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Patient-Reported Outcomes

Health-Related Quality of Life in Children With Sickle Cell Anemia in Malaria-Endemic Regions: The Impact of Disease States and Malaria Prevention Strategies

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ABSTRACT

Objectives: To assess the health-related quality of life (HRQoL) of children with sickle cell anemia (SCA) in Uganda and Malawi during steady disease states and sick attacks and to examine the impact of malaria chemoprevention with weekly dihydroartemisinin-piperaquine compared to monthly sulfadoxine-pyrimethamine.

Methods: This cohort study was nested within a clinical trial comparing weekly dihydroartemisinin-piperaquine with the standard of care (monthly sulfadoxine-pyrimethamine) among children with SCA. HRQoL was assessed using EQ-5D tools during steady states and sick attacks. Ordinary least squares regression identified factors associated with HRQoL.

Results: A total of 633 children with SCA were enrolled (mean age 8.1 years, standard deviation [SD] 3.7). HRQoL was higher during steady states but deteriorated during sick attacks, with the most problems reported in pain and discomfort. Older children (ages 12-16: mean difference [MD] = 0.09, $P < .0001$) experienced higher HRQoL during steady states but lower HRQoL during sick attacks. Hospitalization negatively affected HRQoL; children hospitalized 1 to 3 times (MD = −0.27, $P = .01$) or ≥4 times (MD = −0.24, $P = .02$) had substantially lower HRQoL. There were no HRQoL differences between treatment arms.

Conclusions: The HRQoL of children with SCA was relatively high during steady states but declined substantially during sick attacks, especially because of severe pain and discomfort. HRQoL is influenced by a child's age and frequency of hospitalization. Results provide information for calculation of quality-adjusted life years for future economic evaluation.

Keywords: Malawi, Uganda, quality of life, sickle cell anemia, sub-Saharan Africa.

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Introduction

Sickle cell anemia, an inherited red blood cell disorder, greatly contributes to childhood mortality and morbidity. Globally, over 400 000 children are born with sickle cell anemia (SCA) worldwide, of which 80% reside in malaria-endemic regions in sub-Saharan Africa (SSA).[1,2] SCA is characterized by repeated severe acute illnesses, chronic morbidity leading to frequent hospitalizations, and early mortality.[3] SCA is characterized by repeated episodes of bodily pain and infections, vitality and social function impairments, anemia, acute chest syndrome with breathing complications, and stroke.[4-10] The prevalence of the sickle cell gene is linked to malaria, and in the endemic regions of SSA, the gene prevalence increases with transmission intensity.[11] In Malawi and Uganda, the national prevalence of SCA is high.[12,13] Malaria is frequent precipitant of these SCA-related illnesses and early death.[14-16] The high morbidity and mortality in these children impedes progress toward achieving sustainable development goal 3, which aims to ensure healthy lives and reduce childhood mortality.[17]

Similar to many other chronic diseases, recurrent illness episodes negatively affect the health-related quality of life (HRQoL) of SCA patients. The HRQoL is a patient's appraisal of their health based on the physical, psychological, and social domains of health but is also influenced by an individual's value systems, standards, concerns, experiences, expectations, and perceptions.[18] HRQoL measures are useful to assess the impact and severity of disease, detect changes in a patient's health status over time, the effectiveness and efficiency of treatment interventions, and aid in identifying inequities in health.[19-21]

Several studies concur that patients with SCA have a low HRQoL.[4,22-27] SCA has been found to adversely affect children's physical, emotional, psychological (anxiety and depression, neurocognitive impairment), educational, recreational, social, and social well-being, including their independence and environment.[7,26,28-31] Evidence also highlights that low HRQoL scores in children with SCA patients are influenced by gender, age, disease complications, family demographics (parents' education and income/financial resources), residing in rural areas, existing medical

and neurobehavioral comorbidities, and the use of hydroxyurea.[7,8,24,32-35] Previous studies in Uganda and Malawi[26,27] have used the pediatric quality-of-life questionnaire (PedsQL) that describes the clinical situation of SCA patients but have not evaluated HRQoL over time or distinguished between crises and steady disease states. Additionally, these results do not directly apply to the calculation of quality-adjusted life years (QALYs) for economic evaluation, which requires a preference-based generic instrument.[36] We therefore sought to understand how HRQoL is affected in children with SCA in malaria-endemic regions of East and Southern Africa using a generic, preference-based instrument. We explored the factors associated with HRQoL scores during steady and sick states.

Methods

Study Design and Participants

This study was part of an individually randomised, double blind, placebo controlled parallel-group, superiority trial of weekly dihydroartemisinin-piperaquine (DP) compared to monthly sulfadoxine-pyrimethamine (SP) (CHEMCHA, NCT04844099). The trial was conducted among children aged 6 months to 15 years with SCA conducted in 2 hospitals in Uganda (Jinja Regional Referral Hospital and Kitgum General Hospital) and 2 hospitals in Malawi (Queen Elizabeth Central Hospital in Blantyre and Kamuzu Central Hospital in Lilongwe). The study protocol is published.[37]

