Quality of Life Research (2019) 28:473–479
https://doi.org/10.1007/s11136-018-2031-0

# Hemoglobin F as a predictor of health-related quality of life in children with sickle cell anemia

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Accepted: 16 October 2018 / Published online: 22 October 2018


## Abstract

**Purpose** As treatment options for children with sickle cell anemia (SCA) continue to expand survival, evaluation of factors associated with health-related quality of life (HRQoL) is becoming an important aspect for further improving clinical management. Although the general features of SCA are similar, factors influencing HRQoL within a country may differ from those of other countries, therefore this study aimed to explore factors affecting HRQoL in children with SCA living in the Sultanate of Oman.

**Methods** This was a cross-sectional study in which the PedsQL™ Sickle Cell Disease Module was used to evaluate the overall HRQoL in children with SCA. The socio-demographic data, clinical, and treatment outcomes were collected. Univariate and multivariate linear regression analyses were used to identify predictors of HRQoL.

**Results** A total of 123 children with SCA, aged from 2 to 16 years were enrolled. The mean total HRQoL score was 52 ± 15% (9–94), where Worry II scale recorded the highest score. The multiple regression analysis revealed that the only predictors of total HRQoL score were hemoglobin F ($B = 0.64$, 95% confidence interval [CI] 0.149–1.118, $P = 0.009$) and to a lesser degree white blood cell count ($B = -0.99$, 95% CI −1.761 to −0.198, $P = 0.01$), independently of other study parameters such as age, gender, spleen status, and hydroxyurea therapy.

**Conclusions** Collectively, these findings indicated that hemoglobin F out-weighted white blood cell count in predicting HRQoL in Omani children with SCA. Recognition of these factors could help health professionals to develop effective strategies to improve the overall HRQoL in these young patients.

**Keywords** Hemoglobin F · Predictor · Quality of life · Sickle cell anemia

## Introduction

Since its initial description, major advances have been made in understanding the pathogenesis of sickle cell disease (SCD). Indeed, the introduction of pneumococcal vaccines, implementation of newborn screening programs, use of hematopoietic stem cell transplantation (HSCT), and development of disease-modifying agents such as hydroxyurea, has extended life expectancy of patients with SCD [1–3]. However, despite these encouraging measures, patients with SCD continue to develop higher rates of certain disease-related complications that profoundly alter their health-related quality of life (HRQoL). As a consequence, there has been growing interest in incorporating HRQoL assessments in routine healthcare practices for improving long-term survival and functional outcomes of patients with SCD [4].

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Over the past few years, several studies have evaluated the overall HRQoL in children and adolescents with SCD following specific interventions and treatments [5–7]. Overall, the findings of these studies revealed that HRQoL of patients with SCD is generally poor but specific treatments such as regular blood transfusion, hydroxyurea, physical therapy, or HSCT may improve the overall HRQoL [8–11]. This improvement effect was mainly noticed in the physical functioning domains of HRQoL, which assessed the impact of pain on well-being and functioning. In addition to the medical consequences of the disease burden, some studies have reported the potential detrimental effects of family income and social crisis on HRQoL, while others have demonstrated that parental stress and family functioning negatively impact on HRQoL of patients with SCD [12–16]. The conclusions drawn from the aforementioned studies support a model in which multiple potential etiologies are contributing to the decreased HRQoL, and therefore highlighting the need to identify key factors that may help formulate a set of management strategies and measures in order to improve treatment outcomes, and thus the overall HRQoL in patients with SCD.

The overall HRQoL could be influenced by several determinants including cultural background, educational systems, religious and geographical variations as well as different perceptions by children and parents from diverse populations [7, 17, 18]. Thus, factors influencing HRQoL within a country may differ from those of other countries, although the general features of SCD are similar. Identifying these specific factors is crucial for developing effective counseling plans to improve or maintain a good HRQoL in patients with SCD living in different geographical areas. Therefore, this study aimed to elucidate the level of HRQoL and determine factors related to HRQoL in children with sickle cell anemia (SCA) living in the Sultanate of Oman. Considering the variety of factors affecting HRQoL in SCD, this study raised the hypothesis of whether the disease-modifying determinants could predict HRQoL in children with SCA.

