

Health-related quality of life predictors in children and adolescents with sickle cell disease: a systematic review.

Abstract-

Aim: The aim of this systematic review is to examine the predictors of HRQL in children and adolescents (aged 18 years and under) with SCD.

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.

Result: 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.

Introduction

Sickle Cell Disease (SCD) is a hereditary haematological disorder with severe physical, psychological and social consequences for both those affected and their families (United Nations, 2008). The World Health Organisation has adopted a management and prevention agenda for the disease as a global public health priority (World Health Organisation, 2010, 2006). 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 (Centre for Disease Control and Prevention, 2016).

SCD affects 10,000-15000 people in both the United Kingdom and France (Brousse, Makani, & Rees, 2014). 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 (Ojodu, Hulihan, Pope, & Grant, 2014). In the Eastern province of Saudi Arabia, the prevalence was 21% SCT and 2.6% SCD (Jastaniah, 2011). SCT prevalence ranges between 10% and 40% across equatorial Africa and 15% to 30% in West Africa (Anie, Egunjobi, & Akinyanju, 2010). SCD is responsible for the equivalent of 5% of under-five deaths in Africa with up to 16% in West Africa (Anie *et al.*, 2010). 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 (Piel *et al.*, 2013; Carey, 2014). The disease is estimated to affect 0.5% of people in Nigeria, with 24% SCT prevalence (WHO, 2006). Annual new-borns with SCD has been projected to reach 140,000 in Nigeria by 2050 (Piel *et al.*, 2013). 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 ((Mvundura, Amendah, Kavanagh, Sprinz, & Grosse, 2009).

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 (Elmariah *et al.*, 2014), this was 14.3 years four decades ago (Diggs, 1973). 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 (Yanni, Grosse, Yang, & Olney, 2009; CDC 2016). 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.

50 The concept of health-related quality of life (HRQL) emerged in the 1970s as a
51 construct to define QoL with respect to how an illness, its complications and treatments affect
52 the patient (Ferrans 2005; Panepinto 2008). Advantageously, QoL evaluation puts patients at
53 the centre of inquiry and gives weight to their opinions (Berlim & Fleck, 2003).

54 The HRQL of chronic disease patients is generally low and for SCD, studies have
55 shown that patients generally have impaired HRQL compared to those without SCD
56 (Dampier *et al* 2010; McClish *et al*, 2005; Trzepacz, Vannatta, Gerhardt, Ramey, & Noll,
57 2004). Various instruments have been developed to measure the impact of chronic diseases
58 on HRQL. Efforts have also been directed at investigating the factors that affect HRQL in
59 order to minimise the negative impact of the disease. This study aims to systematically
60 review work exploring HRQL in children and adolescents living with SCD (CALSCD) and to
61 identify the determinants.

62 ***Methods***

63 This study followed the format of the Preferred Reporting Items for Systematic Reviews and
64 Meta-Analysis (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The
65 electronic databases searched included Science Direct, MEDLINE, CINAHL and
66 PsyARTICLES. Search terms consisted of (Health-related quality of life OR HRQL OR
67 HRQL OR quality of life OR QOL OR health status OR patient-reported outcome OR Well-
68 being) AND (Sickle cell anaemia OR sickle cell disease OR haemoglobinopathies OR HbSS
69 OR HbSC OR SCD OR SCA OR sickle cell disorder).AND (predictors OR factors OR
70 determinants).

71 *Inclusion criteria:*

- 72 • Articles published in English language.

- 73 • Children and adolescents (aged ≤ 18) with SCD.
- 74 • HRQL measured with a validated instrument.
- 75 • Any reported variable associated with HRQL.
- 76 • Articles published between January 2000 and December 2015.
- 77 • Peer-reviewed articles with full-text available online.

78 *Exclusion criteria:*

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

82 **Results**

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

87 *Insert Figure 1 about here*

88 ***Characteristics of Studies Reviewed***

89 Ten of the studies originated from the USA, two from Saudi Arabia and one each from
 90 Brazil, India, Netherlands and Nigeria (Table 1). The mean ages of participants ranged from
 91 8.97 ± 5.28 to 16.9 ± 1.7 . Three of the studies focused specifically on adolescents while others
 92 combined children and adolescents together. Two of the studies were longitudinal, one a
 93 prospective study, nine cross-sectional and four case-control studies. The proportion of HbSS
 94 phenotype ranged between 62.5% and 95.2% among the participants.

