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HEMATOLOGY: RESEARCH ARTICLE

Health-related quality of life in infants, toddlers and young children with sickle cell disease

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Abstract

Background: Little is known about health-related quality of life (HRQoL) in young children with sickle cell disease living in a European country.

Methods: A retrospective cross-sectional evaluation of TNO-AZL Preschool Children Quality of Life questionnaire (TAPQOL, 0–1 year) and Pediatric Quality of Life Inventory (PedsQL, 2–7 years) data was conducted. Study participants included caregivers of children with sickle cell disease aged 0–7 years attending the sickle cell centre at the Erasmus Medical Center or the Amsterdam University Medical Centers between April 2012 and October 2020. Comparisons were made with normative data on HRQoL in the general paediatric population.

Results: The study enrolled 136 caregivers of 136 children. In children aged 0–5 years, no significant differences emerged between children with sickle cell disease and the general population. However, in children aged 5–7 years, children with sickle cell disease scored significantly lower on all subscales except for emotional functioning. Multiple regression models showed a negative association between age and HRQoL. No association was found between HRQoL and disease severity or sociodemographic characteristics.

Conclusions: This study demonstrates that HRQoL is negatively correlated with age in young children with sickle cell disease with a significantly lower HRQoL in 5- to 7-year-olds when compared to the general population. Our study underlines the importance of measuring HRQoL in young children to identify patients with impaired HRQoL early in life in order to be able to intervene accordingly. Future research should focus on deepening the knowledge of factors influencing HRQoL in children with sickle cell disease.

KEYWORDS
child, infant, patient-reported outcomes, quality of life, sickle cell disease

Abbreviations: Hb, haemoglobin; HRQoL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory; SD, standard deviation (statistics); SE, standard error (statistics); TAPQOL, TNO-AZL Preschool Children Quality of Life questionnaire.

1 | INTRODUCTION

1.1 | Sickle cell disease

With millions affected worldwide and an estimated 300,000 newborns annually, sickle cell disease is the most common monogenetic disease.[1,2] Seventy-five percent of the global burden of sickle cell disease occurs in sub-Saharan Africa. However, due to migration, substantial numbers of children are now being born in parts of the world where sickle cell disease was previously considered rare, such as the United States and Europe.[2] In the Netherlands, approximately 1500 individuals have sickle cell disease, of which half are children.[3,4]

Sickle cell disease is characterised by the production of abnormal haemoglobin (Hb), leading to chronic haemolytic anaemia, functional asplenia, painful vaso-occlusive ischaemic crises and progressive organ failure.[1] The majority of children with sickle cell disease in sub-Saharan Africa do not reach their fifth birthday due to a lack of diagnostic facilities and prophylactic therapies, including antibiotics and vaccines.[2,5] In contrast, significant advances in health care have improved the life expectancy in well-resourced countries, resulting in an observed median survival of more than 60 years.[6] Still, life expectancy is more than two decades lower when compared to the general population.[7,8] However, with prolongation of survival, greater attention must be focused on outcomes beyond survival including health-related quality of life (HRQoL) to assess the multidimensional impact of sickle cell disease on patient's overall well-being.

1.2 | Health-related quality of life

The World Health Organization (1946) defines health as 'not only the absence of disease and infirmity, but also the presence of physical, mental and social well-being'.[9] Depending on the age of the child, HRQoL can be reported by the caregiver (proxy-report) or by the child directly (self-report).

Due to painful vaso-occlusive crises and manifestations of organ damage,[1,8] sickle cell disease has a substantial impact on daily functioning and well-being of children and their families. Children with sickle cell disease often have limited physical, psychological and social well-being,[10,11] as well as a higher risk of developing depressive symptoms when compared to the general paediatric population.[12–14] Baseline HRQoL in children with sickle cell disease is lower compared to the general paediatric population and an even more profound decrease in HRQoL is associated with severe disease,[10,15–19] whereas disease-modifying therapy improves HRQoL.[20]