Evaluation of HRQoL

First, we collected sociodemographic data on children and parents at enrolment, including their age, gender, levels of education, religion, marital status, ethnic background, occupation, housing conditions, ownership of household assets, literacy/education, water sources, and type of latrine facilities. We then measured the HRQoL using the 3-level version of the Euroqol Group tool (EQ-5D-3L) to facilitate the calculation of QALYs.[38] The first part of the EQ-5D tool measures health status using 5 dimensions for describing health states: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension, respondents rated their situation by selecting one of the 3 levels: no problems, some problems, or a lot of problems, giving 243 possible health states.[39] Each respondent's health profiles were converted into a single utility score based on a value set. The second part of the questionnaire measures a respondent's self-rated health on a linear visual analog scale (EQ-VAS) that captures the respondent's overall assessment of their health on a scale of 0 (worst imaginable) to 100 (best health imaginable).[39] Different versions of the EQ-5D tools were used according to the child's age.[39] The EQ-5D-Y proxy versions were used for children aged 4 to 7 years because these tools were designed for proxies, meaning caregivers, in this case, responded on behalf of the children. The EQ-5D-Y-3L interview administered version was used for children aged 8 to 11, whereas the EQ-5D-3L tool was used for older children aged 12 to 15. The EQ-5D-Y-3L is based on the EQ-5D-3L. Children under 4 years of age did not participate in study. The EQ-5D tool was administered through face-to-face interviews by trained study personnel at enrolment, during sick attacks, and at the end of the study.

Data Analysis

We used Hungarian value sets for the EQ-5D-Y and EQ-5D-3L responses for the base-case analysis because there was no available EQ-5D-Y-3L value set for a young African population.[40-42] In scenario analyses, we compared the application of alternative value sets. In scenario 1, we used the Zimbabwean value set (EQ-5D-Y and the EQ-5D-3L) for all ages,[43] whereas in scenario 2, we used the Hungarian value set (EQ5D-Y-3L) for children 4 to 11 years and the Zimbabwean value set (EQ-5D-3L) for children 12 to 16 years. The Zimbabwe value set was considered because it is the only EQ-5D-3L value set from an African country.

Descriptive statistics such as frequencies/counts, means, and SDs were used to describe categorical variables, the EQ-5D VAS score, and the EQ-5D index score, and compare the distribution of demographic factors among the study population by study arm and study visit type. We calculated summary statistics, including the numbers and proportions of children reporting each severity level in the 5 dimensions. We grouped the summary scores by age category and treatment allocation arm.[44] We measured household socioeconomic status and constructed wealth indices using principal component analysis.[45] We used household characteristics, such as household assets, occupation, literacy/education, housing conditions, water source, and type of latrine facility, to construct the indices.[46] The score was then categorized into tertials. We used multivariate ordinary least square regression[47,48] to explore associations during baseline, sick and endline visits. The main outcome was the EQ-5D index scores (HRQoL) reported during the study visits. We explored how the individual characteristics, disease complications, treatment options, and household-level socioeconomic status influence the HRQoL. Data were analyzed with Stata v18 (StataCorp).[49]

Ethical Considerations

We obtained ethical approval from the Makerere University School of Medicine Research and Ethics Committee (SOMREC 2020-103), Uganda National Council of Science and Technology (UNCST HS709ES), National Health Science Research Committee (19/11/2442), the Regional Ethics Committee of Norway (REK 30992), and the Liverpool School of Tropical Medicine (LSTM REC 19-105) institutional review boards. Permission was sought from the hospitals where the study was conducted. Written consent was obtained from caregivers of the children eligible to participate in the study at the time of enrolment and throughout the child's participation. In addition, assent was obtained from children aged ≥8 years. The study staff used consent forms in English or the local language of choice.

Results

Patient Characteristics at Baseline

A total of 631 children with SCA were included; 378 from Uganda and 253 from Malawi. The mean age was 8.2 (SD 3.4) in Uganda and 8.0 (SD 4.0) in Malawi (Table 1). Half the children were male (51%) and attending primary school (54%). Most children had been hospitalized at least once in the last year (49%) and had ever received a blood transfusion (81%). Forty-two percent had ever received hydroxyurea treatment (15% in Uganda and 83% in Malawi). Only 39% of the children were on hydroxyurea at baseline, with the majority (94%) in Malawi. Many parents/caregivers were married (78%). Over 40% had no formal education or only achieved primary education. The most frequent main source of income was farming (38%) (49% in Uganda and 24% in Malawi). In both countries, 51% of the children were randomized to DP and 49% to SP.

Impact of SCA on Children's Health-Related Quality of Life

During steady states (baseline and endline) children in Malawi reported more problems than those in Uganda. At baseline, the

Table 1. Sociodemographic characteristics of the children with sickle cell anemia at baseline.

Variable	Uganda (*n* = 378) *n* (%)	Malawi (*n* = 253) *n* (%)	Total (*n* = 631) *n* (%)
Children's characteristics			
Average age	8.2 (3.4)	8.0 (4.0)	8.1 (3.7)
Sex of the child			
Male	196 (52)	124 (49)	320 (51)
Female	182 (48)	129 (51)	311 (49)
Age of the child			
4-7	167 (44)	93 (37)	260 (41)
8-11	126 (33)	85 (34)	211 (33)
12-16	85 (23)	75 (29)	160 (26)
School grade			
Preschool	125 (33)	46 (18)	171 (27)
Primary school	164 (43)	180 (71)	344 (54)
Secondary school	6 (2)	4 (2)	10 (2)
Not In school	83 (22)	23 (9)	106 (17)
No of hospitalizations in past year			
None	110 (29)	86 (34)	196 (31)
1-3	188 (50)	121 (47)	309 (49)
≥4	80 (21)	46 (19)	126 (20)
Ever had a blood transfusion			
Yes	312 (82)	198 (78)	510 (81)
No	66 (18)	55 (22)	121 (19)
Ever used hydroxyurea			
No	323 (85)	43 (17)	366 (58)
Yes	55 (15)	210 (83)	265 (42)
Currently on hydroxyurea*			
No	347 (92)	12 (6)	359 (61)
Yes	31 (8)	198 (94)	229 (39)
Parent's Marital status*			
Single	29 (8)	8 (3)	37 (6)
Married	278 (74)	208 (84)	486 (78)
Other	68 (18)	32 (2)	100 (16)
Parents' education level			
Primary or lower	153 (41)	114 (50)	267 (44)
Secondary	160 (41)	85 (38)	245 (40)
Tertiary/University	40 (11)	27 (12)	67 (11)
No school	25 (7)	-	25 (5)
Main source of income			
Farmer	177 (47)	59 (23)	236 (38)
Employed	99 (27)	43 (17)	142 (22)
Self employed	21 (6)	73 (29)	94 (15)
Casual worker for wages	39 (10)	62 (25)	101 (16)
Others	38 (10)	16 (6)	54 (9)
Wealth index*			
Poor	128 (34)	88 (34)	216 (34)
Middle	133 (36)	83 (33)	216 (34)
Less poor	114 (30)	82 (33)	196 (32)