## Patients and methods

### Ethical considerations

This study was performed according to the Declaration of Helsinki and approved by the Institutional Research Ethic Committee of the Sultan Qaboos University (SQU), Sultanate of Oman. Further approval was obtained from the hospital management before accessing the medical records of patients.

### Study design and subjects

This was a cross-sectional study conducted at the SQU Hospital (SQUH) over a period of 6 months from January 1, 2016 to July 31, 2016. Data were collected from children with SCA attending the Hematology clinics at SQUH, which provides a free-of-cost medical care to all Omanis. All patients with SCA were included from age 2 to 16 years coming for their regular follow-up visits. Consents, verbal and written, were taken from guardians and parents. Patients who had SCD-related acute or chronic complications were included. Whereas patients who had other medical conditions that can affect the cognition were excluded.

### Medical information and data collection

A special case report form was used to extract the data from the SQUH electronic database. For each participant, the socio-demographic characteristics, clinical and laboratory data, treatment details, and outcomes were abstracted. The spleen status, frequency of vaso-occlusive crisis (VOC), and number of transfusions were recovered over the last year. All completed data collection forms were examined for clarity and consistency by two independent investigators.

### Health quality of life measures

The HRQoL of participants was assessed by the PedsQL™ 4.0 SCD Module Scale as previously reported [19]. This questionnaire was recently used in children with thalassemia major by our group [20]. Given that all parents and children spoke Arabic, the validated Arabic version of this questionnaire was used throughout the study period. Of note, no changes in the number of items or in the administration instructions were made. In brief, the questionnaire consists of nine scales including pain and hurt scale, pain impact scale, pain management scale, worry I scale, worry II scale, emotion scale, treatment scale, communication I scale, and communication II scale. During the administration of the questionnaire, children were asked to assess each problem based on their experience in the previous month. Participants aged more than 7 years were asked to complete the questionnaire by themselves. However, investigators administered the questionnaire to children aged between 5 and 7 years, and parent–proxy report was used for patients aged from 2 to 4 years.

### Statistical analysis

The Statistical Package for Social Sciences program version 23 was used for statistical analysis (IBM, SPSS, USA). Data

were summarized using mean, standard deviation (SD), and range. Group differences in patient characteristics were evaluated using student's *t* test. To further evaluate study parameters, continuous variables were dichotomized according to their median values to form high and low groups, which were then compared. Associations among total HRQoL score and study variables were assessed by univariate linear regression. Multivariable linear regression analysis was used to identify predictors of HRQoL. In order to control for confounding, all variables were tested regardless of their significance in the multivariate models. A $P$ value $< 0.05$ was considered as significant.

## Results

### Demographic and clinical data

A total of 127 children with SCA were consecutively recruited in this study. Four children were excluded for having double heterozygote sickling disorders, leaving 123 children in the final analysis. At diagnosis, hemoglobin level ranged from 5.8 to 11.8 g/dL with a mean of $8.9 \pm 1.4$ g/dL and white blood cell and platelet counts were $10.5 \pm 4.1 \times 10^9$/L (3.5–22.8) and $336 \pm 13 \times 10^9$/L (108–695), respectively. The mean hemoglobin S level was $79 \pm 5.8$% (72.1–93.3) while the mean values of hemoglobin A2 and F levels were $3.8 \pm 0.7$% (0.5–4.9) and $13.2 \pm 6.6$% (1.7–24.9), respectively, at the diagnosis. The clinical and demographic characteristics of study population at the time of the administration of questionnaire are summarized in Table 1. Overall, the study population had equal gender proportions and all children were native Omanis. Of note, 24 (19.5%) children were aged less than 4 years and 6 (5%) had also glucose-6-phosphate dehydrogenase deficiency. None of the patients was infected with hepatitis C or human immunodeficiency virus, while five children (4%) were infected with hepatitis B virus (HBV), as confirmed by the HBV polymerase chain reaction test. The mean duration of hydroxyurea therapy among the 66 patients enrolled was $1549 \pm 140$ days (42–3564). Acute splenic sequestration was the main indication of splenectomy, which was performed in 15% of the study cohort, followed by hypersplenism.