The majority of studies on HRQoL in children with sickle cell disease have focused on children older than 5 years of age[10,11,13,15,17,19,21,22] or are based on data from Northern America.[10,13,15–19] Due to large differences in societal infrastructure and health care systems, reported HRQoL may not be generalisable to European countries. For example, children with sickle cell disease in the Netherlands receive comprehensive follow-up care at specialised outpatient clinics, whereas care in Northern America is generally more focussed on episodic (i.e., acute) care.[23] Reports are lacking on HRQoL in infants (0–1 year), toddlers (2–4 years) and young children (5–7 years) with sickle cell disease in the European setting. In order to improve HRQoL early in life, these data are important and provide insight into those areas that most urgently require improvement.[24] Therefore, the primary aim of this study is to evaluate HRQoL in children with sickle cell disease aged 0–7 years old, living in a European country and to compare it with HRQoL in the general paediatric population. The secondary aim is to analyse whether there is an association in these young children with sickle cell disease between HRQoL and (a) patient's age, (b) disease severity, and (c) caregiver's sociodemographic characteristics.

2 | METHODS

2.1 | Study design and participants

In this retrospective study, a cross-sectional evaluation of proxy-reported outcomes was conducted. Study participants included caregivers of children referred for clinical follow-up at the two largest sickle cell comprehensive care centres in the Netherlands, the Erasmus Medical Center - Sophia Children's Hospital and the Amsterdam University Medical Centers - Emma Children's Hospital, between 1 April 2012 and 1 October 2020. Caregivers completed the TNO-AZL Preschool Children Quality of Life (TAPQOL) or Pediatric Quality of Life Inventory 4.0 (PedsQL 4.0) in the digital KLIK patient-reported outcome measures (PROM) portal (https://www.hetklikt.nu/) as a part of their children's comprehensive care programme. Only the first completion of both the TAPQOL and PedsQL were included in the study and both were analysed separately. Normative data on HRQoL in the general population aged 0–7 years were extracted from the literature of an affiliated study group.[25] These normative data were collected with the TAPQOL and PedsQL, for research purposes only and reflects a representative sample of the general population living in the Netherlands.

This project was approved by the Medical Research Ethics Committee of the Erasmus University Medical Center and the Amsterdam University Medical Centers, and judged not to be subject to the 'Medical Research in Human Subjects Act' and adhered to the Declaration of Helsinki.[26] Participants were included if they were caregivers of children with a confirmed diagnosis of sickle cell disease aged 0–7 years, were literate in Dutch or English, and if informed consent to use their data for scientific purposes was provided. Age categories were congruent with the normative data and defined as infants (0–1 year; 0–24 months), toddlers (2–4 years) and young children (5–7 years).

2.2 | Measures

2.2.1 | TAPQOL

The TAPQOL questionnaire was used to collect caregiver proxy-reported outcomes of children aged 0–1 year.[27] The TAPQOL uses a 3-month recall period and encompasses 12 multi-item scales: sleeping,

appetite, lungs, stomach, skin, motor functioning, social functioning, problem behaviour, communication, anxiety, positive mood and liveliness. The scales social functioning, motor functioning and communication are only relevant for children aged 1.5 years and older. All scales measure frequency of a specific complaint or limitation, as scored on a three-point Likert response scale (never; occasionally; often). Additionally, if such a complaint or limitation is reported for seven TAPQOL scales (sleeping, appetite, stomach, skin, lung, motor functioning and communication), the well-being of the child in relation to the concerning complaint or limitation is measured, using a four-point Likert response scale (fine; not so good; quite bad; bad). Scale scores were calculated by merging and linearly transforming item scores to a 0–100 scale such that higher scores indicate better HRQoL.

2.2.2 | PedsQL generic scale 4.0

The generic PedsQL 4.0 was used to collect caregiver proxy-reported outcomes of children aged 2–4 years and 5–7 years.[28] The PedsQL uses a recall period of 1 week and encompasses 23 items across four multi-item scales: physical, emotional, social and school functioning. All items use a five-point Likert response scale (never; almost never; sometimes; often; almost always). The wording and content are as similar as possible across two age-category forms. A psychosocial health scale score was computed by calculating the mean as the sum of the items over the number of items answered in the emotional, social and school functioning scales. A total scale score was computed by calculating the mean of all 23 items. All items are reversed scored and linearly transformed into a 0–100 scale such that higher scores indicate better HRQoL.

