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Health-related quality of life in adults with sickle cell disease in Duhok-Iraq

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Abstract:

BACKGROUND: Sickle cell disease (SCD) is the second-most common hemoglobin disorder in Duhok governorate. Health-related quality of life (HRQoL) instrument provides physicians with the patient's perspectives of their disease and thus more patient-oriented care.

MATERIALS AND METHODS: In this case–control study, a total of 70 adults (≥18 years old) registered as SCD at the center for blood diseases in Duhok as well as 70 age- and sex-matched healthy controls were enrolled. Enrolled patients had their records and treatment reviewed, were clinically assessed, and appropriately investigated. All patients and controls had their HRQoL scored using the SF36 questionnaire, which consists of eight domains, namely physical function, role limitation physical, role limitation emotional, vitality, emotional well-being, social function, bodily pain, and general health perception.

RESULTS: The mean standard deviation age of the SCD patients enrolled was 26.2 (8.9) years and included 32 males and 38 females. The patients had significantly lower HRQoL scores in all eight domains when compared to their matched controls. The most affected domain was general health. Within the patients' group, it was noted that HRQoL scores were negatively correlated with age in several domains, most significantly with general health ($P = 0.011$). On the other hand, there was no significant difference in HRQoL in relevance to gender, marital status, education, or employment. The most significant negative correlations of HRQoL scores were documented with the annual number of pain episodes and hospital admissions observed with all eight domains.

CONCLUSIONS: The current study documented that in adults with SCD, HRQoL in all domains was significantly worse than in healthy controls and that it gets worse with age. The most significant contributors to the worse HRQoL are pain episodes and hospital admissions. The study underscores the importance of HRQoL assessments to enable attending physicians provide more patient-centered management.

Keywords:

Health-related quality of life, health-related quality of life, Iraq, SF36, sickle cell disease

Introduction

Sickle cell disease (SCD) is an autosomal recessive inherited hemoglobin disorder. It is due to a single gene defect in the β-globin gene leading to the substitution of valine for glutamic acid at position 6 of the β-globin chain. This substitution will lead to a hemoglobin variant that polymerizes upon deoxygenation and red cell sickling.[1] In Iraq, sickle carrier state is present in polymorphic frequencies in the extreme South (Basrah governorate) and the extreme North (Duhok governorate), while other parts of the country are almost spared. SCD is the second-most frequent hemoglobin disorder in Duhok, outnumbered only by thalassemia major.[2] SCD is chronic hemolytic anemia presenting early in life, complicated by a variety of sickle cell crises, the most frequent of which being vaso-occlusive ones. The latter may involve bone, brain, lungs, mesenteric vessels, or penis (priapism).[1] Thus, SCD is a multisystem disorder of variable severity

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with consequent physical, mental, and social disruption of everyday activity, affecting patients' quality of life.

The assessment of health-related quality of life (HRQoL) gained popularity over the past two decades since it measures the patient's perception of the impact of the disease on his/her well-being and ability to function in physical, mental, and social domains of life.[3] The HRQoL instruments vary between those applicable to children and those more suited for adults. Furthermore, there are generic and specific tools to assess HRQoL. The most frequently used generic tool in children is PedsQL core scale,[4,5] while its counterpart in adults is the medical outcome study 36-item short form (RAND 36 [SF-36]) which evolved as the most popular generic instrument in this age group.[3,6]

Studies on HRQoL in SCD in Iraq are scarce, particularly as far as adults are concerned. Thus, we initiated this study to determine the HRQoL among adult SCD patients from Duhok and determine the contributing factors to HRQoL scores in this governorate.

Materials and Methods

A total of 70 SCD patients aged 18 years or older were enrolled. All enrollees were registered patients at the center for blood disorders at Duhok-Iraq. In addition to the latter patients, another 70 healthy age- and sex-matched controls from the general population were recruited at the same time frame. The patients had their socioeconomic, employment, marital, and education status scrutinized. Furthermore, the patients were interviewed and had their records checked for the following: the number of painful crises, hospitalizations and transfusions over the last year, history of priapism, cerebrovascular events, acute chest syndrome, avascular necrosis of the femoral head (AVNFH), splenectomy, and leg ulcers. Their current treatments were also checked. All patients were also investigated at the time of enrollment by full blood counts using an electronic hematology analyzer (Swelab, Sweden), reticulocyte counts, serum lactic dehydrogenase (LDH), and serum bilirubin by standard Laboratory methods. Hemoglobin F was also assayed using high-performance liquid chromatography by Bio-Rad D-10 (Bio-Rad-CA, USA). Hepatitis C antibodies were assessed using Cobas c501 instrument (Roche Diagnostics, Hitachi, Tokyo, Japan).