### Outcome measures

All children completed the PedsQL™ SCD Module with a response rate of 100%. The overall HRQoL score is depicted in Fig. 1. Scores in each scale ranged from 0 to 100, where 0 and 100 reflected the poorest and perfect HRQoL, respectively. The mean total HRQoL score was $52 \pm 15$% (9–94). As expected, the pain impact scale recorded the lowest score with a mean of $41 \pm 21$% (2.5–100), indicating that pain is negatively affecting HRQoL. In contrast to pain impact scale, Worry II scale recorded the highest score with a mean of $70 \pm 28$% (12.5–100) followed by the treatment score and communication 1 score.

To further examine the influence of study variables on the total HRQoL score, the data were categorized into two groups according to the median values of each study variable. A significant difference was found in total HRQoL score between children with hemoglobin F $\leq 10$% [$49 \pm 13$%, (9–83)] and those with hemoglobin F $> 10$% [$55 \pm 15$%, (18–93), $P = 0.03$]. Similarly, a significant difference was noticed in total HRQoL score between children with white

**Table 1** Socio-demographic and clinical characteristics of study participants

| Characteristics | Study population ($n = 123$) |
|---|---|
| Age (years) | $9 \pm 4$ (2–16) |
| Male [*n* (%)] | 67 (55) |
| Hemoglobin (g/dL) | $9 \pm 1.2$ (6.3–11.7) |
| White blood cells ($\times 10^9$/L) | $10 \pm 4.3$ (2.6–24.3) |
| Platelet counts ($\times 10^9$/L) | $359 \pm 16$ (108–854) |
| Hemoglobin F (%) | $11.9 \pm 6.6$ (1.2–27.6) |
| Frequency of VOC over the last year [*n* (%)] | |
| Frequent VOC ($\geq 3$ admissions) | 5 (4%) |
| Infrequent VOC ($\leq 2$ admissions) | 118 (96%) |
| Number of transfusion over the last year [*n* (%)] | $4 \pm 1$ (0–9) |
| Hydroxyurea therapy [*n* (%)] | |
| Yes | 66 (54) |
| No | 57 (46) |
| Spleen status [*n* (%)] | |
| Splenectomized | 19 (15) |
| Non-splenectomized | 104 (85) |

Data are shown as mean ± SD and (range)

*VOC* vaso-occlusive crisis

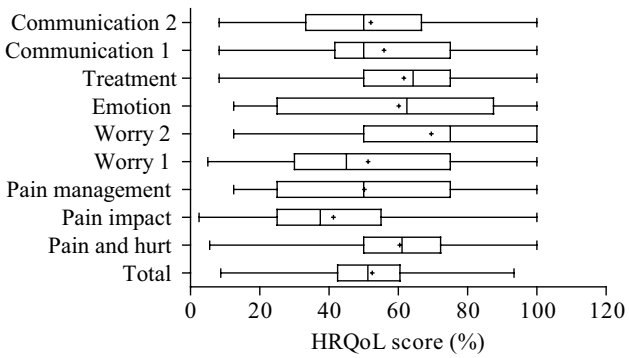


**Fig. 1** Health-related quality of life scores in children with sickle cell anemia. The minimum, maximum, and median values for each boxplot are shown. The cross indicates the mean

blood cell (WBC) count ≤ 10% [55 ± 16%, (9–93)] and those with WBC count > 10% [48 ± 11%, (27–83), $P = 0.04$]. In contrast, no difference between the two groups for the total HRQoL score was evidenced in children taking or not taking hydroxyurea therapy (Fig. 2). Likewise, for other study variables including gender, age, total hemoglobin, platelet count, mean cell volume, spleen status, frequency of VOC, number of transfusions, and duration of hydroxyurea therapy, no differences were evidenced between the two groups for total HRQoL score.