2.2.3 | Disease-related characteristics

Sickle cell genotype (i.e., HbSS, HbSC, HbSβ^+, HBSβ^0 or other), number of painful vaso-occlusive crises, hospital admissions and emergency room contacts during the year prior to time point of measurement were determined from structured review of available medical records. Number of painful vaso-occlusive crises was based on caregiver proxy-report during outpatient appointments.

2.2.4 | Caregiver's sociodemographic characteristics

Caregivers completed a sociodemographic information form that included information about the caregiver, including country of birth, educational level (classified according to the International Standard Classification of Education 2011), marital status and employment.

2.3 | Statistical analyses

All statistical analyses were conducted in Statistical Package for Social Sciences (SPSS) version 23.0 for Windows. Descriptive statistics were generated for all age categories. Comparisons between characteristics of children with sickle cell disease and the general paediatric population were made by conducting two-sample independent *t*-tests (for age) and chi-square test (for patient's sex and caregiver's country of birth, educational level and employment status). Internal reliability of the measures was assessed by calculating Cronbach's coefficient alpha,[29,30] with a value of ≥.7 indicating acceptable reliability.[31]

Two-sample independent *t*-tests were conducted to examine the difference between HRQoL scales of children with sickle cell disease and the general paediatric population across the three age categories. For our primary outcome, Bonferroni correction was applied to compensate for multiple comparisons. Effect sizes (*d*) were calculated by dividing difference in mean score between children with sickle cell disease and the general paediatric population by the pooled standard deviations (SDs) of both groups. Effect sizes between 0.2 and 0.5 were considered small, effect sizes between 0.5 and 0.8 moderate, and effect sizes of above 0.8 large.[32]

Multivariate analyses of HRQoL in children with sickle cell disease were performed using three multiple linear regression models. Associations were evaluated between HRQoL scale scores and (a) age; (b) number of painful vaso-occlusive crises, hospital admissions or emergency department contacts; and (c) caregiver's country of birth, educational level, marital status or employment. Unstandardised regression coefficients (*B*) were compared to estimate the impact of these variables on scale scores. Statistical significance was set at $p \leq .05$.

3 | RESULTS

3.1 | Patient and family characteristics

A total of 136 caregivers of 136 children with sickle cell disease who visited the paediatric sickle cell comprehensive care centres of Rotterdam and Amsterdam consented to participate in this study. Among the participants, 46 completed the TAPQOL and 112 completed the PedsQL, whereof 22 participants completed both measurements (Table 1). This resulted in a sample size of caregivers of 46 infants (0–1 year), 19 toddlers (2–4 years) and 93 young children (5–7 years) with sickle cell disease. Eighteen sociodemographic forms were missing in the TAPQOL group (0–1 year) and 30 forms were missing in the PedsQL group (2–7 years). Medical records were not available for all patients, leading to missing disease-related information of nine patients in the TAPQOL group and eight patients in the PedsQL group. In children with sickle cell disease, the mean age of the TAPQOL group (0–1 year) was 1.07 (SD 0.480) and 45.7% were female. The mean age of the PedsQL group (2–7 years) was 6.09 (SD 1.300) and 43.8% were female. Table 1 provides an overview of the characteristics per age category of the children with sickle cell disease and the general paediatric population. Significant differences between patients and the general population were found in children's gender (in 5–7 years), caregiver's country of birth (in 0–1, 2–4 and 5–7 years), educational level (in 0–1 and 5–7 years) and employment status (in 0–1, 2–4 and 5–7 years).

