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Authors

Oliveira, Claudia
Kelly, Shannon
de Almeida-Neto, Cesar
et al.

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QUALITY OF LIFE IN PRE-ADOLESCENT CHILDREN WITH SICKLE CELL DISEASE IN BRAZIL

Claudia Di Lorenzo Oliveira, MD, PhD[1], **Shannon Kelly, MD**[2], **Cesar de Almeida-Neto, MD, PhD**[3], **Anna Barbara Carneiro-Proietti, MD, PhD**[4], **Fabiana Chagas Camargo, MD, PhD**[5], **Tassila Salomon, PhD**[4], **Miriam V. Flor-Park, MD, PhD**[6], **Claudia Maximo, MD, PhD**[7], **Daniela Werneck Rodrigues, MD, PhD**[4], **Rosimere Afonso Mota, MD**[4], **Carolina Miranda Teixeira**[4], **Paula Loureiro, MD, PhD**[8], **Ester Cerdeira Sabino, MD, PhD**[9], **Brian Custer, PhD, MPH**[2], **Recipient Epidemiology and Donor Evaluation Study (REDS-III) International Component, Brazil**

[(1)]Universidade Federal de São Joao del-Rei, Brazil

[(2)]VitalantResearchInstitute, San Francisco, CA, USA

[(3)]Fundação Pro-Sangue, São Paulo, Brazil

[(4)]Fundação Hemominas, Minas Gerais, Brazil

[(5)]Universidade Federal de Minas Gerais, Brazil

[(6)]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Instituto da Criança, São Paulo, Brazil

[(7)]Fundação Hemorio, Rio de Janeiro, Brazil

[(8)]Fundação Hemope, Recife, Brazil

[(9)]Universidade de São Paulo, Brazil

Abstract

Sickle cell disease (SCD)affects more than 13 million people and can have a significant impact on the quality of life (QoL) of those persons. We performed a cross-sectional study to evaluate the QoL in SCD children 8–12 years old enrolled from November 2014 to March 2016 in a large multi-center cohort study in Brazil. The PedsQL™ SCD Module was used to evaluate QoL in 412 children from six Brazilian health centers. The mean age of participants was 10.5 years and 193(46.7%) were female. The mean global score was 60.7, with a Cronbachś alpha of 0.92. There were significant differences in socioeconomic demographics and treatments among participants at the six centers, but age, income, SCD genotype, and use of hydroxyurea did not significantly affect the QoL scores. After adjustment for all of these variables in a linear regression model, a significant difference was observed by site in global QoL score and the dimensions ‘worry II’ ($\beta 0=20.7, p<0.00$), ‘treatment´($\beta 0=66.8, p<0.00$) and communication II’($\beta 0=45.8, p<0.00$). These dimensions are affected by the capacity of health professionals to provide clinical and psychological support to patients. Our results suggest that QoL of this patient population varied

Corresponding author: Claudia Di Lorenzo Oliveira (claudia.dlorenzo@gmail.com).

according the health center even adjusted by sociodemographics characteristics. Additional training of health professionals in psychological and clinical support could directly reduce patient apprehension about the disease its clinical complications.

Keywords

sickle cell disease; children; quality of life; PedsQL

Introduction

Sickle cell disease (SCD) is an inherited disease caused by a genetic mutation in the β subunit of hemoglobin. SCD manifestations include many complications such as vaso-occlusive pain episodes, acute chest syndrome, stroke and multiple other problems that can significantly impact the patient's health-related quality of life (QoL).SCD is an important public health problem with over three hundred thousand homozygous SS babies born globally in 2010.(1)In the United States, 1 in every 1,941 neonates born in the last 20 years has SCD, among African Americans the rate increases to 1 in 360 newborns.(2) In Brazil, approximately 3500 children are born with SCD each year. The prevalence is variable among different regions country, but an estimated 30,000 people are living with SCD in Brazil.(3)

