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Health-Related Quality of Life of Adolescents with Sickle Cell Disease on Hydroxyurea: A Case-Control Study

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Abstract:

BACKGROUND: Sickle cell disease (SCD) is a chronic multisystem disorder associated with acute and chronic complications that may negatively impact the quality of life (QoL). The study aimed to assess the health-related QoL (HRQoL) of patients with SCD on hydroxyurea (HU) and the factors affecting HRQoL domains.

MATERIALS AND METHODS: This case-control study included 174 patients with SCD (12–18-year-old); 87 were on HU for at least 1 year and 87 were not receiving HU. It also included 174 healthy adolescents of the same age group. The HRQoL was assessed using the Short Form 36 Health Survey version 2 (SF-36v2). A multivariate linear regression analysis was performed to assess the independent effect of studied variables on HRQoL dimensions.

RESULTS: Patients with SCD who were not on HU were found to have significantly lower SF-36 v2 scores (all domains) compared to those on HU and control group, $P < 0.001$. While patients on HU had significantly lower SF-36 v2 scores in physical functioning, role physical (RP), general health, and physical health component score only compared to the control group, $P < 0.001$. Multivariate linear regression analysis revealed significant associations between duration of HU therapy and RP ($R^2 = 0.208$, $P = 0.021$) and mental health component score ($R^2 = 0.389$, $P = 0.047$) and between hemoglobin levels with social functioning ($R^2 = 0.370$, $P = 0.023$).

CONCLUSIONS: HU has improved the HRQoL of SCD patients, in almost all domains, in addition to the improvement in many disease-related complications, mainly painful episodes. The positive impact of HU on HRQoL was significantly associated with the duration of therapy.

Keywords:

Hydroxyurea, quality of life, sickle cell disease

Introduction

Sickle cell disease (SCD) is a chronic and complex multisystem disorder associated with multiple acute and chronic complications including painful vasoocclusive events, cerebral vasculopathy, priapism, and renal or lung disease. SCD, as a chronic incurable disease, requires comprehensive care that includes screening, prevention, health education, and management of acute and chronic complications.[1-3]

Health-related quality of life (HRQoL) is an important patient-reported outcome measure for children and aids in the understanding of the well-being of children with SCD.[4] It provides an assessment of how an illness, its complications, and its treatment are experienced by a patient.

The wide clinical variability of the disease and frequent hospitalizations for SCD complications, mainly the pain, may negatively impact the quality of life (QoL) of patients,[3] beside that increased life expectancy in patients with SCD due to recent medical advances has increased

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the need to understand the QoL and factors predicting disease adaptation.[5] The severity of SCD is, in general, inversely proportional to QoL.[6]

The management of SCD continues to pose a challenge to hematologists and patients. Treatment advances over a generation have greatly improved the QoL and longevity of patients. However, the identification of the clinical implications of psychological complications and multidisciplinary management remains unsatisfactory.[7]

Hydroxyurea (HU) is the sole approved pharmacological therapy for SCD. It had a role in preventing and treating SCD-related complications such as painful events, acute chest syndrome (ACS), transfusion, and hospitalization, and may prevent chronic organ damage.[8-10] HU also reduces mortality, improves survival and the HRQoL especially in those with high fetal hemoglobin (HbF) response.[11-13]

SCD is an important health problem in Basra, especially with the absence of effective prevention program. Therefore, this case-control study was carried out to assess the HRQoL of patients with SCD aged 12–18 years and to evaluate the HRQoL dimensions among patients with SCD on HU in comparison with those not receiving HU and to look for the possible factors affecting HRQoL dimensions among patients with SCD on HU.

Materials and Methods

This case-control study was carried out on patients with SCD who have been registered at the Center for Hereditary Blood Diseases (CHBD) over the period from October 2015 through September 2016. It included 174 patients (107 males and 67 females) with SCD, 12–18-year-old, and 174 apparently healthy adolescents of the same age group. The HRQoL was assessed using the short-form health survey 36 version 2 (SF-36 v2).

Patients with sickle cell disease

Patients' data included; date of birth, parental educational levels, date and age of diagnosis, type of SCD, drugs mainly HU, and iron chelation.