The RAND-36 (SF36) questionnaire was used to assess the HRQoL of both patients and controls. SF36 is multidimensional questionnaire with 36-item subcategorized into eight domains, namely physical functioning (10 domains), emotional well-being and general health (5 items each), role limitation due to physical health and energy fatigue (4 items each), role limitation due to emotional problem (3 items), and social functioning and pain (2 item each). The scoring process is a two-step process, as detailed previously.[7] The resultant scores range from 0 to 100, where lower scores represent the worse quality of life, while higher ones represent better quality.[3,8]

All statistical analyses were done using SPSS software (Statistical Package for the Social Sciences software) (release 22; SPSS, Chicago, IL, USA). All results reported as mean values (standard deviations). Independent *t*-test was used to compare continuous variables between patients and controls and between various subcategories of patients; Pearson's correlations were used to assess the association of two continuous variables in the patients' group, while Chi-squared test was used to assess association in categorical variables. Two-tailed $P < 0.05$ was considered significant. Finally, the study was approved by the Ethics Committee at the Iraqi Board of Medical Specialties, Baghdad-Iraq, and informed consent was obtained from all participants.

Results

The mean age of the patients was 26.2 years (standard deviation [SD]: 8.9), and included 32 males and 38 females, while the mean age of the controls was 28.2 years (SD 9.1), and included 30 males and 40 females. There were no significant differences in age or in gender between patients and controls ($P = 0.201$ and 0.7336, respectively). Forty-eight patients (68.6%) had sickle cell anemia (HbSS), while 22 patients (31.4%) had S/β-thalassemia. Table 1 outlines some of the demographic data of the enrollees, including literacy, employment, and socioeconomic and marital status.

Table 1: Some demographic features of 70 enrolled sickle cell disease patients

Clinical features	*n* (%)
Age (years), mean±SD	26.2±8.9
Gender (male: female)	32:38
Socioeconomic status	
Low	51 (72.9)
Intermediate/high	19 (27.1)
Education	
Illiterate	29 (41.4)
Some level of education	41 (58.6)
Employment	
Employed	16 (22.9)
Unemployed	54 (77.1)
Marital status	
Married	13 (18.6)
Not married	57 (81.4)
Having children	
Yes	9 (12.9)
No	61 (87.1)

SD: Standard deviation

The most frequently encountered complication was pain episodes, occurring at a mean (SD) of 6.71 (3.54) episodes per year, while the mean (SD) annual admissions for various SCD events were 2.87 (1.98). Twelve patients needed transfusion including five receiving ≥12 transfusions annually. Sixty-two patients were on hydroxyurea, while 13 patients were on chelation therapy with deferasirox [Table 2].

Using the SF36 instrument, it was found that the mean HRQoL scores in all eight domains were significantly lower in the patients' group compared to their age and sex-matched controls. The least mean score was in general health, followed by energy/fatigue and emotional well-being, while the domain least affected was physical function [Table 3].

When HRQoL scores were assessed within the patients' group, no significant differences in any of its domains as it relates to gender or employment were observed ($P > 0.05$ in all). Furthermore, lower socioeconomic, lower education status, and being married were associated with lower mean scores in several domains; however, none reached significance (all with $P > 0.05$). However, there was a significant negative correlation of age with the following HRQoL domains: general health, social function, energy/fatigue, and emotional well-being, with the highest Pearson's correlation coefficient observed with general health ($P = 0.011$) and emotional well-being ($P = 0.031$) [Figure 1 and Table 4]. There was a significant positive correlation of hemoglobin with emotional well-being ($P = 0.044$), while there were negative correlations between reticulocyte counts and physical function ($P = 0.002$) and of LDH with role limitation emotional and physical domains (P=0.032 and 0.048, respectively) [Table 4]. Neither serum bilirubin nor hemoglobin F (%) was significantly correlated with any of the HRQoL domains ($P > 0.05$).

The two most significant correlations out of all clinical and laboratory parameters were those of annual frequencies of pain episodes and hospital admissions, which were both significantly correlated with lower scores in all eight domains [Table 4 and Figure 2]. Of the cumulative sickle cell events, the only one that yields to statistical analysis was AVNFH, which was significantly associated with a lower mean physical function HRQoL score ($P = 0.002$).