There are important reasons to assess health-related quality of life (QoL) in children with SCD, including providing a better understanding of the difficulties faced by patients and their parents, as well as establishing an objective score that can be measured to define the impact of treatments.(4) QoL is a complex concept that encompasses the physical, social and emotionalimpactof the disease and is influenced by many aspects of life, such as functional capacity and social relationships. In recent decades, the importance of QoL as a key patient-centered health outcome metric has been increasingly recognized.(5)

We hypothesized that QoL of SCD children varied according socio demographics status and hemocenters. We evaluated the QoL of SCD children in six clinical healthcare centers in Brazil. Previous studies have analyzed the quality of life among children with SCD, but most used generic instruments for collecting QoL data.(6–8) We administered the Pediatric Quality of Life Inventory (PedsQL)™ SCD Module, a questionnaire specifically developed to measure the quality of life in children with SCD.(9, 10). The advantage of a SCD-specific instrument is to allow analysis of the unique, disease-specific ways that SCD may impact QoL.(10)

Methods

Study population

This study is part of the Brazil component of the multi-center Recipient Epidemiology and Donor Evaluation (REDS-III) program funded by the National Heart, Lung, and Blood Institute (NHLBI) of the USA National Institutes of Health. The REDS-III program conducts research focused on blood safety and availability, and the impact of transfusion on recipients in the USA, Brazil, China and South Africa.(11)

The REDS-III Brazil SCD cohort study was designed to assess SCD pathogenesis and the impact of transfusion on disease outcomes. The study is a collaboration between Vitalant Research Institute in San Francisco, CA and six participating centers in Brazil: Hemope in Recife; Hemorio in Rio de Janeiro, Hemominas in the cities of Belo Horizonte (HBH), Montes Claros (MOC) and Juiz de Fora (JFO); and Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Instituto da Criança in the city of São Paulo. Details of the cohort study procedures and enrollment findings have been described previously.(12)Briefly, randomly selected SCD patients were enrolled at routine patient care visits in six clinical care centers, called hemocenters, in Brazil from November 2013 to May 2015.Up to three annual follow-up visits were conducted through 2018. QoL was measured during the first follow-up visit in the period between November 2014 and March 2016.

Measures

As part of the first follow-up visit, the PedsQL™ Sickle Cell Disease Module instrument was administered to children between the ages of 8 to 12 years. The PedsQL™SCD Module was previously validated and translated to Brazilian Portuguese.(8, 9, 13)The instrument is a Likert-type response scale that includes 43 questions, distributed among nine scales in 5 main domains: pain, worry (I and II), emotion, treatment and communication (I and II).

The pain domain was subdivided in three scales: Pain and hurt has nine questions about the intensity and location of the pain; the second subgroup of questions (pain impact) asks 10 questions about the impact of pain; the third scale has two questions about the ability to control pain (management of pain). The worry domain has two scales: Worry I includes five questions regarding worry associated with pain or visits to an emergency room, hospital or other places outside of home. The second scale (worry II) has two questions regarding specific worries related to stroke or chest crisis. The emotion dimension asks two questions related to feeling mad due to SCD. The treatment dimension has seven questions about the difficulty to comply with SCD treatment. Finally, the communication dimension includes three questions in two scales to evaluate the difficulty to discuss the disease with health care professionals(communication I)or other people (communication II).

All scales have response options ranging from 0 to 4 with0=never a problem, 1= almost never a problem, 2=sometimes a problem, 3=often a problem, 4=almost always a problem. Each question inquires about the last 30 day period. The questionnaire was administered by trained interviewers and the questions about quality of life were answered by the children. Others questions collected outside of the PedsQL™ such as monthly income of the family were answered by the parents or guardians.