### Factors associated with HRQoL

In order to evaluate factors that may predict HRQoL, univariate and multivariate regression analyses were performed. All study variables regardless of their statistical significance in the comparison analyses were tested. In univariate analysis, hemoglobin F levels and white blood cell counts were the only variables significantly associated with total HRQoL score, with beta coefficient values of 0.29 ($P = 0.002$) and −0.24 ($P = 0.01$), respectively (Table 2). Interestingly, both variables remained significantly associated with total HRQoL score in multivariate analysis. Of importance, hemoglobin F levels were found to be positively associated while white blood cell counts. None of the remaining variables were associated with total HRQoL score, except hemoglobin levels but did not reach statistical significance ($P = 0.06$).

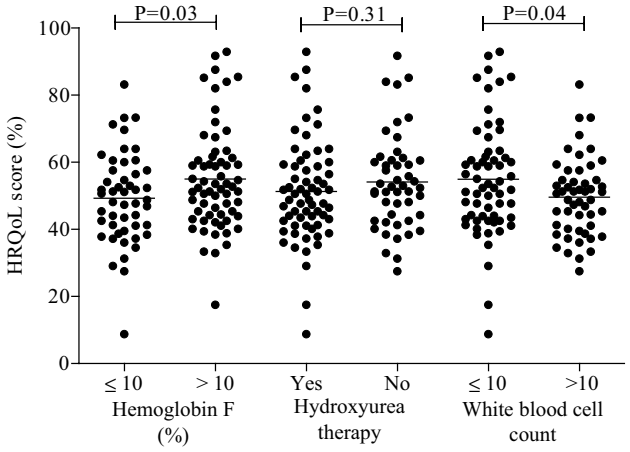


**Fig. 2** Associations among hemoglobin F, hydroxyurea therapy, white blood cell counts, and the overall health-related quality of life scores in children with sickle cell anemia. The *P* values for each study parameter are shown. Bars indicate the mean

## Discussion

As treatment options for patients with SCD continued to expand survival, HRQoL is becoming an important aspect of care for further improving clinical outcomes and management of the disease. To date, several studies have contributed to the broad understanding of HRQoL in children with SCD [7, 21–24], but still many questions are only partially answered especially those related to factors associated with HRQoL, which may vary considerably across countries. To the best of our knowledge, little is known about determinants of HRQoL in children with SCA living in Oman, where SCD is the most common hemoglobinopathy, with a prevalence of 0.3% [25].

So far, there is no consensus regarding the best performing instruments for evaluating HRQoL outcomes. While some instruments perform better in certain specific disease areas, others are preferred for their practical capacity and easy administration [4]. In the present study, the PedsQL™ SCD Module was used to assess the HRQoL of children with SCA, as this instrument has shown high level of reliability, and was validated in Arabic in children suffering from hemoglobinopathies with a wide age range [19, 20, 26]. Regardless of HRQoL domains, previous studies have

