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Quality of Life in Thalassemia: A Comparison of SF-36 Results from the Thalassemia Longitudinal Cohort to Reported Literature and the US Norms

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Abstract

Thalassemia is a chronic, inherited blood disorder, which, in its most severe form, causes life-threatening anemia. Advances in treatment have led to increased life expectancy however the need for chronic blood transfusions and chelation therapy remains a significant burden for patients. Our study compared health related quality of life (HRQOL) from the Thalassemia Clinical Research Network's (TCRNs) Thalassemia Longitudinal Cohort (TLC) study to US norms and assessed association with clinical variables. There were 264 patients over age 14 who completed the Medical Outcomes Study 36-Item Short Form Health Survey version 2 (SF36v2) baseline assessment. When compared to US norms, TLC patients had statistically significant ($p<0.05$) worse HRQOL on 5 of the 8 subscales (physical functioning, role-physical, general health, social functioning and role-emotional) and on both summary scales (physical component summary and mental component summary). Women, older patients, and those with more disease complications and side effects from chelation reported lower HRQOL. In general, adolescents and adults with thalassemia report worse HRQOL than the US population, despite contemporary therapy. The SF-36 should become a standard instrument for assessing HRQOL in thalassemia to determine predictors of low HRQOL which may be better addressed by a multidisciplinary team.

Keywords

thalassemia; quality of life; North America; UK; adult

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Although medical advances in the treatment of thalassemia have led to increased survival patients still suffer disease complications. These, along with the significant burden from chronic treatment with transfusions and chelation, can adversely impact patient's quality of life (1, 2). Health Related Quality of Life (HRQOL) refers to the patient's perception of their physical and mental health. Measuring of HRQOL is important to assess the impact that a chronic disease has on a patient's everyday life, to compare different groups of patients, and to measure the effect of an intervention(3).

There are several main gaps in the literature of HRQOL in thalassemia which our study will help fill. Most HRQOL studies have focused on children, whereas adult studies have been relatively small and included non-thalassemia patients (4, 5). While lower HRQOL has been described in thalassemia patients, it is not known what clinical factors have a significant impact on HRQOL, nor have there been prior studies which follow patients over time (3, 4). Our study will fill some of these gaps in the literature by focusing on the baseline data in a large adult population of thalassemia patients with robust clinical data as well as HRQOL evaluations.

The goal of our study is to define the HRQOL in adolescents and adults with thalassemia by describing the quality of life in a cohort of North American and UK patients with thalassemia, comparing those results with US norms, and evaluating the association between HRQOL and clinical factors. We hypothesized that patients with thalassemia will report lower HRQOL than the standard US population. Furthermore we hypothesized that HRQOL will be lower in 1) patients with more severe disease since those patients will require more regular transfusion, and are more likely to suffer from disease and transfusion related complications, 2) patients on non-oral chelation, since there is some literature to suggest that oral chelation is associated with greater patient satisfaction (6) and 3) patients who report problems with chelation adherence.

Our study included 264 patients over age 14 with self-reported SF-36 scores. Basic patient demographics are shown in table 1. As expected TLC patients reported significantly lower HRQOL compared to the US norm in 7 domains; physical functioning, role-physical, general health, social functioning, role-emotional and both the physical and mental summary scores (see Table 2). Effect size calculations demonstrated a clinically significant but small effect in role-physical, social functioning, role-emotional, and the physical summary score, and a large effect on general health. When limited to US patients HRQOL remained significantly lower in 5 domains; role-physical, general health, social functioning, role-emotional and the physical summary score with a clinically significant effect size in general health (large) and the physical summary score (small).

In univariate analysis lower HRQOL was associated with female gender, older age, receiving treatment in the UK, having a higher number of complications, and having a higher number of chelation side effects (for patients on oral chelator). Higher HRQOL was associated with being transfused (general health domain only) and being on an oral chelator. There was no association between any measure of compliance and HRQOL for patients on DFO alone. Race and ferritin were not associated with differences in SF-36 scores. In multivariate analysis (controlling for gender, race, chelator choice, frequency of side effects

from chelation, country, number of complications, ferritin and transfusion status), older age, greater number of side effects, country (UK), and number of complications were the major factors associated with lower HRQOL, with race and gender showing a more limited effect, and chelator choice and ferritin showing no association with HRQOL in any SF-36 domain (Table 3).