The SCD genotype was classified using allele-specific pyrosequencing to identify the hemoglobin mutation and confirmed with Sanger sequencing when necessary.(12)Race categories used in this analysis are consistent with those defined by the Brazilian Institute of Geography and Statistics (IBGE). IBGE conducts the Brazilian census and classifies the Brazilian population into five categories: black, white, mixed, yellow and indigenous. In this analysis, yellow and indigenous groups were combined into an'other' category because of limited number of respondents in those groups.

Statistical analysis

Each scale score of the PedsQL™ SCD was calculated according to the scoring algorithm developed by Panepinto et al.(9) In this algorithm, the ordinal data item response answers are reversed, scored and transformed into a 0–100 scale, where 0=100, 1=75, 2=50, 3=25 and 4=0. To obtain the mean value, answers of all participants are summed and divided by the number of questions in each scale. For the global score, we summed all results and divided by 43, the total number of questions on PedsQL™ SCD Module. Higher sores imply higher quality of life.

After calculating the score, the percentage of scores at the extremes of the scaling range for PedsQL™ SCD Module(i.e. % floor and ceiling) were calculated. Floor or ceiling effects were considered present if at least 15% of respondents reached the lowest or the highest possible score, respectively. Internal consistency of the global scores and each dimension were evaluated using the Cronbach's alpha coefficient, which measures the correlation among answers in a questionnaire in order to evaluate the reliability of the domain. Cronbach's alpha coefficient was considered adequate if the values were >0.70.(14)

We calculated the global score in addition to a score for each dimension within categories defined by gender, race, clinical center, income, current treatment with hydroxyurea and SCD genotype. To evaluate for statistically significant differences among the groups, Wilcoxon rank-sum test was used for gender and current hydroxyurea treatment (2 groups each) and Kruskal-Wallis rank test was used for the others (>2 groups).Quartiles were calculated for the QoL score to compare the results among the health centers. Because there is no defined threshold for 'good' quality of life, we assumed a score above the median(>60.5) would be considered 'good' and a score above the fourth quartile (>74) would be considered 'excellent'.

Finally, a linear regression model was fit using the global QoL score as the outcome and hemocenter as the primary predictor to assess for site specific differences in QoL. Separate linear regression models for each of the nine dimensions using the domain specific QoL score as the outcome were also fit. All models were adjusted for age, income, race, and SCD genotype. All analyses were performed using STATA13.0® (College Station, Texas) and p-values<0.05 were considered statistically significant.

Human Subjects Protections

Local ethical committee approval was obtained at all participating sites and by the National Ethics Committee in Brazil (CONEP approval number 02790812.0.1001.0065). Institutional Review Board approval in the USA was obtained from UCSF, the IRB of record for Vitalant Research Institute, and Research Triangle Institute, International, the data coordinating center for REDS-III. Age-appropriate assent was obtained for participating children in addition to parental consent.

Results

Out of approximately 10,000 patients actively receiving care for SCD at the six clinical sites, 4,956 were randomly selected as eligible to participate in the cohort study. Of the 3,029

recruited, 2,793 (92.2%) were ultimately included in the cohort as participants.(12)Among the 414 children enrolled in the REDS-III cohort who were age 8–12 years at the time of their follow-up visit1, one patient (0.24%) did not answer the questionnaire and another (0.24%) was excluded because he was considered cured of SCD after bone marrow transplant. Therefore, 412 patients were included in this analysis. All 412 answered all questions on the PedsQL™ SCD Module. The socio-demographics and some clinical characteristics of participants a represented by hemocenter in Table 1. The mean age of participants was 10.5 years and 193(46.7%) were female. There were no significant differences in age or sex of respondents among hemocenters. Race (skin color), income, use of hydroxyurea, and the distribution of SCD genotype, were significantly different among hemocenters (all $p<0.001$). Most patients reported mixed race (63.4%) and most (76.3%) had a family income below R$1400.00 per month (approximatelyUS$526.00 in 2015). The percentage of patients who reported white race in the Sao Paulo sitewas higher than other centers (>40% versus <20%). The site in Montes Claros had the highest percentage of population with lowest income. The use of hydroxyurea also varied according to the hemocenter from 23.7% in Montes Claros to 65.5% in Sao Paulo.