95

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Insert Table 1 about here

97 ***Measures of HRQL in children and adolescents with SCD***

98 Two types of ratings were employed in all included studies: self-reported measures for
99 children over 8 years who are literate and can understand, and caregiver proxy-reports, for
100 children ages 0 to 8 years, or for older children for purpose of comparison. HRQL
101 instruments are broadly categorised in the literature as either generic or disease-specific.
102 Generic HRQL instruments are useful for comparison across populations with chronic
103 diseases or healthy populations in order to facilitate broader understanding about the burden
104 of the SCD. Disease-specific instruments enhance the specificity in measuring HRQL to
105 sensitively discriminate within patients (Panepinto, 2012). All papers included in the review
106 employed generic HRQL instruments.

107 ***Paediatric Quality of Life Inventory fourth edition. (PedsQL 4.0)***

108 Seven of the studies employed the PedsQL 4.0 (Varni, Seid, & Rode, 1999) generic core
109 scales to investigate HRQL in CALSCD. PedsQL comprises 23 items that assess the child's
110 functioning in four domains, physical, emotional, social and school (role) functioning.
111 PedsQL4.0 has been translated into multiple languages (Dale, Cochran, Roy, Jernigan, &
112 Buchanan, 2011; Varni, Burwinkle, Seid, & Skarr, 2003). The patient-proxy version has also
113 demonstrated criterion validity with the ability to differentiate between specific subgroups of
114 children and also distinguish disease severity within a chronic condition and in children with
115 SCD (e.g. children with or without pain, or neurobehavioral complications) (McClellan,
116 Schatz, Sanchez, & Roberts, 2008; Schlenz, Schatz, McClellan, & Roberts, 2012). The use of
117 the instrument has been endorsed in the study of paediatric SCD population and has been
118 found to have internal consistency for caregivers for SCD patients (McCellan *et al.*, 2008;
119 Panepinto, Pajewski, Foerster, Sabnis, & Hoffmann, 2008; Fisak, Belkin, von Lehe, &

120 Bansal, 2011).

121 ***Child Health Questionnaire (CHQ) and CHQ-PF50***

122 Four of the studies (Table 1) used the CHQ (Palermo, Schwartz, Drotar, & McGowan, 2002)
123 which was the first comprehensive and multidimensional tool developed to measure HRQL in
124 children aged 5-18 along with a parent proxy CHQ-PF50. Widely used, the tool has been
125 useful in comparing HRQL of children with chronic health conditions (eg. asthma, epilepsy,
126 survivors of cancer) and healthy control groups, and has been found to be a valid predictor of
127 psychosocial and physical health (McCullough & Parkes, 2008; Wrotniak, Schall, Brault,
128 Balmer, & Stallings, 2012). Individual scores of the 14 subscales are aggregated into two
129 summary scores, the physical health summary and the psychosocial health summary. The
130 instrument also has been shown to have good discriminant validity when compared with
131 other chronic illness and scores in normative samples (McCullough and Parker, 2008;
132 Wrotniak *et al.*, 2012) and was first used to measure HRQL in children with SCD in 2002
133 (Palermo *et al.*, 2002).

134 ***Medical Outcome Study (MOS) Short Form-36 (SF-36)***

135 The SF-36 (Ware & Sherbourne, 1992) contains 36 items that measure quality of life across 8
136 domains and has been widely accepted and used in general and specific populations to
137 compare relative burden of diseases in more than 200 diseases and conditions. The instrument
138 has been translated into over 50 languages while the psychometric properties have been
139 validated in many studies. Four studies used the SF-36 as a measure of HRQL either as self-
140 reported by adolescents or caregiver proxy-report (Table 1).

141 ***HRQL in SCD patients compared with other groups.***

142 The identified studies consistently showed that the HRQL is affected in CALSCD (Table 2).

Palermo *et al.* (2002) found that 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 (Palermo *et al.*, 2002). Between 53% and 63% of CALSCD would be 'at risk' for impaired overall HRQL and physical HRQL respectively (Dale *et al.*, 2009).

In a group comparisons, Palermo *et al.* (2002) 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 (Palermo *et al.*, 2002). Another study showed that HRQL was lower in CALSCD compared with other chronic non-communicable diseases except in the domain of social functions (Bhagat, Baviskar, Mudey, & Goyal, 2014). 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. (Bhagat *et al.*, 2014).

