. Palermo TM, Riley CA, Mitchell BA. Daily functioning and quality of life in children with sickle cell disease pain: Relationship with family and neighborhood socio-economic distress. The Journal of Pain. 2008;9(9):833–840.
DOI: 10.1016/j.jpain.2008.04.002
41. Barakat LP, Lutz M, Smith-Whitley K, Ohene-Frempong K. Is treatment adherence associated with better quality of

life in children with sickle cell disease? Quality of Life Research. 2005;14(2):407–414.
DOI: 10.1007/s11136-004-5328-0

42. Barakat LP, Patterson CA, Daniel LC, Dampier C. Quality of life among adolescents with sickle cell disease: Mediation of pain by internalizing symptoms and parenting stress. Health and Quality of Life Outcomes. 2008;6(1): 60.
DOI: 10.1186/1477-7525-6-60

43. Menezes AS de O. da P, Len CA, Hilário MOE, Terreri MTRA, Braga JAP. Quality of life in patients with sickle cell disease. Revista Paulista de Pediatria. 2013;31(1): 24–29.
DOI: 10.1590/s0103-05822013000100005

44. Weiss MG, Ramakrishna J, Somma D. Health-related stigma: Rethinking concepts and interventions 1. Psychology, Health & Medicine. 2006;11(3):277–287.
DOI: 10.1080/13548500600595053

45. Bhatia M, Kolva E, Cimini L, Jin Z, Satwani P, Savone M, et al. Health-related quality of life after allogeneic hematopoietic stem cell transplantation for sickle cell disease. Biology of Blood and Marrow Transplantation. 2015;21(4):666–672.
DOI: 10.1016/j.bbmt.2014.12.007

46. Danckaerts M, Sonuga-Barke EJS, Banaschewski T, Buitelaar J, Döpfner M, Hollis C, et al. The quality of life of children with attention deficit/hyperactivity disorder: A systematic review. European Child & Adolescent Psychiatry. 2009;19(2): 83–105.
DOI: 10.1007/s00787-009-0046-3

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