TABLE 1 Characteristics per age category of children with sickle cell disease

	Sickle cell disease			General paediatric population		
	Infants (0–1 year)	Toddlers (2–4 years)	Young children (5–7 years)	Infants (0–1 year)	Toddlers (2–4 years)	Young children (5–7 years)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
n	46	19	93	227	293	274
Demographic characteristics patients						
Age in years, mean (SD)	1.07 (0.48)	3.67 (0.74)	6.59 (0.69)	0.98 (0.52)	3.47 (0.86)	6.52 (0.87)
Sex, female	21 (46)	9 (47)	40 (43)*	113 (50)	137 (47)	177 (65)
Sociodemographic characteristics of caregivers						
Missing data	18 (39)	0 (0)	30 (32)			
Country of birth						
The Netherlands	14 (50)*	10 (53)*	26 (41)*	221 (97.4)	276 (94.2)	264 (96.4)
Sub-Saharan Africa	7 (25)	3 (16)	18 (29)			
Netherlands Antilles or Suriname	7 (25)	6 (32)	19 (30)			
Educational level[a]						
Low	5 (18)	3 (16)	13 (21)*	17 (7.5)	34 (12)	29 (11)
Intermediate	16 (57)*	11 (58)	37 (59)*	81 (28)	129 (44)	123 (45)
High	7 (25)*	5 (26)	13 (21)*	145 (64)	126 (43)	121 (44)
Marital status						
Single	15 (54)	8 (42)	29 (46)			
Married or in partnership	13 (46)	11 (58)	34 (54)			
Employment						
Paid employment	18 (64)*	11 (58)*	40 (64)*	198 (87)	251 (86)	234 (85)
Disease-related characteristics						
Missing data	9 (20)	3 (16)	5 (5.4)			
Sickle cell genotype						
HbSS–HbSβ0	23 (62)	10 (63)	55 (63)			
HbSC–HbS$\beta \pm$ others	14 (38)	6 (38)	33 (38)			
Sickle cell crises/year, mean (SD)[b]	1.46 (2.13)	0.88 (1.96)	1.44 (1.99)			
Hospital admissions/year, mean (SD)[b]	0.49 (1.46)	0.25 (0.58)	0.34 (0.74)			
Emergency department contacts/year, mean (SD)[b]	0.78 (1.22)	0.19 (0.54)	0.41 (0.79)			

Abbreviation: SD, standard deviation.

[a]Highest educational level completed. Low: Primary education, lower vocational education, lower or middle general secondary education; intermediate: middle vocational education, higher secondary education, pre-university education; high: higher vocational education, university.

[b]Number of sickle cell crises, hospital admissions and emergency department contacts in the year prior to time point of measurement.

*p-Value $< .05$ children with sickle cell disease versus the general paediatric population.

3.2 | Internal consistency of TAPQOL and PedsQL 4.0

Cronbach's alpha scores for TAPQOL were lower than .7 (.65–.68), except for four scales (liveliness .73, problem behaviour .72, social functioning .71 and positive mood .70). Therefore, TAPQOL data were excluded for multivariate analyses in this study. The PedsQL Cronbach's alpha scores were above .7 for all PedsQL 4.0 generic scales, ranging between .89 and .93.

3.3 | Comparison of HRQoL scores with general paediatric population

Table 2 depicts HRQoL in children with sickle cell disease per age category, compared to the general paediatric population. After correcting for multiple testing, infants (0–1 year) with sickle cell disease scored significantly lower than the general infant population on two out of 12 TAPQOL scales, namely, skin ($p = .043$, $d = 0.43$) and positive mood ($p = .034$, $d = 0.49$). There was no significant

TABLE 2 Health-related quality of life in children with SCD versus the general paediatric population