continued on next page

Table 1. Continued

In both countries, 51% of the children were randomized to DP, whereas the rest were randomized to SP.
*Missing data.

most reported problems in Ugandan children were pain and discomfort (14%), limitations in mobility (10%), and/or self-care (9%) dimensions (Fig. 1). In Malawi, children reported the most problems with pain and discomfort (59%) and self-care (44%) dimensions. By the end of the study, the proportion of children reporting problems had reduced. However, children still reported problems, especially with pain and discomfort (8% in Uganda and 45% in Malawi). During sick attacks, the burden of reported problems increased, particularly for pain and discomfort (77% in Uganda and 96% in Malawi) and limitations in conducting usual activities (66% in Uganda and 89% in Malawi). In addition, for children in Malawi, self-care problems (85%) were reported (Fig. 1).

The overall mean EQ-VAS score at was 85 (SD 12) at baseline and 87 (SD 10) at the end of the study. This decreased to 63 (SD 15) during sick attacks (Table 2). Children in Malawi reported slightly higher EQ-VAS scores at both baseline (86 [SD 8]) and during sick attacks (70 [SD 11]) compared to Ugandan children (baseline: 83 [SD 16], sick attacks: 61 [SD 18]) (Table 2). Younger children aged 4 to 7 had the lowest mean scores at baseline (83 [SD 14]) and at the end of the study (86 [SD 10]) (Table 2).

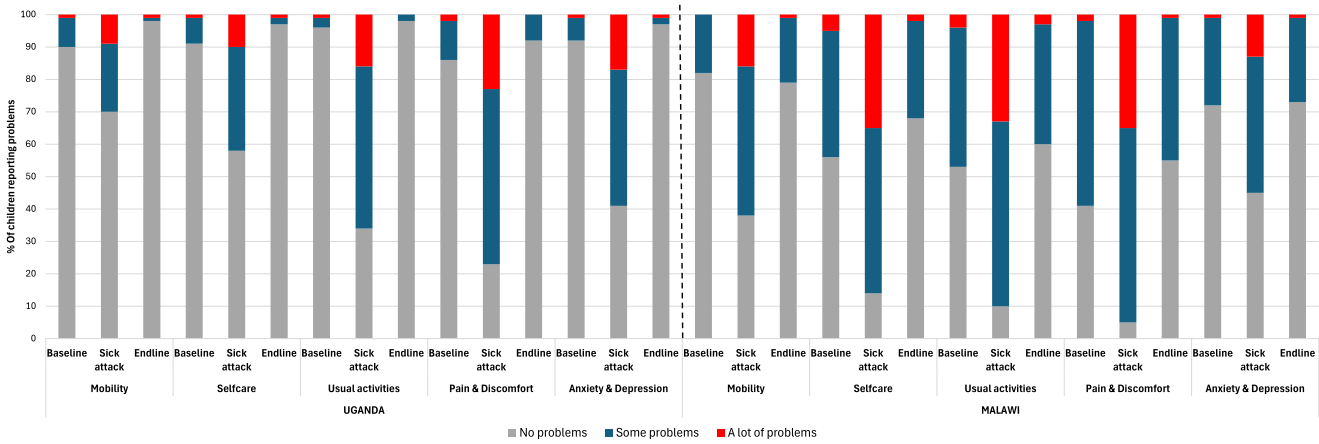
EQ5D indices were also high during steady states and decreased during sick attacks. Children in Uganda reported higher index scores at baseline and endline than children in Malawi (Table 2). At baseline, the overall EQ-5D index in Uganda and Malawi was 0.89 (SD 0.16) at baseline and 0.94 (SD 0.11) at the end of the study. This score decreased to 0.60 (SD 0.31) during sick attacks (Table 2). The scenario analyses (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101120) showed slight differences in the index scores during steady states. Overall, index scores reported using the Hungarian value set had higher index values than those valued using the Zimbabwean value set. During sick attacks, indices reported using the Hungary value set were lower than those reported using the Zimbabwean value set.

Factors Associated With Health-Related Quality of Life

During steady states, HRQoL was positively associated with age at baseline. Older children aged 12 to 16 had a higher HRQoL than those aged 4 to 7 (mean difference [MD] = .09, $P < .0001$) (Table 3). Having previously been hospitalized 1 to 3 times (MD = −0.03, P = .09) was also negatively associated with HRQoL at baseline but only borderline significantly. At the end of the study, children whose parents were divorced or cohabited had a slightly higher quality of life (MD = 0.05, P = .06). Further, children in Malawi had lower HRQoL at both baseline (MD = −0.10, $P < .0001$) and endline (MD = −0.08, $P < .0001$) visits compared to children in Uganda.