**Table 2** Univariate and multivariate analyses of prognostic factors for the overall health-related quality of life in children with sickle cell anemia

| Characteristics | Univariate analysis | | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | 95% confidence interval | | | | 95% confidence interval | | | |
| | *B* | *P* values | Lower bound | Upper bound | *B* | *P* values | Lower bound | Upper bound |
| Age | −0.37 | 0.28 | −1.066 | 0.314 | −0.14 | 0.71 | −0.625 | 0.925 |
| Sex | 1.32 | 0.63 | −4.241 | 6.888 | 0.74 | 0.79 | −6.610 | 4.665 |
| Hemoglobin (g/dL) | 0.52 | 0.64 | −2.736 | 1.689 | 2.31 | 0.06 | −4.588 | 0.176 |
| White blood cells ($\times 10^9$/L) | −0.81 | 0.01 | −1.439 | −0.191 | −0.99 | 0.01 | −1.761 | −0.198 |
| Platelet counts ($\times 10^9$/L) | 0.009 | 0.29 | −0.025 | 0.008 | 0.01 | 0.33 | −0.011 | 0.030 |
| Hemoglobin F (%) | 0.63 | 0.002 | 0.231 | 1.038 | 0.64 | 0.009 | 0.149 | 1.118 |
| Spleen status | −3.44 | 0.38 | −11.171 | 4.275 | −2.23 | 0.61 | −11.084 | 6.023 |
| Hydroxyurea therapy | 2.81 | 0.32 | −2.781 | 8.408 | 2.98 | 0.33 | −3.137 | 9.067 |

reported that children with SCD exhibited a wide range of HRQoL mean scores, which were lower compared to their counterparts in general population [7, 26]. The results of this study confirm and extend those findings by showing a reduced HRQoL score in children with SCA. Interestingly, total HRQoL mean score gathered from the cohorts in this study appeared to be quite low than previously reported in children with SCD and therefore showed HRQoL to be more impaired and worse comparatively to other pediatric patients with SCD [7]. In addition to cultural differences, a number of methodological reasons could explain these findings, including type of instrument used for assessing HRQoL, age of study population, SCD genotype, and haplotypes as well as the total population under study. On the other end of the spectrum, these differences highlight that meaningful change in HRQoL values may vary according to the population and context, thus the HRQoL scores should be obtained from the specific populations that share the same cultural, and ethnic characteristics, as well as socioeconomic status, rather than external-reported HRQoL values.

The current exploratory analysis also extends on the impact of the disease-modifying agent, hydroxyurea, on HRQoL in children with SCA. In fact, subdividing the study cohort into groups of children taking or not taking hydroxyurea did not reveal interesting differences in overall HRQoL scores. Moreover, the duration of hydroxyurea therapy did not affect HRQoL scores in the current study population, regardless of adherence level. These findings are similar to those reported by Thornburng et al. who did not observe improved HRQoL over 2-year treatment period with hydroxyurea in children with SCA [27]. Conversely, other studies have demonstrated that children and adolescents with SCD taking hydroxyurea exhibited significantly better HRQoL than those not taking hydroxyurea, particularly in the physical health domain [8, 9]. Collectively, these findings highlight the need for further prospective large studies to address the effectiveness of hydroxyurea in improving HRQoL in children with SCA. In addition to the impact of hydroxyurea, the effect of HbF on overall HRQoL scores was also explored. HbF is known to play a key role in modulating the phenotype of SCA. Interestingly, when a cut-off of 10% was applied a significantly reduced HRQoL scores was found in children with HbF levels less than 10%, suggesting that higher HbF levels are associated with better overall HRQoL. This result may be related to better coping with SCA as children with high HbF levels showed few clinical events [28]. Although it was expected HbF and hydroxyurea therapy to be positively correlated, no statistically significant relationship between HbF levels and length of time on hydroxyurea in the subgroup of children with SCA was found. A possible explanation is that despite clinical response to hydroxyurea, children with SCD may deal with a chronic disease on daily basis, which may affect their well-being, hence impacting negatively on the overall HRQoL. Another explanation is that in some patients receiving hydroxyurea with a good clinical response, no detectable rise in HbF has been noticed, indirectly reflecting the lack of association between HbF and hydroxyurea therapy [29]. An additional explanation is that the coexisting of hereditary persistence of fetal hemoglobin may ameliorate the course of SCD, thereby improving the overall HRQoL, without requiring hydroxyurea therapy [30].