	Children with SCD		General paediatric population		General versus SCD		
	n	Mean (SD)	*n*	Mean (SD)	*p*-Value	Bonferroni *p*-value	Effect size
Parent proxy-report TAPQOL							
Infants (0–1 year)							
Sleeping	46	77.99 (17.17)	227	75.90 (19.45)	.499	1.000	0.11
Appetite	46	82.07 (17.83)	227	89.68 (15.65)	.004	.086	0.45
Lungs	46	88.04 (16.91)	227	92.88 (14.41)	.045	1.000	0.31
Stomach	46	86.05 (18.43)	227	86.20 (15.92)	.955	1.000	0.01
Skin	46	84.60 (19.40)	227	91.56 (12.11)	.002	.043	0.43
Motor functioning[a]	15	86.25 (26.11)	58	94.50 (12.72)	.084	1.000	0.40
Social functioning[a]	15	87.78 (26.33)	58	92.53 (15.35)	.369	1.000	0.22
Problem behaviour	46	88.51 (14.32)	227	85.15 (14.63)	.155	1.000	0.23
Communication[a]	15	90.83 (9.99)	58	88.47 (14.98)	.566	1.000	0.19
Anxiety	46	84.78 (22.99)	227	86.27 (15.35)	.585	1.000	0.01
Positive mood	46	92.39 (13.01)	227	98.24 (10.83)	.001	.034	0.49
Liveliness	46	97.10 (9.50)	227	97.65 (11.49)	.761	1.000	0.05
Parent proxy-report PedsQL 4.0							
Toddlers (2–4 years)							
Total score	19	88.54 (12.21)	293	88.55 (10.10)	.997	1.000	<0.01
Psychosocial health	19	88.97 (12.31)	293	86.53 (11.14)	.359	1.000	0.21
Physical health	19	87.83 (14.50)	293	91.84 (11.22)	.140	1.000	0.31
Emotional functioning	19	85.26 (14.48)	293	78.45 (14.74)	.052	1.000	0.47
Social functioning	19	92.11 (14.46)	293	90.09 (13.71)	.536	1.000	0.14
School functioning	19	89.91 (12.60)	293	94.06 (12.49)	.162	1.000	0.33
Young children (5-7 years)							
Total score	93	73.85 (16.58)	274	86.05 (11.59)	<.001	<.001	0.85
Psychosocial health	93	74.00 (16.59)	274	83.38 (13.65)	<.001	<.001	0.62
Physical health	93	73.59 (22.36)	274	91.06 (12.64)	<.001	<.001	0.96
Emotional functioning	93	73.82 (18.47)	274	77.93 (16.70)	.036	.859	0.26
Social functioning	93	78.55 (20.92)	274	86.39 (16.70)	<.001	.005	0.41
School functioning	93	69.62 (20.41)	274	85.82 (15.41)	<.001	<.001	0.90

Abbreviations: SCD, sickle cell disease; SD, standard deviation.
[a]TAPQOL scale only contains items for children aged ≥1.5 years.

difference between HRQoL scores of toddlers (2–4 years) with sickle cell disease and the general toddler population. Young children (5–7 years) with sickle cell disease scored significantly lower than the general young paediatric population on PedsQL total score ($p < .001$, $p = .85$) and four out of five PedsQL subscales, namely, psychosocial health ($p < .001$, $d = 0.62$), physical health ($p < .001$, $d = 0.96$), social functioning ($p = .005$, $d = 0.41$) and school functioning ($p < .001$, $d = 0.90$). Mean scale scores per age category are visualised in Figure S1.

3.4 | Associations of clinical and demographic parameters with HRQoL scores

3.4.1 | Age

Table 3 shows that HRQoL negatively correlates with age in children with sickle cell disease on all PedsQL scales (all $p < .05$). The highest regression coefficient was found on school functioning (beta −6.294, standard error [SE] 1.831, $p = .001$). The total PedsQL score was also

TABLE 3 Unstandardised regression coefficients estimating the association between health-related quality of life and age in children with sickle cell disease aged 2–7 years, controlled for gender, genotype, disease-related and sociodemographic characteristics

	Age	
	B (SE)	*p*-Value
Parent proxy-report PedsQL 4.0		
Toddlers and young children (2–7 years) (*n* = 69)		
Total score	−4.356 (1.287)	.001
Psychosocial health	−4.369 (1.324)	.002
Physical health	−4.331 (1.868)	.024
Emotional functioning	−4.040 (1.487)	.009
Social functioning	−3.164 (1.454)	.034
School functioning	−6.294 (1.831)	.001

Abbreviations: *B*, unstandardised regression coefficient; SE, standard error.