During sick attacks, HRQoL was associated with age. Children aged 8 to 11 years (MD = −0.98, P = .08) had lower HRQoL than

Figure 1. Proportion of children reporting problems in Uganda and Malawi during steady states and sick attacks. The cumulative bar charts show the proportion of children reporting problems by dimension (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) at baseline, sick attacks, and at the end of the study.



those aged 4 to 7 years, but only borderline significantly (Table 3). Being hospitalized 1 to 3 times (MD = −0.27, $P = .01$) or more than 4 times (MD = −0.24, $P = .03$) during the study was associated with substantially lower HRQoL. Children whose parents had achieved a primary (MD = 0.26, $P = .01$), secondary (MD = 0.28, $P < .0001$) or university/tertiary (MD = 0.30, $P = .01$) had significantly higher HRQoL compared to children whose parents had no education.

EQ-VAS Scores and EQ5D Indices by Treatment Group (SP vs DP)

The EQ-VAS scores and the EQ5D indices followed a similar trend as discussed above and were similar across treatment arms (see Appendix Fig. 1A in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101120). The scores were 86 (SD 12) for SP and 85 (SD 12) for DP at baseline and 87 (SD10) and 88 (SD10) at endline. During sick attacks, the overall EQ-VAS scores declined substantially to 62 in the SP arm (SD 17) and 62 in the DP arm (SD 18) (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101120).

Similarly, the EQ-5D indices in Uganda and Malawi (see Appendix Fig. 1B in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101120) were similar across treatment arms at baseline (0.90 [SD 0.14] for SP and 0.88 [SD 0.18] for DP)

Table 2. EQ-VAS and EQ-5D Indices in Uganda and Malawi at baseline, sick attacks, and end of study visits.

	Uganda			Malawi			Overall		
EQ-VAS scores									
Age	**Baseline Visit**	**Sick attack**	**Endline Visit**	**Baseline Visit**	**Sick attack**	**Endline Visit**	**Baseline Visit**	**Sick attack**	**Endline Visit**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
4-7	79 (19)	63 (17)	86 (10)	86 (8)	71 (10)	86 (10)	83 (14)	64 (17)	86 (10)
8-11	86 (13)	60 (18)	88 (10)	87 (7)	67 (12)	87 (10)	87 (10)	61 (17)	87 (10)
12-16	86 (14)	58 (19)	89 (10)	87 (10)	72 (12)	90 (7)	87 (12)	59 (19)	90 (9)
Overall	83 (16)	61 (18)	87 (10)	86 (8)	70 (11)	87 (10)	85 (12)	63 (15)	87 (10)
EQ5D index scores									
Age	**Baseline Visit**	**Sick attack**	**Endline Visit**	**Baseline Visit**	**Sick attack**	**Endline Visit**	**Baseline Visit**	**Sick attack**	**Endline Visit**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
4-7	0.94 (0.19)	0.65 (0.32)	0.98 (0.07)	0.80 (0.17)	0.40 (0.37)	0.84 (0.16)	0.86 (0.18)	0.62 (0.33)	0.93 (0.13)
8-11	0.96 (0.10)	0.57 (0.27)	0.98 (0.07)	0.84 (0.13)	0.35 (0.36)	0.85 (0.16)	0.90 (0.13)	0.53 (0.29)	0.93 (0.13)
12-15	0.96 (0.04)	0.75 (0.21)	0.97 (0.04)	0.95 (0.10)	0.92 (0.18)	0.95 (0.10)	0.92 (0.11)	0.75 (0.23)	0.96 (0.05)
Overall	0.95 (0.15)	0.63 (0.28)	0.98 (0.06)	0.87 (0.15)	0.58 (0.40)	0.88 (0.15)	0.89 (0.16)	0.60 (0.31)	0.94 (0.11)

SD indicates standard deviation.

Table 3. Factors associated with quality of life among children with sickle cell anemia during steady states and sick visits.