Table 2: The main clinical features in seventy enrolled patients with sickle cell disease

Feature	*n* (%) unless otherwise specified*
Number of Pain episode/yr. [mean (SD)]*	6.71 (3.54)
Number of Admissions/yr. [mean (SD)]*	2.87 (1.98)
Number of Blood transfusion /yr.	
0 /yr	58 (82.8)
1 /yr	2 (2.9)
2-3 /yr	3 (4.3)
>3 /yr	7 (10)
On Chelation therapy	13 (18.6%)
On Hydroxyurea therapy	62 (88.6)
Splenomegaly	7 (10%)
Lifetime cumulative incidence of specific complications	
Presumed acute chest syndrome	4 (5.8)
CVA	2 (2.9)
Leg ulcer	0
AVNFH	5 (7.1)
Priapism	1 (3.1) (of males)

CVA: Cerebrovascular accident; AVNFH: Avascular necrosis of femoral head

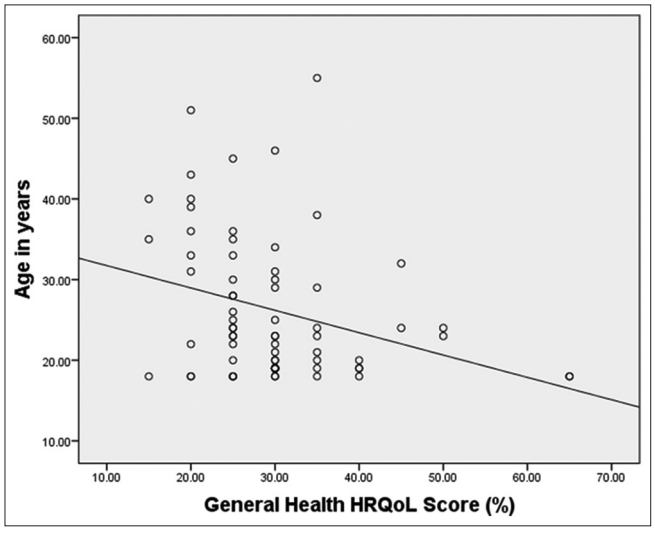

Figure 1: A scatterplot showing the correlation between the age and HRQoL score in the general health domain. HRQoL: Health-related quality of life

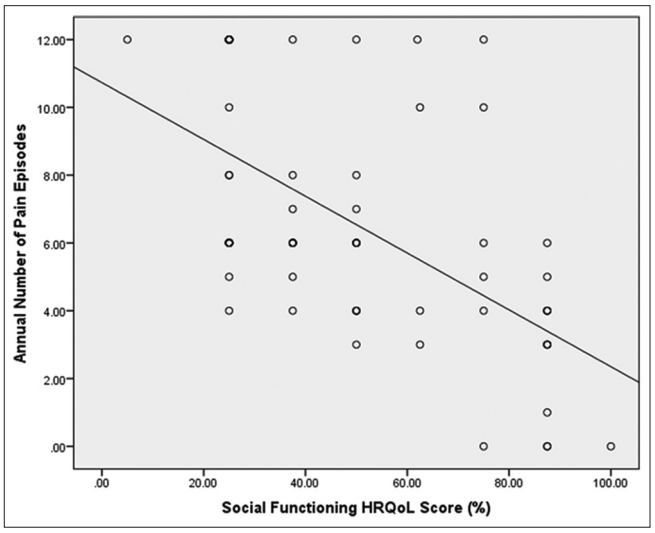

Figure 2: A scatterplot showing the correlation between the annual number of pain episodes and the HRQoL score in the social functioning domain. HRQoL: Health-related quality of life

Table 3: Health related quality of Life (SF36) score (%) comparison between adult patients with sickle cell disease and healthy controls

Category	HRQoL (mean±SD)								
	Age	Physical function	Role of physical	Role of emotional	Energy fatigue	Emotional well being	Social function	Pain	General health
Patient	26.23±8.89	56.36±20.64	38.93±31.46	40.45±31.54	33.71±11.15	34.57±9.66	47.92±24.49	48.14±26.36	29.86±9.67
Control	28.19±9.12	90.79±8.7	90.36±14.30	89.98±15.42	71.43±10.04	70.90±10.82	88.46±13.35	86.14±15.12	81.36±10.60
P	0.201	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

HrQoL: Health-related quality of life, SD: Standard deviation

Although HRQoL mean scores were lower in HCV antibody-positive patients, this was only significant in association with role limitation of physical function score ($P < 0.001$). As far as hydroxyurea therapy is concerned, such therapy was not significantly correlated with any of the HRQoL domains ($P > 0.05$).