TABLE 4 Unstandardised regression coefficients estimating the association between health-related quality of life and disease-related characteristics in children with sickle cell disease aged 2–7 years, controlled for age, gender, sickle cell genotype and sociodemographic characteristics

	Sickle cell crises		Hospital admissions		Emergency department contacts	
	B (SE)	*p*-Value	*B* (SE)	*p*-Value	*B* (SE)	*p*-Value
Parent proxy-report PedsQL 4.0						
Toddlers and young children (2–7 years) (*n* = 74)						
Total score	0.207 (0.793)	.795	1.006 (3.172)	.752	2.976 (3.018)	.328
Psychosocial health	0.115 (0.829)	.890	1.557 (3.309)	.640	2.986 (3.154)	.347
Physical health	0.408 (1.105)	.713	0.260 (4.424)	.953	3.063 (4.221)	.471
Emotional functioning	−0.307 (0.945)	.747	1.438 (3.778)	.705	4.901 (3.571)	.175
Social functioning	1.534 (0.925)	.102	7.159 (3.670)	.056	3.341 (3.598)	.357
School functioning	−0.796 (1.097)	.471	−3.639 (4.381)	.409	0.564 (4.220)	.894

Abbreviations: *B*, unstandardised regression coefficient; SE, standard error.

significantly associated with age, with a regression coefficient (*B*) of −4.356 (1.287 SE, $p < .001$).

3.5 | Disease severity

No significant association was found between PedsQL scales and disease-related characteristics, that is, number of crises, hospital admissions and emergency contacts (Table 4).

3.6 | Sociodemographic characteristics

The association between HRQoL and sociodemographic characteristics, including country of birth, marital status, employment and educational level of the caregiver, are presented in Table 5. Having a caregiver born in sub-Saharan Africa was positively associated with the PedsQL subscales psychosocial health (B 8.280, SE 3.708, $p = .042$) and school functioning (*B* 12.442, SE 5.313, $p = .022$). However, on other subscales, including total PedsQL score, no association was found between caregiver's country of birth and HRQoL scores. Unemployment of the caregiver showed a positive association with emotional functioning of the child (*B* 7.494, SE 3.740, $p = .049$). Still, no significant association was found on the other scales, nor on the total score ($p = .306$). Marital status and educational level of the caregiver were not found to be significantly associated with HRQoL on any scale of the PedsQL.

4 | DISCUSSION

We assessed HRQoL in infants (0–1 year), toddlers (2–4 years) and young children (5–7 years) with sickle cell disease by analysing and comparing proxy-reported HRQoL scores of children with sickle cell disease with the age-specific general population.

In our study, the overall difference in HRQoL between children with sickle cell disease and the general paediatric population was small or

TABLE 5 Unstandardised regression coefficients estimating the correlation between health-related quality of life and sociodemographic characteristics in children with sickle cell disease aged 2–7 years, controlled for age, gender, genotype and disease-related characteristics

	Country of birth						Marital status		Employment		Educational level	
	The Netherlands		Sub-Saharan Africa		Netherlands Antilles and Suriname		Single		No paid employment		Low	
	B (SE)	*p*-Value	*B* (SE)	*p*-Value	*B* (SE)	*p*-Value	*B* (SE)	*p*-Value	*B* (SE)	*p*-value	*B* (SE)	*p*-Value
Parent proxy-report PedsQL 4.0												
Toddlers & Young Children (2-7 years) (n = 77)												
Total score	−1.336 (3.101)	.668	5.836 (3.708)	.120	−2.964 (3.275)	.369	0.187 (3.172)	.953	3.236 (3.138)	.306	2.208 (3.929)	.576
Psychosocial health	−3.382 (3.357)	.317	8.280 (3.987)	.042	−2.509 (3.575)	.485	0.944 (3.453)	.785	4.620 (3.398)	.178	0.466 (4.288)	.914
Physical health	2.532 (4.280)	.556	1.358 (5.212)	.795	−3.909 (4.528)	.391	−1.312 (4.381)	.765	0.726 (4.368)	.868	5.440 (5.402)	.317
Emotional functioning	−0.720 (3.778)	.849	7.904 (4.493)	.083	−4.921 (3.965)	.219	2.416 (3.849)	.532	7.494 (3.740)	.049	4.949 (4.756)	.312
Social functioning	−2.413 (3.805)	.528	4.719 (4.602)	.309	−0.450 (4.047)	.912	−1.048 (3.896)	.789	3.228 (3.865)	.406	−2.521 (4.829)	.603
School functioning	−7.059 (4.462)	.118	12.442 (5.313)	.022	−2.262 (4.811)	.640	1.166 (4.638)	.802	2.824 (4.612)	.542	−1.501 (5.757)	.795