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 (Hijmans *et al.*, 2010). 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 (Dale *et al.*, 2009). 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 (Amr, Amin, & Al-

Omair, 2011). Poorer behaviour, worse mental health, and lower self-esteem were reported among CALSCD (Palermo *et al.*, 2002). Sehlo and Kamfar (2015) 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 (Palermo *et al* 2002). Thus, SCD in children and adolescents was associated with limitations in most aspects of HRQL (Menezes, Len, Hilário, Terreri, & Braga, 2013)

Insert Table 2 about here

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

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 (Palermo *et al.*, 2002; Panepinto *et al.*, 2008; Sehlo & Kemfar, 2015). Disease severity is also associated with a history of pneumonia and asthma (Palermo *et al.*, 2002), recurrent priapism (Panepinto *et al.*, 2008), and disease genotype (Sehlo & Kemfar, 2015). Seven of the papers reviewed (Table 2) identified disease severity/complications as a predictor of HRQL in CALSCD (Adeyemo, Ojewunmi, Diaku-Akinwumi, Ayinde, & Akanmu, 2015; Amr *et al.*, 2011; Fisak, Belkin, von Lehe, & Bansal, 2011; Palermo *et al.*, 2002; Palermo, Riley, & Mitchell, 2008; Panepinto *et al.*, 2008; Sehlo & Kamfar, 2015) while one did not (Barakat, Lutz, Smith-Whitley, & Ohene-Frempong, 2005). Total number of disease-related complications was associated with worse physical health ($r=-0.91$) (Palermo *et al.*, 2002). In another study (Parlemo *et al.*, 2008), disease severity was a predictor of psychosocial HRQL ($\beta= -0.5$,

p≤0.01). Also, the presence of SCD was associated with 4 times higher odds of having worse HRQL (Panepinto *et al.*, 2008).

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 (Amr *et al.*, 2011). Disease severity was also a predictor of poor HRQL in CALSCD (Fisak *et al.*, 2011; Sehlo & Kamfar 2015). 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 (Adeyemo *et al.*, 2015). Disease severity also had individual and joint effects with social support and depression on the HRQL of CALSCD (Sehlo & Kamfar 2015).

Comorbidities

Medical co-morbidity and neurobehavioral co-morbidity were both associated with worse HRQL (Panepinto *et al.*, 2008) while behavioural comorbidity predicted physical health of the HRQL (Wrotniak *et al.*, 2012).

Hospitalisation

The frequency of hospitalisation predicted lower overall HRQL (Dale *et al.*, 2009; Amr *et al.*, 2011), physical health summary and mental health of the HRQL (Wrotniak *et al.*, 2012) and school functioning scores and the psychosocial domain (Dale *et al.*, 2009). The frequency of hospitalisation actually predicted worse HRQL in CALSCD in all the 8 domains of SF-36 HRQL subscales (Adeyemo *et al.*, 2015). Increased emergency department visits were associated with higher scores on the emotional role dimension of the HRQL subscales (Dale *et al.*, 2009).

215 *Pain episodes*

216 Frequency of pain was a predictor of change in HRQL (Schlenz *et al.*, 2012), physical
217 functioning and self-esteem (Barakat *et al.*, 2008). Pain also predicted low HRQL in
218 CALSCD (Menezes *et al.*, 2013).

219 *Depression*

220 Depression was a predictor ($\beta = 0.77$, $p < 0.001$) of the psychosocial HRQL domain (Palermo
221 *et al.*, 2008) and associated with poor quality of life (Sehlo & Kamfar, 2015). Mediator
222 variables consisting of internalizing symptoms and disease-related parenting stress correlated
223 with HRQL domains (Barakat, Patterson, Daniel, & Dampier, 2008). Moreover, depression
224 also predicted self-esteem while anxiety predicted physical functioning (Barakat *et al.*, 2008).

225 *Stigma*

226 Health-related stigma is characterised by discrediting of individuals and populations as a
227 result of a health condition resulting in adverse effects on health (Weiss, Ramakrishna, &
228 Somma, 2006). Stigma was associated with worse HRQL in all domains of the SF-36 HRQL
229 measure (Adeyemo *et al.*, 2015).

230 *Parental support*

231 A high level of parental support significantly reduced depression in CALSCD and predicted
232 better HRQL in CALSCD (Sehlo & Kamfar, 2015).