The mean global and individual scale scores, with Cronbachś alpha and the percentage of floor and ceiling are shown in Table 2. The results demonstrated a good agreement (alpha >0.70) with the exception of the emotions, treatment, and communication I scales. The percentage of floor and ceiling responses was greater than 15% in some scales. For example, the worry 2 scale demonstrated a very high floor and ceiling. The majority of participants (71.1%) chose extreme answers of 0 (never) or 4 (almost always) in this scale, but the high Cronbachś coefficient alpha suggested a strong agreement in their answers for this dimension (0.91).

Quality of Life scores did not significantly differ by age,self-reported race, use of hydroxyurea and type of SCD (data not shown).For gender, only the dimension worry 1 and communication 1 differed, with males demonstrating significantly higher scores in these two scales. In general, lower income was associated with lower quality of life score. However, it was only statistically significant for the scales of pain and hurt, and worry I.

Hemorio demonstrated the highest percentage of patients in the lowest QoL quartile, with 42.3% scoring below 47. In contrast, the center in Sao Paulo had the highest percentage of scores in the fourth quartile, with 38% of participants demonstrating an excellent (>74) quality of life score. The median of score was 60.5 and the range varied from 8.1 to 100.

The results of the adjusted linear regression model showed a statistical difference among hemocenters for the global score (Table 3). After adjusting for age, income, race, or SCD genotype, an increase in the global score from 8.3 (HBH) to 14.7(ICr-HCFMUSP) points in the basal score (52.6) is observed compared to the Hemorio. In addition, the analyses for the specific domain scores shows a variation among the centers and the dimensions. (Table 4). For the dimensions worry II, treatment and communication II the results were similar. For the dimension pain and hurt the hemocenters HBH, JFO and Instituto da Criança in Sao Paulo were significantly differently from the Hemorio, but MOC and Hemope did not differ.

For two scales related to pain (pain impact and management of pain) we did not observe differences among the hemocenters.

Discussion

In this study, we measured the QoL in children 8–12 years of age in a large, multi-center SCD cohort in Brazil. The mean global score was 60.7, which is consistent with mean scores reported by other international groups using the PedsQL™ SCD Module to assess QoL in children with SCD.The dimensions pain and hurt, and worry II had the highest and lowest scores, respectively.We observed significant differences among the participating centers inBrazil with the lowest scores observed in the center in Rio de Janeiro (Hemorio).Age, income, SCD genotype, and use of hydroxyurea did not significantly affect the QoL score.

To our knowledge this is the first time the PedsQL™ SCD Module has been used in Latin America. We included pre-adolescent patients from four different States in Brazil in six different health centers. Although this is not a representative sample of the entire country, the sample was representative of the places where the study was conducted. The reliability of the instrument in our study population was very good, demonstrating it was well adapted for SCD patients in Brazil. The results are consistent with the study conducted by Panepinto et al. that validated the PedsQL™ SCD Module in the US SCD population. That study identified a global score of 62.4 in 243 SCD children ages 5–18 years in five sites in the US. (9). A second study conducted in the Sultanate of Oman reporteda global score of 52 in 123 children with SCD.(15)

These studies used the PedsQL™ SCD Module, therefore only reported on QoL in children with SCD. However, other studies using a generic instrument, PedsQL™ Generic Core Scale, to compare children with SCD to non-SCD controls have demonstrated lower QoL scores in children with SCD. Bakshi et al. reported a significantly lower QoL in 33 children with SCD compared to 27 African-American children (either siblings or other African-American controls from similar communities).(16) This study also used the PedsQL™ SCD Module to calculate the SCD specific QoL score and reported a global score of 59.9, similar to our results and other published literature using the SCD Module.