Abbreviations: *B*, unstandardised regression coefficient; SE, standard error.

nonsignificant in infants (0–1 year) and toddlers (2–4 years). However, there was a significant difference between patients and the general population in young children (5–7 years). This is in line with our secondary finding that a higher age was related to lower HRQoL scores in children with sickle cell disease. Similar findings have been demonstrated in previous studies on HRQoL in older children and adolescents (aged 5–18 years) with sickle cell disease, where HRQoL was also significantly lower compared to HRQoL in the general paediatric population.[10,13,15,17,18] It is well known that the decline of foetal Hb during the first year of life and the accumulation of organ damage as patients age are both associated with clinical deterioration.[1,33] Lower HRQoL scores in older children may also be the result of 'growing into deficit', a phenomenon that is described in children with chronic diseases or brain damage. While children may function normally at a very young age, over time with increasing day-to-day demands, they may fail to acquire normal, age-appropriate developmental milestones.[34–37] As a result, psychological problems may become more visible over time when higher cognitive functions, such as emotion regulation, are required.

In contrast to previous studies, we did not find an association between HRQoL subscale scores and disease severity. A possibility for this discrepancy in study results is the relatively low prevalence of reported painful vaso-occlusive crises, hospital admissions and emergency department contacts in our cohort. Studies in Northern America have reported a higher number of painful vaso-occlusive crises[15,18,19] and more than six times higher frequencies of acute care visits to the emergency department[15,16,18,19] when compared to our study population. As age-related increases in frequency and prevalence of acute and chronic complications are well recognised,[38–40] the relatively young age of our cohort may account for the much lower number of painful vaso-occlusive crises. Furthermore, the number of vaso-occlusive crises was based on subjective caregiver proxy-report and some caregivers' definition of a crisis may ignore pain treated at home. Many studies have documented such misunderstandings between patients and/or caregivers and physicians about painful vaso-occlusive crises.[41–43] The consistent use of established definitions from the perspective of patients and caregivers are needed to further explore the association between disease severity and HRQoL in future research.[44]

We also did not find a clear association between sociodemographic characteristics of caregivers (i.e., country of birth, marital status, employment and educational level) and HRQoL in toddlers and young children with sickle cell disease. Conversely, several studies worldwide have reported that HRQoL in the general paediatric population is associated with caregiver's educational level, socioeconomic status and ethnicity.[11,45–48] Furthermore, in children and adolescents with sickle cell disease (aged 6–18 years), lower socioeconomic status is associated with impaired HRQoL when compared to the general population.[11,48] In the Netherlands, almost all sickle cell disease families belong to ethnic minority groups due to a history of recent migration.[2] The lack of variability in sociodemographic status in our study or the relatively small study group may account for the fact

that we did not find an association between socioeconomic status and HRQoL.

In our study, of all PedsQL subscales, school functioning was most strongly affected in children with sickle cell disease, and related to age. Learning difficulties have been recognised as the 'new hidden morbidity' in children with chronic diseases or pain.[49–52] Furthermore, cognitive deficits could be caused by the relatively high frequency of silent cerebral infarctions, which are known to develop in children with sickle cell disease as young as 1 year of age.[53] Early identification of impaired school functioning in children with sickle cell disease should mandate more comprehensive and focused neuropsychological evaluation as well as targeted intervention programmes.