The patients have to fulfill the following inclusion criteria; patients diagnosed and registered at CHBD to have SCD by high-performance liquid chromatography (HPLC), age between 12 and 18 years, free from handicapping conditions,[5] and were in steady-state.

Steady-state is defined as absence of any crises in the preceding 4 weeks, no recent drop in the Hb level, and the absence of any symptom or sign attributable to an acute illness and ≥10 weeks posttransfusion.[14,15]

The study populations were divided into two equal groups who were matched for age, gender, and residence.

1. HU group: it included 87 cases who were on HU for at least 1 year
2. No HU group: it included 87 cases who were not receiving HU.

Patients on chronic blood transfusions were excluded from the study as chronic blood transfusions are regarded as disease-modifying therapy.[9,16,17] Children with any chronic physical illnesses, and health-related problems within the past 4 weeks of data collection were also excluded.[18]

Disease-severity measures

Clinical criteria

The severity of SCD was assessed according to clinical criteria; frequency of VOC requiring hospitalization/year, frequency of blood transfusion/year and history of stroke, ACS and/or avascular bone necrosis (AVN). The patient is classified to have severe disease when the frequency of VOC requiring hospitalization (≥3/year), frequency of blood transfusion (≥3/year), and disease-related complications at least one ACS, AVN) and/or stroke.[9]

Genotype

The type of SCD also reflects disease severity, where those with SCA and HbS/β^0 thalassemia are regarded to have severe disease, while those with other types like HbS/β^+ thalassemia have milder disease.[19,20]

Hydroxyurea therapy

For patients on HU, date of starting HU, dose of HU (mg/kg), and total dose/day were recorded.

In the CHBD; indications of HU include frequent pain crises (≥3 severe VOC during the last year), ≥2 ACS requiring hospitalization during the last 2 years, severe anemia with Hb levels <7.0 g/dl and/or requiring more than one transfusion per month to maintain Hb level over 8.0 g/dl, severe complications without benefit from standard therapy (priapism, leg ulceration, ACS), and abnormal Transcranial Doppler refusing transfusion therapy.[9,21,22]

Patients on HU are followed up every 4 weeks in the outpatient clinic of the CHBD and the laboratory workup had been done in the laboratory department of the same center. The HPLC findings (at diagnosis) and after a period of 1 year of HU therapy, mean Hb before and after 1 year of HU therapy were recorded. The mean Hb was divided into two groups Hb >9 g/dl and <9 g/dl.[23]

Levels of HbF were expressed as absolute levels of HbF in g/dl (HbF [g/dl] = HbF [%] × hemoglobin concentration [g/dl]).[23] HbF was divided in to two groups (>0.8 g/dl and <0.8 g/dl).

Data were collected by direct interview with patients and/or one of their parents who have consulted the CHBD for routine follow-up.

Control group

It included age- and gender-matched adolescents with no history of any chronic diseases (including hemoglobinopathies) or positive family history of SCD or other hemoglobinopathies.

Data were collected from the control group from the outpatient clinic of Basra Maternity and Children Hospital and by visiting five schools (1 Primary School, 1 Intermediate School, and 3 Secondary schools) and two Primary Health Centers. A total of 174 participants were included in the control group.

Informed consent was obtained from all participants before recruitment in the study.

Methods

Health-related quality of life questionnaire (The SF-36 v2 questionnaire)

The short-form health survey 36 version 2 (SF-36 v2) questionnaires were used in this study to assess HRQoL as reported by all participants.

The SF-36 v2 is a well-recognized generic measure to assess the functional health and well-being from the patient's point of view and can be self-administered or administered by a trained interviewer.

It consists of eight subscales and two major (summary) measures. The eight subscales include physical function (PF), Role physical (RP), Bodily pain, General health (GH), Vitality (VT), Social function (SF), and Role emotion (RE) and Mental health (MH).