Variable	Variable categorisations	Baseline		End line		Sick attacks	
		Coef (95% CI)	*P* value	Coef (95% CI)	*P* value	Coef (95% CI)	*P* value
Childs age	4-7	Ref		Ref		Ref	
	8-11	0.04 (−0.01;0.09)	.13	0.01 (−0.03;0.04)	0.60	−0.98 (−0.23;0.01)	0.08*
	12-16	0.09 (0.03;0.15)	<.000†	0.03 (−0.01;0.07)	0.16	0.12 (−0.03;0.27)	0.11
Child's gender	Male	Ref		Ref		Ref	
	Female	0.01 (−0.02;0.05)	.39	0.00 (−0.02;0.02)	0.87	0.05 (−0.04;0.12)	0.27
Children's education	Not in school	Ref		Ref		Ref	
	Preschool	0.02 (−0.04;0.07)	.60	0.00 (−0.03;0.04)	0.78	0.25 (−0.09;0.13)	0.67
	Primary school	−0.00 (−0.07;0.06)	.92	−0.01 (−0.05;0.03)	0.53	0.09 (−0.06;0.23)	0.24
	Secondary school	−0.10 (−0.30;0.09)	.30	0.02 (−0.09;0.12)	0.73	−0.03 (−0.48;0.42)	0.89
Caregiver marital status	Single	Ref		Ref		Ref	
	Married	−0.01 (−0.09;0.06)	.71	0.03 (−0.01;0.07)	0.19	−0.01 (−0.19;0.13)	0.88
	Other (divorced, cohabiting)	−0.05 (−0.13;0.04)	.26	0.05 (−0.00;0.10)	0.06*	0.01 (−0.04;0.18)	0.94
Wealth status	Poorest	Ref		Ref		Ref	
	Middle	−0.00 (−0.04;0.03)	.81	0.02 (−0.01;0.05)	0.21	−0.08 (−0.19;0.03)	0.14
	Least poor	0.00 (−0.04;0.05)	.96	0.01 (−0.02;0.04)	0.68	−0.07 (−0.19;0.04)	0.20
Caregiver education	No school	Ref		Ref		Ref	
	Primary school	0.04 (−0.05;0.12)	.40	−0.00 (−0.06;0.06)	0.10	0.26 (0.07;0.45)	0.01‡
	Secondary school	0.07 (−0.02;0.16)	.12	0.01 (−0.05;0.06)	0.79	0.28 (0.09;0.47)	0.00‡
	University/tertiary	0.07 (−0.03;0.18)	.16	−0.03 (−0.09;0.03)	0.40	0.30 (0.08;0.51)	0.01‡
Hydroxyurea use at baseline	No	Ref					
	Yes	−0.03 (−0.08;0.02)	.29				
Blood transfusion (baseline)	No	Ref					
	Yes	−0.02 (−0.06;0.03)	.47				
Blood transfusion (baseline)	No	Ref					
	Yes	−0.02 (−0.06;0.03)	.47				
Country	Uganda	Ref		Ref		Ref	
	Malawi	−0.10 (−0.15;−0.04)	<.000†	−0.08 (−0.11;−0.05)	<0.000†	−0.05 (−0.20;0.09)	0.50
Hospitalization	None	Ref		Ref		Ref	
	1-3 times	−0.03 (−0.07;0.01)	.09*	0.01 (−0.03;0.04)	0.68	−0.27 (−0.47;0.08)	0.01‡
	>4 times	−0.02 (−0.09;0.05)	.52	0.02 (−0.03;0.07)	0.48	−0.25 (−0.47;−0.08)	0.03‡
Malaria Episodes (During the study)	None			Ref		Ref	
	1-3 times			0.00 (−0.03;0.04)	0.92	0.11 (−0.01;0.22)	0.07
	>4 times			0.03 (−0.05;0.10)	0.48	0.15 (−0.09;0.38)	0.22
Treatment arm	SP			Ref		Ref	
	DP			0.01 (−0.02;0.03)	0.54	0.00 (−0.09;0.09)	0.97
Duration on hydroxyurea (during the study)	<4 months			Ref		Ref	
	5-9 months			−0.01 (−0.04;0.02)	0.39	0.02 (−0.08;0.12)	0.69
	>10 months			0.01 (−0.02;0.04)	0.69	−0.01 (−0.11;0.09)	0.84
Blood transfusion (during the study)	No			Ref		Ref	
	Yes			−0.00 (−0.03;0.03)	0.99	0.02 (−0.09;0.12)	0.77

P values that were significant:
*$P < .1$.
†$P < .01$.
‡$P < .05$.
CI indicates confidence interval; DP, dihydroartemisinin-piperaquine; Ref, reference category; SP, sulphadoxine-pyrimethamine.

and endline (0.93 [SD 0.12] for SP and 0.94 [SD 0.10] for DP). During sick attacks, the overall EQ-5D indices declined to 0.62 (0.31) in the SP arm and 0.59 (0.18) in the DP arm (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2025.101120).

Discussion

This study examined the HRQoL of children with SCA during steady states and sick attacks in Uganda and Malawi. We found that the HRQoL of children with SCA was relatively high

during steady states but deteriorated substantially during sick attacks. Pain and discomfort were the leading problems affecting HRQoL, also associated with age and hospitalization frequency. During steady states, HRQoL was positively associated with age at baseline. However, during sick attacks, older children had lower HRQoL. Children who had been hospitalized more frequently had a lower HRQoL. We did, however, not find any differences in HRQoL according to treatment with SP or DP.

Children with SCA in Uganda and Malawi had relatively high scores during steady states, which suggests they were not acutely ill during those routine visits. During sick attacks, however, the HRQoL deteriorated substantially, especially because of problems with pain/discomfort, performing usual activities, and self-care. These results concur with previous studies showing low HRQoL of children with sickle cell anemia.[26,27,50,51] Pain and discomfort was also the most reported problem during steady states and sick attacks, which underlines the negative association between pain and HRQoL.[27,52-54] Children with SCA experience several pain episodes, especially during sick attacks often caused by repeated episodes of bodily pain and infections, vitality and social function impairments, anemia, and acute chest syndrome with breathing complications; this worsens their HRQoL.[34,50,53,54] Previous HRQoL studies among children with SCA in Uganda and Malawi have used the Pediatric Quality-of-Life Inventory (PedsQL)TM or Short Form Survey (SF-36) tools to assess the quality of life only during sick attacks.[26,27] Hence, these results are not directly comparable to our findings.