Discussion

The introduction of the HRQoL instruments around two decades ago was a major milestone the assessment of the disease burden from the perspective of the patients. It leads to a better understanding of this burden not only to the attending physicians and families but also to the patients themselves. Furthermore, HRQoL instruments were used to assess various management options from the patients' perspectives, with the prospect of tailoring these options to patient's needs and concerns and thus was relevant to the eventual disease outcomes. The use of HRQL assessments improved patient-provider communication, ultimately securing a more patient-oriented environment.[9,10] Our choice of SF-36 hQoL instrument for the current study was appropriate since its validity was proven by earlier studies, and it is among the most common methods used to measure the HRQoL in adults with hemoglobin disorders and enabled the comparison with healthy individuals.[6]

In the current study, it was demonstrated that mean scores of all eight domains of HRQoL were significantly lower in patients compared to controls. The most affected domain in SCD patients enrolled in the current study was general health, and this observation is similar to the reports by Dampier *et al*. and McClish *et al*. on African American SCD patients.[11,12] Likewise, Vilela *et al*. and Rodrigues *et al*. found that general health had the lowest scores in SCD Brazilian patients.[13,14] Other researchers implicated other more affected HRQoL domains in their studies. Studies on Bahraini, Saudi Arabian, Nigerian, and Iranian patients found that the role limitation of physical health was the most effected domain in HRQoL,[15-18] while another study on Nigerian SCD patients found that physical function was the most affected.[19] This heterogeneity in the HRQoL-affected domains in different populations suggests that the impact of SCD on HRQoL varies with geographical location. This may partly be the consequence of the variability in underlying genotypes or haplotypes between these populations (thus disease severity), as well as variability in the governmental, social, and psychological support networks, or it may be related to the adequacy and compliance with the management in different populations.[11,19]

Several studies have documented lower HRQoL scores among adult females with SCD compared to males including a study of McClish *et al*. on American SCD patients who found that all domains except social function were lower among females,[12] while other studies on Nigerian and Bahraini patients found that scores of at least some domains were lower in females.[15,19] This is contrary to our study where no difference in HRQoL was detected between males and females. Our findings are consistent with earlier studies from Iran and northern Iraq which also failed to find differences in HRQoL between males and females.[17,20]

The current study unveiled significant correlations between age and several HRQoL domains including general health, emotional well-being, social function, and energy/fatigue. This is similar to that reported among Bahraini and American SCD patients, where the HRQoL scores decreased with increasing age.[11,12,15] Contrary to the latter findings, other authors did not observe any such correlation between HRQoL and age in Iranian, Nigerian, and Saudi patients.[16,17,19] Reduction in HRQoL with increasing age in SCD is the likely consequence of increased disease-related complications.[11] Furthermore, it has been documented that older people are less able to cope with pain and other complications of SCD, subsequently impacting their HRQoL more than their younger counterparts.[21]

In relevance to socioeconomic and educational status, and though we did not observe any significant correlations with HRQoL, it was observed that those with lower socioeconomic or educational status had lower mean scores in several domains. Previous studies had documented that lower socioeconomic status correlates with low HRQoL scores, including those on SCD patients from northern Iraq and Bahrain.[15,20] Other

Table 4: Correlation of certain laboratory and clinical parameters with health-related quality of life domains in 70 sickle cell disease patients enrolled (bold font for significant results)

Parameters	Pearson's correlation coefficient (*P*)							
	Physical function	**Role limitation of physical health**	**Role of emotional problem**	**Energy/fatigue**	**Emotional well-being**	**Social function**	**Pain**	**General health**
Age	−0.135 (0.264)	−0.026 (0.832)	−0.023 (849)	−0.245 (0.041)	−0.258 (0.031)	−0.251 (0.036)	−0.181 (0.133)	−0.302 (0.011)
Hemoglobin	0.230 (0.055)	0.203 (0.092)	0.151 (0.212)	0.081 (0.503)	0.241 (0.044)	0.026 (0.830)	−0.015 (0.904)	0.068 (0.575)
Reticulocyte count	−0.370 (0.002)	−0.158 (0.191)	−0.105 (0.386)	0.107 (0.376)	0.023 (0.853)	−0.091 (0.453)	−0.103 (0.394)	−0.086 (0.481)
Bilirubin	0.006 (0.962)	0.050 (0.679)	0.028 (0.816)	−0.180 (0.136)	−0.098 (0.418)	−0.157 (0.194)	−0.131 (0.282)	0.002 (0.99)
LDH	−0.203 (0.092)	−0.237 (0.048)	−0.257 (0.032)	−0.218 (0.070)	−0.058 (0.635)	−0.069 (0.571)	−0.105 (0.388)	−0.180 (0.135)
Hb F (%)	0.105 (0.385)	0.132 (0.277)	0.148 (0.223)	−0.033 (0.785)	0.100 (0.409)	0.038 (0.752)	0.029 (0.811)	−0.038 (0.752)
Number of pain episode/year	−0.377 (0.001)	−0.341 (0.004)	−0.284 (0.017)	−0.456 (<0.001)	−0.307 (0.01)	0.580 (<0.001)	−0.567 (<0.001)	−0.418 (<0.001)
Number admission to hospital/year	−0.413 (<0.001)	−0.443 (<0.001)	−0.434 (<0.001)	−0.504 (<0.001)	−0.450 (<0.001)	−0.513 (<0.001)	−0.437 (<0.001)	−0.475 (<0.001)