We observed the highest mean score in the dimension Pain and Hurt. The centers in Belo Horizonte and Sao Paulo demonstrated an elevation in the score of more than 10 points ($p<0.001$). These findings mean that patients from the both centers had lower influence of pain in their quality of life. In the same direction, the dimensions communication I & II were particularly significant in all hemocenters compared to Hemorio. The dimension worry II, which evaluates the concern about specific complications, was particularly lower in Hemorio compared to other centers. However, the percentage of floor and ceiling was the highest in worry II, which is different than reported in the study from Oman (15), but for which we do not have a specific explanation. The capacity of patients to talk with health professionals and other people from their community is also related to the support they have received during the treatment.(17)Patients who are not able to talk about their disease may feel worse than those that can communicate their feelings and therefore receive feedback and help.(10)

The Brazilian National Health Care System (SUS) provides treatment for all patients. A national protocol to treat patients with SCD was recommended by SUS, but there are regional differences among health centers regarding clinical care, access to care, and infrastructure. These factors may directly affect the perception of patients about their treatment and influence their quality of life. Thus, differences between centers in our results may be mainly related to the treatment, communication, and worry about the disease.

Although low income has been associated with lower quality of life in previous studies(18), we did not find differences among QoL score related to income in Brazil. However, our study population was generally homogenous in terms of income withmost of the participants in the middle incomegroup (63%). According to IBGE in 2017, based on the Continuous National Household Sample Survey(19) of the states in our study Pernambuco has a lower average per capita earning than the states of Sao Paulo and Minas Gerais. Nevertheless, differences among quality of life scores related to the income were not observed in our study population.

Some studies support the idea that quality of life would be more affected by the social and environmental factors than the health conditions.(20, 21) QoL could be influenced by different factors related to the environmental such as urban violence, leisure and recreational facilities, as well as the distance and opportunity to reach for health center. Many of patients from Hemorio may live in the favelas (slums), but patients from the other centers may have similar socio-demographic conditions. Thus, the underlying reasons for the lower scores in Rio de Janeiro need further investigation.

Many studies have been evaluated QoL according to the different treatments for SCD (7, 22–24). The use of blood transfusion was associated with better QoL (22, 24),but the relationship between hydroxyurea and QoL remains unclear. Although some studies have reported an impact of hydroxyurea on QoL(6, 25, 26) this has not been replicated in other studies (15, 27).We also did not find an association between use of hydroxyurea and QoL. Hydroxyurea is the only approved SCD modifying medication in the US, Brazil and most other countries. In our study we asked about the current use of hydroxyurea and perhaps some patients could have used the medication in the recent past and therefore the “current use” definition could have led to misclassification and obscured the impact of recent hydroxyurea on QoL for some participants.

Our study has other limitations that should be considered. First, quality of life was only measured at one point in time. Response options can be influenced by the situation of the patient in the moment (clinical status, recent episode of pain or severity). Second, regional differences in language in Brazil are potentially are not captured by the instrument even though the translation to standard Brazilian Portuguese followed an adequate protocol. Third, we did not classify our patients by SCD severity and we not evaluate the patients according clinical features of patients like stroke, transcranial doppler and transfusion dependence, which could influence in the quality of life scores. However, we did use the SCD genotype as a proxy, because some SCD types, such as homozygous SS, have worse prognosis and more severe disease compared to heterogeneous variants, such as SC. After this successful validation that the instrument performs well in pre-adolescent SCD patients

in Brazil, we plan to analyze the QoL based on severity, specific complications and response to therapies such as chronic transfusion therapy.

In summary, this is the first time the PedsQL™ SCD Module has been used in Brazil and these results provide important information regarding the QoL of children with SCD. The results are consistent with QoL measured in pediatric SCD populations in other countries. The patients in the study were between the ages 8 to 12 years, and have reached a level of cognitive development where providing support regarding this life-long chronic disease is very important to help them as well as their families understand the adverse events that may continue to occur and the importance of factors like consistently taking medicine. Our results suggests that the difference of health assistance done by the hemocenters would affected the quality of life beside the others factors such as age, income and sex. Effort to provide enhanced coping tools could improve the QoL for SCD patients, and health professionals should be trained to provide this type of support with the objective of seeking to maximum the QoL of each patient.