Our findings show that HRQoL is influenced by age and hospitalization, both during steady disease states and during sick visits. Older children had a higher HRQoL compared to younger children during steady states. During sick attacks, older children reported to have lower HRQoL. Contrastingly, earlier evidence suggests that older children with SCA report lower HRQoL.[25,55,56] This might be explained by the differences in how HRQoL is valued using disease versus generic-based tools. Additionally, HRQoL measurements among children are challenging because of the dilemma between self-rated versus using proxies, such as parents,[57] which may explain the HRQoL differences. Considering the perspectives of both parent and child is important to understand how SCA affects children.[33]

Children who were hospitalized had a lower HRQoL than those who were not hospitalized during the study or did not have such a history. These findings align with previous results that show a decrease in HRQoL with hospitalization.[58] Some studies have shown that the adverse effects of hospitalization may disappear after 7 days[59,60]; however, some authors argue that the adverse effects of hospitalization in children with SCA persist even up to 12 months after hospitalization, which worsens their HRQoL.[58]

HRQoL differed by country. HRQoL (EQ5D indices) were lower in Malawi compared with Uganda during both steady and sick states; yet, Malawi registered fewer sick attacks. The lower scores may be attributed to the variability in sociocultural contexts, which influence the valuation of HRQoL. Additionally, this may be partly influenced by the type of value set used. We used Hungarian value sets for the EQ-5D-Y and EQ-5D-3L responses for the base-case analysis in the absence of a relevant value set for a young African population. Scenario analyses comparing the Hungarian value set with the Zimbabwean value set shows that there were marginal differences in the HRQoL of children across age groups and countries. EQ5D indices for Malawi were slightly higher using the Hungarian value set than the Zimbabwean value set. The Zimbabwe EQ-5D-3L value set is meant for use among adults/adolescents, and one might argue that it is not suitable to value the HRQoL of young children; however, it is the only value set for the EQ-5D-3L tool from SSA.

We postulate that the few sick attacks may be due to Malawi's higher hydroxyurea coverage. Hydroxyurea is a critical drug that increases fetal hemoglobin levels in children with sickle cell anemia, reduces hospitalization, and improves their quality of life.[34,56,61,62] Even in malaria-endemic regions, hydroxyurea is safe without increased severe malaria, infections, or adverse events.[63] Coverage of hydroxyurea among children with SCA in Malawi was higher compared to Uganda, where only a few children had ever received hydroxyurea, and even fewer children were on hydroxyurea at the beginning of the study. The impact of hydroxyurea therapy on SCA and its effects in malaria-endemic areas of Uganda is being studied and could inform dosage among this vulnerable group.[63]

By treatment arm, there were no significant differences in the HRQoL of children. The potential beneficial effects of DP on HRQoL might have been diminished by the fact that both treatment arms received an active drug, and all children involved in the clinical trial received quality health care compared with the regular standard of care. Previous studies have shown that DP is associated with significant reductions in malaria incidence, parasite prevalence, and parasitemia compared with SP.[64,65] Findings from the main trial (CHEMCHA) show that DP significantly reduced the incidence of clinical malaria, malaria-related hospitalizations, and blood transfusions.[66] However, SP was associated with fewer episodes of nonmalaria-related illness, which is attributed to the malaria-independent effects of SP, including its broad-spectrum antibiotic effects. The malaria-independent effects of SP might include its potential impact on reducing inflammation or other factors contributing to sickle cell crises.

The study has several strengths. First, it used a longitudinal design that followed the children for an average of 1.2 person years in Uganda and Malawi. As such, it provides rich data regarding the HRQoL of children with SCA in malaria-endemic countries. Additionally, the study included parents' perspectives for children aged 4 to 7 and patients' perspectives for children 8 years and older. Furthermore, we conducted the study at high-burden health facilities with high numbers of children seeking care. These results must be interpreted cautiously, considering both strengths and limitations. In this study, we did not use a disease-specific instrument that might capture the nuances of this chronic illness because it presents unique physical and psychosocial problems that differ from other illnesses and can show changes due to therapeutic interventions. Furthermore, data were collected at selected sickle cell clinics, which might have introduced a biased sample of patients with geographical access to a clinic. However, because of the episodes of severe illness, most patients are bound to visit the health facility to receive care. Therefore, our study sample is a good representation of children with sickle cell anemia in these settings. Furthermore, to generate the EQ5DY indexes, we used the Hungarian value set because there are no existing EQ5DY value sets for Uganda or other low-income countries in SSA. There are limitations in the existing value sets because they are primarily conducted in respondents above 18 years and are not available for low-income countries, and this might not be representative of the African population. Also, it has been argued that the EQ-5D-3L may not adequately illustrate slight changes in health improvements or problems experienced by patients between health states.[67] Although ignoring some disease-specific nuances, the EQ-5D tool is generic and preference-based. It is considered appropriate to

inform the estimation of QALY calculations and economic evaluation. Our study, therefore, stands apart from previous studies conducted in Malawi and Uganda.

Conclusions

The HRQoL of children with SCA was relatively high during steady disease states but substantially deteriorated during sick attacks, especially because of pain and discomfort. HRQoL was influenced by a child's age and frequency of hospitalizations. The HRQoL was not significantly different between treatment arms. Results from this study provide information that may be used to calculate QALYs for future economic evaluations.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