There are limitations to this study that warrant consideration while interpreting the results. First, the cross-sectional nature of the study design does not allow for determination of causal relationships between the study variables and HRQoL. Second, there is potential for selection bias, as only caregivers who were literate in Dutch or English could participate in this study. Third, missing data due to the unavailability of some medical records and unanswered sociodemographic questions limited our sample size. In addition, small patient numbers in the toddlers age category ($n = 19$) made the validity to detect significance in this group questionable. Moreover, we were not able to analyse the effect of disease-modifying therapies on HRQoL in our study, as these therapies (e.g., hydroxyurea) were not yet standard of care and mainly prescribed to children with severe disease, leading to biased data. Fourth, literature has generally shown that individuals themselves are the most reliable and accurate observers of their quality-of-life perceptions and experiences. However, in our very young age group, caregiver report was the only feasible metric.[54–56] Fifth, we have used two different measures (TAPQOL and PedsQL), as PedsQL data are not available for infants. Unfortunately, the TAPQOL was found to have questionable reliability in our study. Therefore, we could not include infants (0–1 year) in the multivariate analyses and the presented TAPQOL results should be interpreted with caution. Finally, we compared our data on children with sickle cell disease with previously published data on the general population,[25] and demographic variables varied greatly between the two groups (Table 1). Sickle cell disease patients in Europe often have a history of migration.[2] It therefore remains challenging to incorporate control groups with similar sociodemographic backgrounds. One may question if separating disease effects from sociodemographic data is necessary, if both seem to be related in this patient population.[11] Whether or not our study results were influenced by sociodemographic factors, it provides clear evidence that children with sickle cell disease are vulnerable.

Although we did not find a significant association between HRQoL and disease severity or HRQoL and sociodemographic characteristics, we did observe that HRQoL is negatively associated with age in young children with sickle cell disease, with a lower HRQoL from 5 years of age when compared to the general paediatric population. These findings underline the importance of identifying the needs of children with sickle cell disease at a young age in order to implement support and meaningful interventions. Future research with the use of more precise and consistent definitions of painful vaso-occlusive crises and inclusion of more extensive clinical data (i.e., blood counts, sickle cell disease-related complications, disease-modifying therapies) could aid in addressing knowledge gaps in the association between disease severity and HRQoL in young children with sickle cell disease. Furthermore, research on young siblings of children with sickle cell disease is important in evaluating the confounding role of sociodemographic context regarding lower HRQoL in young children with sickle cell disease.

5 | CONCLUSION

To conclude, our study demonstrates that HRQoL is negatively correlated with age in young children with sickle cell disease, with a significantly lower HRQoL in 5- to 7-year-olds when compared to the general population. Unfortunately, it was not possible to elucidate the causes of these differences and their modifiers. Future research is needed to deepen the understanding of the association between HRQoL and sickle cell disease severity and sociodemographic background. Our study underlines the importance of measuring HRQoL in young children to identify patients with impaired HRQoL as early in life as possible. The recognition of the specific areas that require appropriate interventions will help enable targeting of resources to improve quality of life for children with sickle cell disease.

CONFLICT OF INTEREST

Dr. Marjon H. Cnossen's institution has received investigator-initiated research and travel grants as well as speaker fees over the years from The Netherlands Organisation for Scientific Research (NWO), the Netherlands Organisation for Health Research and Development (ZonMw), the Dutch 'Innovatiefonds Zorgverzekeraars', Pfizer, Baxter/Baxalta/Shire, Bayer Schering Pharma, CSL Behring, Sobi and Biogen Idec, Novo Nordisk, Novartis and Nordic Pharma, and for serving as a steering board member for f Roche, Bayer and Novartis for which fees go to the Erasmus MC as an institution. Dr. Anne P. J. de Pagter has received a grant from Rotary Foundation for the institution. All other authors declare no conflict of interest relevant to the contents of this manuscript.

DATA AVAILABILITY STATEMENT

Data generated at a central, large-scale facility are available upon request.

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SUPPORTING INFORMATION

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