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Table 1.

Socio-demographics and clinical characteristics of population by Hemocenter

Variable	Total N=413*	HBH N=147 n (%)	JFO N=38 n (%)	MOC N=38 n (%)	Hemope N=50 n(%)	Hemorio N=111 n (%)	ICr-HCFMUSP N=29 n (%)	P-value**
Gender								
Female	193 (46.7)	76 (51.7)	10 (26.3)	18 (47.4)	26 (52.0)	52 (46.8)	11 (37.9)	
Male	220 (53.3)	71 (48.3)	28 (73.7)	20 (52.6)	24 (48.0)	59 (53.2)	18 (62.1)	0.09
Age								
8–9	142 (34.4)	49 (33.3)	13 (34.2)	14 (36.8)	16 (32.0)	38 (34.2)	12 (41.4)	
10	108 (26.1)	36 (24.5)	7 (18.4)	9 (23.7)	18 (36.0)	35 (31.5)	3 (10.3)	
11–12	163 (39.5)	62 (42.2	18 (47.4)	15 (39.5)	16 (32.0)	38 (34.3)	14 (48.3)	0.39
Color								
White	60 (14.5)	20 (13.6)	0	6 (15.8)	3 (6.0)	19 (17.1)	12 (41.4)	
Black	79 (19.2)	23 (15.6)	16 (42.1)	3 (7.9)	7 (14.0)	25 (22.5)	5 (17.3)	
Mixed	262 (63.4)	96 (65.3)	21 (55.3)	28 (73.7)	40 (80.0)	66 (59.5)	11 (37.9)	
Others	12 (2.9)	8 (5.5)	1 (2.6)	1 (2.6)	0	1 (.9)	1 (3.4)	0.000
Income (R$)								
<700	52 (12.6)	20 (13.6)	1 (2.6)	12 (31.6)	2 (4.3)	16 (14.4)	1 (3.4)	
700–1400	263 (63.7)	82 (55.8)	30 (78.9)	24 (63.1)	36 (78.3)	77 (69.4)	14 (48.3)	
1401 or more	72 (17.4)	25 (17.0)	7 (18.5)	2 (5.3)	8 (17.4)	18 (16.2)	12 (41.4)	0.000
Unknown	26 (6.3)	20 (13.6)	0	0	4 (8.0)	0	2(6.9)	
Use of hydroxyurea								
Yes	207 (50.1)	67 (45.6)	19 (50)	9 (23.7)	31 (62.0)	62 (55.9)	19 (65.5)	
No	206 (49.9)	80 (54.4)	19 (50)	29 (76.3)	19 (38.0)	49 (44.1)	10 (34.5)	0.002
Type								
SB/SB+severe	14 (3.4)	6 (4.1)	0	0	2 (4.0)	5 (4.5)	1 (3.4)	
SBO	12 (2.9)	7 (4.8)	1 (2.6)	1 (2.6)	1 (2.0)	1 (0.9)	1 (3.4)	
SC	103 (24.9)	51 (34.7)	10 (26.3)	13 (34.2)	3 (6.0)	22 (19.8)	4 (13.8)	
SS	284 (68.8)	83 (56.4	27 (71.1)	24 (63.2)	44 (88.0)	83 (74.8)	23 (79.4)	0.01

*For this analysis we included one patient did not answer the PedsQL.

**Chi2 test

HBH(Hemominas Belo Horioznte), MOC (Hemominas Montes Claros), JFO (Hemominas Juiz de Fora), Hemope (Hemocentro Pernanbuco),Hemorio (Hemocentro Rio de Janeiro),ICrHCFMUSP (Instituto da Criança-do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo).

Table 2.