The two major (summary) measures are the physical health component score (PHCS) and MH component score (MHCS).[24]

The Arabic version of SF-36 v2 was used. Reliability estimates for Physical and Mental Summary Scores usually exceed 0.90. The median reliability coefficients for each of the eight scales were equal to or > 0.80, except for SF, which had median reliability across studies of 0.76. The validity of this questionnaire is 80%–90%.[25]

An evaluation of the cross-cultural adaptations of this instrument indicated moderate to good quality.[25] The median Cronbach's alpha for the Arabic RAND-36 in multiple subgroups exceeded 0.70 for most of the scales.[26]

All scales were transformed linearly to a 0–100 possible range of scores, with 0 representing the least favorable health state and 100 representing the most favorable health state. All scores reflect the percent of the total possible score for that scale.[24]

Statistical analysis

Data were processed and analyzed using the Statistical Packages for the Social Sciences (SPSS) version 20 (IBM Corp., Armonk, N. Y., USA). Comparisons of proportions were performed by cross tab using Chi-square test, and Fischer's exact test.

The independent *t*-test was used for quantitative comparison and between two means of different samples, and Paired Sample *t*-test was done for the mean of two variables with the same sample. Comparisons between groups were made by using the one-way analysis of variance test.

Univariate analysis was used to study the correlation between patient's characteristics and SF-36 v2scores. To examine the independent effect of certain variables (dose and duration of HU therapy, hemoglobin, and fetal hemoglobin levels) on various HRQoL dimensions, a multivariate linear regression analysis was performed. A $P < 0.05$ was considered to be statistically significant.

Results

Sociodemographic factors of studied subjects

A total of 174 patients with SCD and 174 healthy adolescents were recruited in this study. Their ages ranged from 12 to 18 years, with a mean of 14.66 ± 1.93; (14.70 ± 1.93) for patients with SCD and (14.62 ± 1.94) for the control group, $P > 0.05$. The populations in these two groups were matched for age, gender, and residence. Out of the 174 patients with SCD, 24 (13.79%) patients have left the school because of their illness, and 13 (7.49%) did not enter school at all. Furthermore, adolescents and their parents in the control group have significantly higher educational levels and family income compared to SCD patients, $P < 0.001$, Table 1.

Disease-related factors

Among patients on HU therapy, a significant decrease in the frequency of acute painful episodes was reported at the time of the study compared to that before HU therapy (0.97 ± 0.11/year vs. 5.33 ± 0.26/year, respectively) and in BT (0.93 ± 0.11/year vs. 3.32 ± 0.23/year respectively). In addition, both mean Hb and Hb F levels have increased significantly from (7.35 ± 0.89 g/dl and 10.77% ± 1.91%) at baseline to (8.94% ± 0.87 g/dl and 17.73 ± 6.52%), respectively, following HU therapy, $P < 0.01$.

The majority of studied patients, both HU and no HU groups were with SCA and HbS/β^0 thalassemia. Patients on HU therapy had significantly lower frequencies of

Table 1: Selected sociodemographic variables of studied participants

Variable	Patients (*n*=174), *n* (%)	Control (*n*=174) *n* (%)	*P*
Gender			
Male	107	103	0.661*
Female	67	71	
Residence			
Center	81 (46.55)	73 (41.95)	0.515*
Periphery	93 (53.45)	101 (58.05)	
Educational level of subject			
Illiterate	13 (7.49)	1 (0.58)	<0.001†
Primary	47 (27.02)	35 (20.13)	
Secondary	114 (65.49)	138 (79.29)	
Educational level of mother			
Illiterate	21 (12.07)	12 (6.89)	<0.001*
Primary	69 (39.65)	24 (13.79)	
Secondary	74 (42.54)	91 (52.31)	
Higher education	10 (5.74)	47 (27.01)	
Educational level of father			
Illiterate	7 (4.03)	0 (0.00)	<0.001†
Primary	41 (23.57)	6 (3.45)	
Secondary	108 (62.06)	111 (63.79)	
Higher education	18 (10.34)	57 (32.76)	
Family income (ID/month)			
<400,000	61 (35.06)	24 (13.79)	<0.001*
400,000-799,000	43 (24.71)	68 (39.08)	
800,000-1,999,000	59 (33.90)	61 (35.06)	
≥2,000,000	11 (6.33)	21 (12.07)	

*χ^2 was used to assess *P*; †Fisher's exact test was used to assess *P*

VOC and BT and higher Hb and Hb F levels than those not receiving HU, $P < 0.001$, Table 2.

Health-related quality of life scores

Patients with SCD (both groups) had lower HRQoL scores, in all dimensions, compared healthy controls, $P < 0.001$, Table 3.