The findings of this study revealed that the key factors associated with HRQoL were HbF and WBC. Notably, the most important factor in both univariate and multivariate linear regression analyses was HbF followed by WBC, while demographic characteristics and treatment outcomes were not significantly associated with HRQoL. These findings of the study cohorts underscore the importance of HbF as a significant predictor of HRQoL, which is consistent with early studies showing that HbF level is a crucial determinant of clinical expression of SCD [31]. It has been shown that HbF levels predict the severity of disease by decreasing the clinical complications, which in turn influences the overall clinical picture leading to better HRQoL in patients with SCD [28]. In addition to HbF, the second factor associated with HRQoL in this study was WBC count. Of interest, HRQoL was negatively linked with WBC, suggesting that children with SCA who have high WBC counts are more likely to be at risk of poor HRQoL. This was reflected further in this study by the results showing a significant difference in overall HRQoL score between children with high and low WBC counts. Also, consistent with these findings are studies demonstrating that high WBC count predisposes to severe SCD, and reducing the number of WBC ameliorates the clinical manifestations that untimely leads to better HRQoL in patients with SCD [32, 33]. Compared to HbF and WBC, total hemoglobin contributed less to the overall HRQoL in this study, similarly to age, gender, and other study parameters, which were not associated with HRQoL. Conflicting findings have been reported regarding the effects of age and gender as well as other clinical parameters, on HRQoL in children and adolescents with SCD. While some studies revealed that demographic characteristics are significant predictors, others showed the opposite or no associations at all with HRQoL [7]. Whether these are truly insignificant associations among these factors and the overall HRQoL scores require further studies.

This study is subjected to some limitations that deserve to be mentioned. In addition to its cross-sectional study design, participants were recruited in one single institution. This may generate a bias toward enrolling children who were committed to their clinical visits or having less severe disease. However, children were enrolled from out-patient clinics over a period of 6 months, which gave opportunity for children who were infrequently seen to participate in the study. Also, this study was limited to one geographic area;

therefore, the results may not be generalized to other Omani regions. However, this may also be unlikely because children with SCD attending SQUH are coming from all over the country, with a disease burden equitably similar across all regions, and thus the sample used in this study is at least moderately representative of SCA in Oman. Additionally, only those factors available in current clinical setting were considered in the present analysis. Therefore, assessments did not include other measures that may affect HRQoL, especially socioeconomic factors and SCD haplotypes. Furthermore, the psychological aspect was not evaluated in the present study. The psychological support is critical in the patient–doctor relationship, which may affect indirectly the overall HRQoL, as reported in several conditions including kidney disease where patients experiencing chronic pain similar to patients with SCD [34, 35]. Thus, the results of this study cannot be generalized at the moment since further research and studies have to be done to reduce the limitations and better understand the effects of other factors, in addition to taking a larger population sample from different health centers and regions in Oman.

In conclusion, HRQoL score is low in children with SCA, regardless of treatment outcomes. Two factors mainly HbF and to lesser degree, WBC have shown strong associations with HRQoL score in our study population. Collectively, the findings suggest that these two factors could capture, even partially, the impact of the disease burden on HRQoL in children with SCA and hence they could be embedded into the routine care and research studies for further validation to improve the overall HRQoL in these young patients.

**Acknowledgements** We are thankful to all participants and their families and also to the Hospital Information System staff of the SQUH for providing technical assistance. This work was supported in part by grants from The Oman Research Council (#ORG/HSS/13/002) and the Sultan Qaboos University (IG/MED/HAEM/14/01).

**Author contributions** MRB designed, performed, analyzed data, and wrote the manuscript. AB and GH participated in study deign, data collection, and analysis. ME, MS, AB, ZQ, HK, RQ, and YW participated in data collection, reviewed, and critically revised the manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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