233 *Treatment Adherence/barriers to treatment adherence*

234 Treatment adherence predicted poor HRQL in CALSCD though the negative correlation was
235 unexpected (Barakat *et al.*, 2005). This unexpected direction of the relationship may be due
236 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 (Fisak *et al*, 2011).

Child demographics

Age inversely predicted HRQL in CALSCD (Adeyemo *et al.*, 2015; Amr *et al.*, 2011; Palermo *et al.*, 2002; Panepinto *et al.*, 2008) and predicted worse psychological HRQL (Panepinto *et al.*, 2008). In fact, all domains of HRQL on the SF-36 were negatively associated with increasing age of CALSCD (Amr *et al.*, 2011). Female gender was also associated with worse overall HRQL and general health, physical role functioning and body pain domains of HRQL (Amr *et al.*, 2011; Palermo *et al.*, 2002; Wrotniak *et al.*, 2012). Also lower BMI was associated with higher scores on the body pain subscale of HRQL (Wrotniak *et al.*, 2012).

Socio- economic status

Individual/family socioeconomic status were independent predictors of functional disability, physical and psychosocial HRQL in CALSCD (Palermo *et al.*, 2008). Higher parental education predicted better physical HRQL (Palermo *et al.*, 2008; Amr *et al.*, 2011). Also, neighbourhood socioeconomic distress was an independent predictor of physical HRQL (Palermo *et al.*, 2008). Furthermore, low family income predisposed CALSCD to 2.88 times higher odds of worse HRQL (Panepinto *et al.*, 2008) while low socio-economic status of the patient population was associated with low HRQL (Hijmans *et al*, 2010). Moreover, rural residence was a negative predictor of vitality and pain of the HRQL subscales (Amr *et al.*, 2011).

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 (Bhatia *et al.*, 2015). However, a 12-month Vitamin A supplementation had no effect on the HRQL (Wrotniak *et al.*, 2012).

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 (Panepinto, 2012; Varni *et al.*, 1999, 2003). 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 (Panepinto, 2012). 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 (Adeyemo *et al.*, 2015; Amr *et al.*, 2011; Fisak *et al.*, 2011; Palermo, 2002; Palermo *et al.*, 2008; Sehlo & Kamfar, 2015) was in line with the findings of Danckaerts *et al.* (2010) who reported that HRQL grows worse with an increase in severity of the condition in children with ADHD. Factors influencing disease severity include phenotype, fetal Haemoglobin (HbF) where high level of HbF was associated with decreased morbidity and mortality in those with SCD (Panepinto 2012). 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 (Weiss *et al.*, 2006). 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 (United Nations, 2008) to help address the burden of the disease in countries where the relative disease burden is higher.

In summary, 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.

Competing Interest

The authors declare that there is no conflict of interest

Ethical Approval

This review does not require ant ethical approval since it does not have direct contact with human subjects and was a review of information already in the public domain.

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486 Table 1: Characteristics of included studies

Authors Year	Country	Design	Population	Sample size		Mean age with SD	Female (SCD) %	HbSS %	Setting	Outcom e Variabl es	Measures		Rater
				SCD	Non- SCD						HRQL	Others	
Palermo <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> , 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	KIDSCREE N-52	Questionnaire, Dutch norm population data	Self
Amr <i>et al.</i> , 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 <i>et al.</i> 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
Wrotniak <i>et al.</i> , 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 <i>et al.</i> 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 <i>et al.</i> , 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 <i>et al.</i> 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 <i>et al.</i> , 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

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

491

492 Table 2: HRQL of SCD in Children and Adolescents

Author Year	Designs	Main focus	Investigated Determinants	Outcomes	Predictors/ Correlates
Palermo <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> , 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	Disease severity Age medical or neurobehavioral

				severity and 2.88 as a result of low family income.	commodities
Palermo <i>et al.</i> 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 <i>et al.</i> 2009		To assess HRQL 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 <i>et al.</i> , 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 <i>et al.</i> 2011	Cross sectional	To assess the impairment of the different domains of HRQL among adolescents with SCD	Socio-demographic factors, disease-related factors, family	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

		compared to healthy peers.	income		complications
Fisak <i>et al.</i> 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
Wrotniak <i>et al.</i> 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 <i>et al.</i> 2012 L	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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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	To assess the association between social support, disease severity and depression, and their individual or composite effect on HRQL in children	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

	sampling	with SCD			
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Fig. 1: Flow chart of study selection procedure