Concerning SCD patients; patients who were not on HU were found to have significantly lower SF-36 v2 scores (all domains) compared to those on HU therapy, $P < 0.001$, Figure 1. Furthermore, this group of patients was found to have significantly lower HRQol scores compared to the control group, $P < 0.001$. While patients receiving HU therapy had significantly lower SF-36 v2 scores in PF, RP, GH, and PHCS domains only compared to the control group, $P < 0.001$, and no significant difference was reported with other domains, Table 4.

Univariate analysis did not demonstrate a significant association between age, gender, parental education, and different types of SCD with different HRQoL domains, $P > 0.05$. While, significant associations were reported between the frequencies of BT and VOC with HRQoL domains, $P < 0.05$. In addition, patients on HU with Hb >9 g/dl, HbF > 0.8 g/dl, receiving HU in a dose >20 mg/kg/day and for ≥24 months had significantly better HRQoL scores, Table 5.

Multivariate linear regression analysis shows a significant positive association between duration of HU therapy and each of RP (β-coefficient-0.234, $P = 0.021$, R^2 0.208), MHCS (β-coefficient-0.176, $P = 0.047$, R^2 0.389) and a significant positive association between Hb levels with SF (β-coefficient-0.568, $P = 0.023$, R^2 0.370).

Discussion

This study is one of the first studies Iin Iraq particularly in Basra to describe the HRQoL of patients with SCD receiving HU therapy and to assess its effect on all domains of HRQoL. In this study, adolescents with SCD on HU therapy reported better HRQoL in all domains compared to those not taking the medication. In addition, a significant correlation was reported between Hb level, Hb F, doses, and duration of HU therapy and all HRQoL domains.

Treatment of chronic illnesses can affect the patient's psychological, social and economic well-being as well as biological status, and improvement in quality and quantity of life.[27]

HU has been approved for the treatment of SCD by the United States Food and Drug Administration and by the European Medicines Agency as a commonly used disease-modifying agent for SCD patients of all age groups.[28,29]

Table 2: Selected clinical and hematological variables of patients with sickle cell disease

Variables	SCD patients			*P*
	HU (*n*=87), *n* (%)	No HU (*n*=87), *n* (%)	Overall (*n*=174), *n* (%)	
Genotypesn				
HbSS-HbS/β⁰ thalassemia	60 (68.97)	51 (58.62)	111 (63.80)	0.156*
HbS/β⁺ thalassemia-HbS/D disease	27 (30.03)	36 (41.38)	63 (36.20)	
VOC requiring hospitalization/year				
No	0	1 (1.15)	1 (0.57)	<0.001†
<3	5 (5.75)	36 (41.38)	41 (23.57)	
≥3	82 (94.25)	50 (57.47)	132 (75.86)	
BT/year				
No	5 (5.75)	2 (2.29)	7 (40.23)	<0.001*
<3	39 (44.83)	68 (78.16)	107 (61.49)	
≥3	43 (49.42)	17 (19.55)	60 (34.48)	
Stroke	4 (4.49)	1 (1.15)	5 (2.87)	0.180†
ACS	3 (3.44)	1 (1.15)	4 (2.30)	0.317†
AVN	9 (10.34)	4 (4.59)	13 (7.47)	0.019†
Mean HB (g/dl)	8.94±0.87	6.84±0.76	7.36±0.89	<0.001‡
Mean HB F%	17.73±6.52	11.60±3.60	14.21±5.88	<0.001‡

*Chi-square test was used to assess the *P*; †Fisher's exact test was used to assess *P* value; ‡Independent *t*-test was used to assess *P*. SCD=Sickle cell disease; HU=Hydroxyurea; VOC=Vaso-occlusive crises; ACS=Acute chest syndrome; AVN=Avascular bone necrosis; HB=Hemoglobin; HbSS=HB SS; HbS=HB S; BT= Blood Transfusion

Table 3: Mean health-related quality of life scores of all participants aged 12-18 years