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REFERENCES

1. GBD 2021 Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the Global Burden of Disease Study 2021. *Lancet Haematol*. 2023;10(8):e585–e599.
2. Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet*. 2013;381(9861):142–151.
3. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa. *Am J Prev Med*. 2011;41(6 suppl 4):S398–S405.
4. McClish DK, Penberthy LT, Bovbjerg VE, et al. Health related quality of life in sickle cell patients: the PiSCES project. *Health Qual Life Outcomes*. 2005;3:50.
5. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330(23):1639–1644.
6. Kater AP, Heijboer H, Peters M, Vogels T, Prins MH, Heymans HS. Quality of life in children with sickle cell disease in Amsterdam area. *Ned Tijdschr Geneesk*. 1999;143(41):2049–2053.
7. Palermo TM, Schwartz L, Drotar D, McGowan K. Parental report of health-related quality of life in children with sickle cell disease. *J Behav Med*. 2002;25(3):269–283.
8. 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 Qual Life Outcomes*. 2010;8(1):121.
9. Salih KM. The impact of sickle cell anemia on the quality of life of sicklers at school age. *J Fam Med Prim Care*. 2019;8(2):468.
10. Anie KA. Psychological complications in sickle cell disease. *Br J Haematol*. 2005;129(6):723–729.
11. Patrick MT. Time to invest in sickle cell anemia as a global health priority. *Pediatrics*. 2016;137(6):e20160348.
12. McGann PT, Williams AM, Ellis G, et al. Prevalence of inherited blood disorders and associations with malaria and anemia in Malawian children. *Blood Adv*. 2018;2(21):3035–3044.
13. Hernandez AG, Kiyaga C, Howard TA, et al. Trends in sickle cell trait and disease screening in the Republic of Uganda, 2014-2019. *Trop Med Int Health*. 2021;26(1):23–32.
14. Regional Committee for Africa. Sickle-Cell Disease: a strategy for the WHO African Region. World Health Organization. Published May 26, 2011. https://apps.who.int/iris/handle/10665/1682. Accessed February 17, 2021.
15. Makani J, Williams TN, Marsh K. Sickle cell disease in Africa: burden and research priorities. *Ann Trop Med Parasitol*. 2007;101(1):3–14.
16. Serjeant GR, Ndugwa CM. Sickle cell disease in Uganda: a time for action. *East Afr Med J*. 2003;80(7):384–387.
17. United Nations Sustainable Development Goals. Goal 5: achieve gender equality and empower all women and girls. Published 2015. http://www.un.org/sustainabledevelopment/gender-equality/. Accessed April 29, 2025.
18. Ferrans CE. Definitions and conceptual models of quality of life. In: Lipscomb J, Gotay CC, Snyder C, eds. *Outcomes Assessment in Cancer: Measures, Methods, and Applications*. Cambridge, England: Cambridge University Press; 2005:14–30.
19. Whitehead M. The concepts and principles of equity and health. *Int J Health Serv*. 1992;22(3):429–445.
20. Wood D. Assessing quality of life in clinical research: from where have we come and where are we going? *J Clin Epidemiol*. 1999;52(4):355–363.
21. Guyatt GH, Ferrans CE, Halyard MY, et al. Exploration of the value of health-related quality-of-life information from clinical research and into clinical practice. *Mayo Clin Proc*. 2007;82(10):1229–1239.
22. Bhagat VM, Baviskar SR, Mudey AB, Goyal RC. Poor health related quality of life among patients of sickle cell disease. *Indian J Palliat Care*. 2014;20(2):107.
23. Dale JC, Cochran CJ, Roy L, Jernigan E, Buchanan GR. Health-related quality of life in children and adolescents with sickle cell disease. *J Pediatr Health Care*. 2011;25(4):208–215.
24. Asnani M, Reid ME, Ali SB, Lipps G, Williams-Green P. Quality of life in patients with sickle cell disease in Jamaica: rural-urban differences. *Rural Remote Health*. 2008;8(2):890.
25. Amr MAM, Amin TT, Al-Omair OA. Health related quality of life among adolescents with sickle cell disease in Saudi Arabia. *Pan Afr Med J*. 2011;8(1):10.
26. Wachepa S, Bvalani R, Namubiru T, et al. Health-related quality of life of patients with sickle cell disease aged 8-17 years at Kamuzu Central Hospital, Malawi. *Pediatr Blood Cancer*. 2022;69(10):e29876.
27. Kambasu DM, Rujumba J, Lekuya HM, Munube D, Mupere E. Health-related quality of life of adolescents with sickle cell disease in sub-Saharan Africa: a cross-sectional study. *BMC Hematol*. 2019;19(1):1–9.
28. Panepinto JA, Pajewski NM, Foerster LM, Hoffmann RG. The performance of the PedsQL™ Generic Core Scales in children with sickle cell disease. *J Pediatr Hematol Oncol*. 2008;30(9):666.
29. Thomas VJ, Taylor LM. The psychosocial experience of people with sickle cell disease and its impact on quality of life: qualitative findings from focus groups. *Br J Health Psychol*. 2002;7(3):345–363.
30. Fuggle P, Shand PA, Gill LJ, Davies SC. Pain, quality of life, and coping in sickle cell disease. *Arch Dis Child*. 1996;75(3):199–203.
31. Santos JP dos, Gomes Neto M. Sociodemographic aspects and quality of life of patients with sickle cell anemia. *Rev Bras Hematol Hemoter*. 2013;35(4):242–245.