LDH: Lactic dehydrogenase, Hb F: Hemoglobin F

studies from Iran and Saudi Arabia found that HRQoL scores were better in those with university degrees.[16,17] Likewise, Nwogoh *et al*. and Asnani *et al*. reported a positive correlation of education level with general health from Nigeria and Jamaica, respectively.[19,22] A higher socioeconomic status would allow patients better access to medical services, while being better educated is empowering since it may provide patients with better insight into their disease, complications and management options, and thus be better equipped to cope with it. Regarding employment in the current study, there were no differences between HRQoL in employed and unemployed patients. This similar to a Bahraini study which found that HRQoL was not affected by employment.[15] In contrast to the latter observations, a Saudi study reported that employed patients had better scores in vitality and pain compared to the unemployed.[16] Another Nigerian study reported that employment had negative correlation with vitality and pain domains but a positive one with general health.[19] Regarding marital state, the current study found that the social function and general health scores were lower among the married, though it did not reach significance; this is similar to a study from Iran, which also reported no significant difference relevant to marital state.[17] A Saudi study reported low mean scores in vitality, emotional well-being, and social function HRQoL domains among the married.[16] The latter may be related to increased economic and social burdens among the married compared to those who are single.

Pain episodes are the most important and frequent of the vaso-oclusive events in SCD, and they constitute a crucial part of morbidity associated with it. In the current study, all eight domains were significantly correlated with the frequency of pain episodes with the highest Pearson's correlations encountered social function and pain. Likewise, McClish *et al*., Anie *et al*., and Amaeshi *et al*. reported that all HRQoL domain scores were reduced during pain attacks in their African American, British, and Nigerian SCD patients.[12,18,23] It is important to note that there were significant correlations between lower hemoglobin, higher LDH, and reticulocyte counts with lower HRQoL scores, at least with some domains. This is not unexpected since these parameters reflect the severity of hemolytic process and of the disease.[24]

Among the cumulative events related to SCD, the only one which yielded itself to statistical evaluation was AVNFH. Mean physical function scores were found to be significantly lower in those with the latter complication. Other domains involving role limitation of physical function and emotional well-being were also reduced in those with AVNFH, although this did not reach significance. Such observations were noted in African American SCD patients by Dampier *et al*. who found

that physical function was the only significantly reduced HRQoL domain in AVNFH.[11] Likewise, Nwogoh *et al*. found that AVNFH had a negative correlation with physical function, general health, and pain.[19] This is not unexpected since this complication will restrict the movement of the hip joint and is usually associated with pain, and this would impair physical function.

Finally, in the current study, the large majority of enrollees (88.6%) were on hydroxyurea, and we were unable to document any significant difference between the HRQoL in this group and that in the remaining small group not on this medication. Several authors documented that hydroxyurea improves the HRQoL scores since it decreases the pain episodes and reduces transfusion requirements and admissions to hospital.[14,23,25] Absence of a significant difference between HRQoL scores in those on Hydroxyurea and those not receiving it in the current study is unexpected. However, longitudinal studies comparing HRQoL scores prior to initiating therapy and at regular intervals throughout it would have been a more suitable approach to assessing the impact of this medication on HRQoL in SCD.

Conclusions

The current study documented that in adults with SCD, HRQoL in all domains was significantly worse than in healthy matched controls and that patients' HRQoL gets worse with advancing age, while the most significant contributors to the worse HRQoL were the frequencies of pain episodes and hospital admissions. The study underscores the importance of HRQoL assessments to enable attending physicians provide more patient-centered management, taking in consideration the patient's own perspectives.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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