Domain	SCD patient (*n*=174)	Control group (*n*=174)	*P**
PF	62.59±1.33	90.45±0.93	<0.001
RP	66.17±1.58	90.81±1.23	<0.001
BP	82.82±1.14	93.06±0.96	<0.001
General health	54.82±1.16	91.19±0.91	<0.001
VT	77.51±1.12	87.49±1.31	<0.001
SF	79.55±1.43	93.46±1.01	<0.001
RE	66.81±1.65	86.39±1.72	<0.001
MH	82.11±0.98	88.32±1.24	<0.001
PHCS	68.74±1.06	90.57±0.92	<0.001
MHCS	76.07±1.20	89.33±1.21	<0.001

Values are expressed as mean±SD; *Independent *t*-test was used to assess *P*. SCD=Sickle cell disease; SD=Standard deviation; PF=Physical functioning; RP=Role physical; PHCS=Physical health component score; BP=Bodily pain; VT=Vitality; SF=Social functioning; RE=Role emotion; MH=Mental health; MHCS=Mental health component score

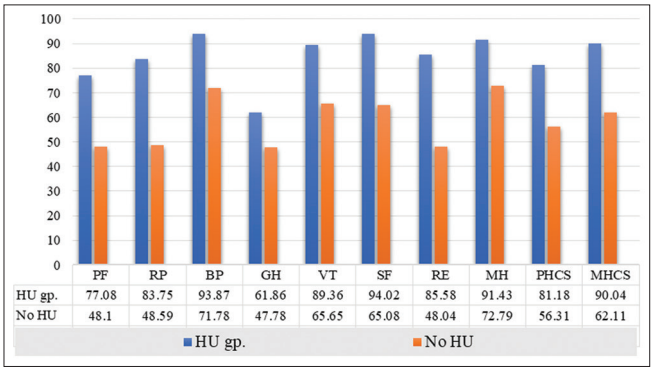

Figure 1: Mean SF-36 v2 scores of patients with SCD in relation to HU intake *P* < 0.001 for all domains. HRQoL indicates health-related quality of life; PF: Physical functioning; RP: Role physical; BP: Bodily pain; GH: General health; VT: Vitality; SF: Social functioning; RE: Role emotion; MH: Mental health; PHCS: Physical health component score; MHCS: mental health component score

The current study demonstrates a significant decrease in the rates of hospitalizations for VOC and BT in patients with SCD after starting HU therapy. Similar findings were reported by other researchers from various countries.[30-33]

The hematological effects of HU as reflected by changes in Hb concentration and HbF level revealed a significant increase in both Hb level and HbF following HU therapy. This is in agreement with Al-Nood *et al*. in Yemen who found that there is increase in both Hb F and Hb levels due to the effect of HU, even at a low dose therapy.[34] Furthermore, in India, Patel *et al*. reported that the HbF, total Hb, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration levels increased significantly after HU therapy.[30]

For the assessment of HRQoL in patients with SCD in Basra, the SF-36 v2 scores as the generic instrumental measure were used, this instrument has been widely validated for numerous professions and patients' groups and can be administered by clinicians or by the patient at home.[25]

The data reported by this study showed that adolescents with SCD experienced a significant impairment in HRQoL with GH being mostly affected followed by PF and RP when compared with their healthy peers. This is in agreement with Dale *et al*. in the USA who demonstrated a lower overall HRQoL in patients with SCD compared to healthy peers.[35] Adeyemo *et al*. in Nigeria[36] and Patel *et al*. in India[37] also reported that SCD impacts the physical, psychosocial emotional

Table 4: Mean health-related quality of life scores of patients with sickle cell disease (in relation to hydroxyurea therapy) and control group

Domain	Patients with SCD		Control group (*n*=174)	*P**
	HU (*n*=87)	No HU (*n*=87)		
PF	77.08±1.28	48.10±0.78	90.45±0.93	<0.001
RP	83.75±1.15	48.59±1.26	90.81±1.23	<0.001
BP	93.87±0.90	71.78±1.28	93.06±0.96	<0.001
GH	61.86±1.48	47.78±1.44	91.19±0.91	<0.001
VT	89.36±0.94	65.65±0.97	87.49±1.31	<0.001
SF	94.02±1.30	65.08±1.32	93.46±1.01	<0.001
RE	85.58±1.07	48.04±1.31	86.39±1.72	<0.001
MH	91.43±0.75	72.79±1.13	88.32±1.24	<0.001
PHCS	81.18±0.80	56.31±0.57	90.57±0.92	<0.001
MHCS	90.04±0.87	62.11±0.70	89.33±1.21	<0.001