PedsQL™ SCD Module scores, means, reliability, percent floor and ceiling for child self-report (8–12 years old).

Module Scale	Number of items	Number of obs *	Mean	% Floor	% Ceiling	Cronbachś alpha
Global	43	412	60.7	0.24	2.43	0.92
Pain and Hurt	9	412	76.6	0.49	28.64	0.87
Pain impact	10	412	50.7	3.16	8.25	0.90
Pain management	2	412	53.03	18.9	26.5	0.84
Worry I	5	412	53.7	9.22	16.99	0.82
Worry II	2	412	48.0	37.9	33.2	0.91
Emotions	2	412	52.9	16.99	20.39	0.61
Treatment	7	412	68.7	0.24	9.22	0.58
Communication I	3	412	66.9	6.55	29.8	0.65
Communication II	3	412	51.2	14.4	16.55	0.72

* One participant did not answer the questionnaire for quality of life and one patient was excluded because he was cured by bone marrow transplant.
Note: % floor & ceiling means the percentage of scores at the extremes of the scaling range

Table 3.

Results of the adjusted linear regression model for the global score *

Variable	Coefficient	95% CI	P value
Hemocenter (reference=Hemorio)			
HBH	8.3	3.7–12.9	0.000
JFO	12.5	5.8–19.3	0.000
MOC	14.8	8.2–21.4	0.000
Hemope	8.1	1.9–14.2	0.010
ICr-HCFMUSP	14.7	7.0–22.4	0.000
Age (reference=8–9 years)			
10 years	4.6	0.6–9.2	0.05
11–12 years	2.8	−1.3–6.9	0.18
Color (reference=white)			
black	−1.2	−7.7–5.1	0.69
mixed	2.2	−3.2–7.6	0.42
others	−1.2	−12.9–10.4	0.83
Income (reference=<700R$)			
700 <1400 (R$)	−4.6	−10.0–0.83	0.09
1401 (R$) or more	3.9	−2.56–10.5	0.23
Type of SC (reference= Sβ/Sβ+severe)			
SBO	9.8	−4.74–24.3	0.18
SC	0.91	−9.8–11.64	0.86
SS	−1.34	−11.6–8.9	0.79

*Constant (β0)=52.6

Table 4.

Results of the adjusted linear regression model for scores for scales*

	β0**	HBH	JFO	MOC	Hemope	ICr-HCFMUSP
Pain and Hurt	62.9	13.8 (0.00)	8.2 (0.03)	4.5 (0.23)	5.7 (0.10)	18.6 (0.00)
Pain impact	45.8	−1.4 (0.69)	6.8 (0.21)	8.8 (0.10)	−4.5 (0.36)	−4.2 (0.50)
Pain management	61.7	−2.4 (0.60)	2.2 (0.75)	−9.3(0.18)	2.4 (0.70)	9.8 (0.22)
Worry I	49.5	3.3 (0.41)	9.8 (0.09)	22.9 (0.00)	7.1 (0.18)	20.4 (0.00)
Worry II	20.7	48.3 (0.00)	58.4 (0.00)	73.6 (0.00)	68.2 (0.00)	79.5 (0.00)
Emotions	54.7	1.1 (0.80)	9.1 (0.16)	17.4 (0.00)	7.2 (0.23)	11.0 (0.14)
Treatment	66.8	9.4 (0.00)	17.7 (0.00)	15.4 (0.00)	11.0 (0.00)	14.0 (0.00)
Communication I	37.8	12.5 (0.00)	14.7 (0.01)	12.5 (0.03)	4.9 (0.35)	22.3 (0.00)
Communication II	45.8	12.4 (0.00)	9.5 (0.13)	29.0 (0.00)	19.5 (0.00)	18.0 (0.01)

*Reference category Hemorio.Values shown for each Hemocenter indicate the change in score relative to Hemorio. All models were adjusted by age, race, income and type of SCD.

**Constant