32. 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. *Qual Life Res*. 2009;18(1):5–13.
33. Panepinto JA, O'Mahar KM, DeBaun MR, Loberiza FR, Scott JP. Health-related quality of life in children with sickle cell disease: child and parent perception. *Br J Haematol*. 2005;130(3):437–444.
34. Panepinto JA, Bonner M. Health-related quality of life in sickle cell disease: past, present, and future. *Pediatr Blood Cancer*. 2012;59(2):377–385.
35. von Rueden U, Gosch A, Rajmil L, Bisegger C, Ravens-Sieberer U. Socioeconomic determinants of health related quality of life in childhood and adolescence: results from a European study. *J Epidemiol Community Health*. 2006;60(2):130–135.
36. Brazier J, Ratcliffe J, Saloman J, Tsuchiya A. *Measuring and Valuing Health Benefits for Economic Evaluation*. Oxford, England: Oxford university press; 2017.
37. Nkosi-Gondwe T, Robberstad B, Opoka R, et al. Dihydroartemisinin-piperaquine or sulphadoxine-pyrimethamine for the chemoprevention of malaria in children with sickle cell anaemia in eastern and southern Africa (CHEMCHA): a protocol for a multi-centre, two-arm, double-blind, randomised, placebo-controlled superiority trial. *Trials*. 2023;24(1):1–14.
38. Group TE. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199–208.
39. Devlin N, Parkin D, Janssen B. *Methods for Analysing and Reporting EQ-5D Data*. Berlin, Germany: Springer Nature; 2020.
40. Euroqol. Valuation–EQ-5D-Y. https://euroqol.org/eq-5d-instruments/eq-5d-y-about/valuation/. Accessed August 16, 2023.
41. Rencz F, Ruzsa G, Bató A, Yang Z, Finch AP, Brodszky V. Value set for the EQ-5D-Y-3L in Hungary. *Pharmacoeconomics*. 2022;40(suppl 2):205–215.
42. Rencz F, Brodszky V, Gulácsi L, et al. Parallel valuation of the EQ-5D-3L and EQ-5D-5L by time trade-off in Hungary. *Value Health*. 2020;23(9):1235–1245.
43. Van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15(5):708–715.
44. Campbell MJ, Machin D, Walters SJ. *Medical Statistics: A Textbook for the Health Sciences*. Chichester, UK: John Wiley & Sons; 2010.
45. Vyas S, Kumaranayake L. Constructing socio-economic status indices: how to use principal components analysis. *Health Policy Plan*. 2006;21(6):459–468.
46. Filmer D, Pritchett LH. Estimating wealth effects without expenditure data—or tears: an application to educational enrollments in states of India. *Demography*. 2001;38(1):115–132.
47. Brazier JE, Yang Y, Tsuchiya A, Rowen DL. A review of studies mapping (or cross walking) non-preference based measures of health to generic preference-based measures. *Eur J Health Econ*. 2010;11(2):215–225.
48. Crott R. Direct mapping of the QLQ-C30 to EQ-5D preferences: a comparison of regression methods. *Pharmacoecon Open*. 2018;2(2):165–177.
49. StataCorp LP. *StataCorp Stata Statistical Software*. College Station, TX: StataCorp LP; 2015. release 14.
50. Ahmed AE, Alaskar AS, Al-Suliman AM, et al. Health-related quality of life in patients with sickle cell disease in Saudi Arabia. *Health Qual Life Outcomes*. 2015;13(1):1–9.
51. 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. *Pediatr Blood Cancer*. 2015;62(7):1245–1251.
52. Panepinto JA, Paul Scott J, Badaki-Makun O, et al. Determining the longitudinal validity and meaningful differences in HRQL of the PedsQL™ Sickle Cell Disease Module. *Health Qual Life Outcomes*. 2017;15:1–12.
53. 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. *J Pediatr Psychol*. 2012;37(7):798–807.
54. Constantinou C, Payne N, Inusa B. Assessing the quality of life of children with sickle cell anaemia using self-, parent-proxy, and health care professional-proxy reports. *Br J Health Psychol*. 2015;20(2):290–304.
55. Dampier C, Lieff S, LeBeau P, et al. Health-related quality of life in children with sickle cell disease: A report from the Comprehensive Sickle Cell Centers Clinical Trial Consortium. *Pediatr Blood Cancer*. 2010;55(3):485–494.
56. Nwenyi E, Leafman J, Mathieson K, Ezeobah N. Differences in quality of life between pediatric sickle cell patients who used hydroxyurea and those who did not. *Int J Health Care Qual Assur*. 2014;27(6):468–481.
57. Ravens-Sieberer U, Erhart M, Wille N, Wetzel R, Nickel J, Bullinger M. Generic health-related quality-of-life assessment in children and adolescents. *Pharmacoeconomics*. 2006;24(12):1199–1220.
58. Vuong C, Moussa I, van Muilekom M, et al. Impact of hospitalization for vaso-occlusive crisis on health-related quality of life in children with sickle cell disease. *Pediatr Blood Cancer*. 2023;70(12):e30691.
59. Anie KA, Grocott H, White L, Dzingina M, Rogers G, Cho G. Patient self-assessment of hospital pain, mood and health-related quality of life in adults with sickle cell disease. *BMJ Open*. 2012;2(4):e001274.
60. Esham KS, Rodday AM, Smith HP, et al. Assessment of health-related quality of life among adults hospitalized with sickle cell disease vaso-occlusive crisis. *Blood Adv*. 2020;4(1):19–27.
61. Ballas SK, Barton FB, Waclawiw MA, et al. Hydroxyurea and sickle cell anemia: effect on quality of life. *Health Qual Life Outcomes*. 2006;4(1):1–8.
62. Strouse JJ, Lanzkron S, Beach MC, et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics*. 2008;122(6):1332–1342.
63. Opoka RO, Ndugwa CM, Latham TS, et al. Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM): a trial for children with sickle cell anemia. *Blood*. 2017;130(24):2585–2593.
64. Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin–piperaquine for the prevention of malaria in pregnancy. *N Engl J Med*. 2016;374(10):928–939.
65. Kajubi R, Ochieng T, Kakuru A, et al. Monthly sulfadoxine–pyrimethamine versus dihydroartemisinin–piperaquine for intermittent preventive treatment of malaria in pregnancy: a double-blind, randomised, controlled, superiority trial. *Lancet*. 2019;393(10179):1428–1439.
66. Idro R, Nkosi-Gondwe T, Opoka RO, et al. Weekly dihydroartemisinin–piperaquine versus monthly sulfadoxine–pyrimethamine for malaria chemoprevention in children with sickle cell anaemia in Uganda and Malawi (CHEMCHA): a randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis*. 2024. https://doi.org/10.1016/S1473-3099(24)00737-0.
67. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5 D-5 L value set for England. *Health Econ*. 2018;27(1):7–22.