Values are expressed as mean±SD. *ANOVA test was used to assess *P*, *post hoc*, LSD test was used to assess the *P* between groups=Group 1 (SCD patients, HU yes and No)=*P*<0.001 for all domains, Group 2 (no HU and controls)=*P*<0.001 for all domains, and Group 3 (HU group and controls), PF, RP, GH, PHCS, *P*<0.001, and for BP, VT, SF, RE, MH and MHCS, *P*>0.05. SCD=Sickle cell disease; SD=Standard deviation; HU=Hydroxyurea; ANOVA=Analysis of variance; LSD=Least significant difference; PF=Physical functioning; RP=Role physical; GH=General health; PHCS=Physical health component score; BP=Bodily pain; VT=Vitality; SF=Social functioning; RE=Role emotion; MH=Mental health; MHCS=MH component score

aspects of the life of the affected persons and negatively alters HRQoL.

The impact of HU therapy as a disease-modifying agent on HRQoL in patients with SCD is well documented,[9,38] which is in agreement with our findings that patients with SCD who are taking HU had better HRQoL in all domains compared to those not taking the medication.

Although the association between various sociodemographic characteristics such as family income, educational status, age, gender, and HRQoL of chronic conditions including SCD has been reported,[39] however, this study demonstrates no significant correlation between any of the studied sociodemographic variables of patients with SCD and all domains of the SF-36 v2 domains.

Amr *et al*. in Saudi Arabia found that all domains of HRQoL were negatively associated with increasing of age, female gender, rural residence, and low family income of the adolescent with SCD, especially in domains of energy, emotional well-being, SF and GH.[5]

The lack of effect of any of the sociodemographic variables on HRQoL in this study may be related to family resources such as positive parent-child relationships, family functioning, active coping, and positive beliefs/attitudes. In addition, In Iraq, the health services are free of charge and all SCD patients can receive HU which can improve the HRQoL. Besides that, families of patients are nearly equally concerned with affected male and female offspring and not essentially with males.

Although the majority of studied patients have homozygous HbS and Sβ^0-thalassemia, no significant association was reported in this study between SCD genotypes and the SF-36 v2 scores. In contrast, Asnani *et al*. in Jamaica observed that having the heterozygous SC disease versus homozygous sickle cell (SS) disease were associated with improved QoL.[40]

This study also shows that there is an inverse relationship between the number of hospitalization and BT and the overall HRQoL domains. In Brazil, a study done by Pereira *et al*. demonstrated that pain crisis, hospitalizations, BT, and other morbidities of SCD had a significant impact on the QoL of these patients.[6]

In terms of hematological and HU variables, a significant correlation was reported between Hb level, Hb F, doses and duration of HU therapy and all domains of the SF-36 v2.

Similarly, Darbari *et al*. showed that the improvement in HRQoL in SCD patients was limited to the patients who received HU over 2 years and who had high Hb F response compared with those with low HbF response.[2]

Estepp *et al*. in their study confirmed greater protection against hospitalization for severe VOC or ACS at HU dose more than 20 mg/kg/day than low-dose approach therapy.[41]

In Kenya, Mulaku *et al*. found that HU therapy is associated with improved HbF level, which in turn reduces risks of sickling events, painful crises, hospitalizations, and improved QoL.[42]

It has been shown that the beneficial effects of HU on laboratory parameters are dose-dependent and "more is better" when considering the therapeutic benefits of HbF induction. Using HU at a maximum tolerated dose typically achieve higher percentage HbF values than lower dose.[43]

The main limitation of the study is that this study was a cross-sectional study that compared the HRQoL of SCD patients on HU with those not receiving the drug. It is better for such studies to follow the patients and assess the HRQoL before and after HU therapy.

In summary, HU has improved the QoL of SCD patients, and its effect was more pronounced with increasing dose and duration of therapy.

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Table 5: Univariate analysis of selected clinical variables and health-related quality of life of adolescents with sickle cell disease on hydroxyurea

Variables	PF	RP	BP	GH	VT	SF	RE	MH	PHCS	MHCS
Blood transfusion										
≥3/years (*n*=8)	58.33±1.57	61.69±1.98	79.75±1.47	52.76±1.41	74.14±1.37	73.04±1.84	61.89±2.06	79.89±1.26	65.40±1.34	72.64±1.50
<3/years (*n*=37)	70.17±2.30	64.64±7.09	88.38±1.74	58.61±2.01	83.26±1.82	87.28±2.07	75.70±2.56	85.53±1.53	74.90±1.83	82.82±1.85
None (*n*=42)	69.42±5.78	75.22±2.46	87.14±3.83	57.14±7.54	84.80±6.07	89.28±5.74	73.77±8.79	90.00±3.45	72.62±4.60	79.45±5.45
P	<0.001	<0.001	0.010	0.060	<0.001	<0.001	<0.001	0.070	<0.001	<0.001
VOCrequiringhospitalization										
≥3/years (*n*=5)	55.00±1.51	40.00±1.73	73.65±2.09	55.00±1.35	56.25±1.22	62.50±1.56	50.00±1.48	72.51±2.09	56.75±1.18	64.10±1.32
<3 (*n*=47)	50.36±1.85	51.33±2.57	77.50±1.27	48.51±2.00	66.76±1.81	66.15±2.43	52.39±2.73	80.00±0.98	57.96±1.46	64.05±1.75
No hospitalization (*n*=35)	66.45	70.97	85.71	56.78	81.00	83.84	71.42	85.11	72.19	79.90
P	<0.001	<0.001	<0.001	0.010	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HB (g/dl)										
≤9 (*n*=34)	69.55±13.61	78.56±12.27	87.71±9.17	59.48±12.48	84.19±10.46	85.00±15.64	79.12±11.47	87.79±7.99	75.89±8.44	83.98±9.43
>9 (*n*=53)	81.90±7.74	87.07±8.18	97.83±4.82	63.39±14.50	92.68±5.44	99.81±1.37	89.73±6.03	93.77±5.18	84.57±4.34	93.92±3.88
P	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Fetal HB (g/dl)										
≤0.8/dl (*n*=37)	70.00±13.28	79.45±12.16	88.43±9.23	60.47±12.66	84.63±10.37	86.22±15.54	79.46±11.04	88.10±8.10	76.59±8.49	84.60±9.30
>0.8g/dl (*n*=50)	82.32±7.58	86.93±8.37	97.90±4.82	62.90±14.64	92.87±5.20	99.80±1.41	90.12±6.00	93.90±4.87	84.57±4.38	94.06±3.89
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	0.009	<0.001	<0.001
HU therapy										
Dose mg/kg										
15 (*n*=50)	69.90±2.04	78.46±1.92	89.56±1.47	54.14±1.95	85.36±1.58	88.48±2.40	81.66±1.82	89.02±1.21	75.48±1.10	86.34±1.51
>15-20 (*n*=30)	83.33±0.96	87.99±0.98	97.88±0.67	66.86±1.65	92.30±0.87	98.78±0.74	88.84±1.11	93.58±0.87	85.67±0.38	93.09±0.77
>20 (*n*=7)	84.28±2.02	91.10±2.29	96.78±3.21	79.28±3.68	96.42±1.26	100.00±0.00	90.41±1.18	93.57±2.36	89.57±1.01	94.64±0.84
P	<0.001	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Duration (months)										
≤24 (*n*=36)	69.72±13.36	79.23±12.26	88.11±9.14	60.07±12.59	84.20±10.18	85.84±15.58	79.35±11.18	87.91±8.13	76.26±8.36	84.37±9.33
>24 (*n*=51)	82.27±7.51	86.94±8.29	97.94±4.78	63.13±14.59	93.01±5.25	99.80±1.40	89.98±6.01	93.92±4.82	84.65±4.37	94.03±3.85
P	<0.001	0.002	<0.001	0.299	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

HRQoL=Health-related quality of life; PF=Physical functioning; RP=Role physical; BP=Bodily pain; GH=General health; VT=Vitality; SF=Social functioning; RE=Role emotion; MH=Mental health; PHCS=Physical health component score; MHCS=MH component score; HU=Hydroxyurea; HB=Hemoglobin

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Conflicts of interest
There are no conflicts of interest.

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