This is one of only a few published reports of HRQOL in thalassemia patients, and the first to look at clinical associations with HRQOL. As expected, we found that adolescent and adult patients with thalassemia had impaired HRQOL compared to US norms. After controlling for demographic and clinical variables, we found that older age, greater number of side effects, country (UK), greater number of complications, and to a lesser extent female gender, Asian race, and not being transfused were associated with lower HRQOL.

Older age and female gender were associated with lower HRQOL in the TLC patients, but are known to be associated with lower HRQOL in the general population as well. After controlling for population differences in HRQOL we found no effect of gender over and above that of the general population; however HRQOL is lower in the older TLC patients than would be expected in the general population. This difference was primarily seen in areas of patient reported physical health rather then mental health and remained even after removing UK patients from the analysis.

This conclusion, that HRQOL is lower than expected in older TLC patients, must be interpreted with caution. Since this initial evaluation is a cross-sectional analysis, older TLC patients were diagnosed in an earlier era and may have been receiving transfusion and chelation therapy for longer. Also oral chelation is a relatively new therapeutic option in the US, which may give a generational effect on HRQOL. It will be enlightening to follow TLC patients over time and see if this age effect on HRQOL persists.

Our multivariate results are quite striking, especially since chelator choice was not associated with HRQOL in any domain after adjusting for other variables. This is in contrast with some literature which suggests oral chelation is associated with higher patient satisfaction. This may be due to the fact that patients are free to choose their own chelation, or may reflect the importance of adding clinical variables to the analysis.

Country remained a significant factor across domains, even after controlling for multiple variables, with UK patients reporting lower HRQOL compared to US or Canadian patients, however the number of UK patients is too small to make many conclusions about this finding.

We have attempted to demonstrate which HRQOL differences are clinically relevant to the population. There is a growing literature on minimal clinically important difference (MCID) which can be loosely defined as the smallest change that is important, or seen by the patient as an improvement. A difference in 2-5 points on the normalized (mean of 50) SF-36 scores is often used as an approximation of the MCID (7, 8). By that measure we can see that many factors (such as age, gender, side effects and country) have a large effect which is likely to be clinically relevant.

Our findings show some differences from other published literature, although interestingly two Italian thalassemia studies showed contrasting results as well. Messina et al showed striking impairments in social functioning, role-emotional and the mental component summary (9). However Scalone et al showed SF-36 scores for thalassemia patients which were close to country norms, and in some cases even higher (10). By contrast our results show HRQOL lower than US norms with the greatest effect in general health and the physical domains. It is unclear why the Messina study showed such extremely low scores for social functioning, role-emotional, and the mental summary score, although this may be in part because of the higher average age of the patients in that study. Our findings are however similar to two studies by Payne et al. In a UK study they report SF-36 scores that were lower than age- and gender-matched country specific norms for all domains and both summary scores, with much lower scores for physical functioning and general health (5). In a US study they found that patient reported lower HRQOL than US norms with general health showing the most impact (4).

It is important to keep in mind that HRQOL is in many ways a social construct, since it relies on a person's expectation of health. Thus SF-36 norms vary by country with Italian norms being lower than US. For a disease such as thalassemia, which occurs in different populations, and is seen increasingly in immigrants in the US, these cultural differences are an important area for further study.

As we continue to make medical advances and improve life expectancy in thalassemia, HRQOL become an even more important marker of treatment success. The fact that the SF36 is widely validated and accepted in many countries makes it a good choice to be a standard assessment in thalassemia. Poor HRQOL in TLC patients is due to a complex combination of living with a chronic disease, medical complications, and side effects from chelation therapy. By identifying specific factors associated with lower HRQOL, we can help patients and health care providers focus on those areas likely to have the largest impact. As we follow our patient cohort over time we will also be able to examine associations between clinical changes and changes in HRQOL, which will add valuable information to how we can maximize HRQOL while striving to reduce the clinical burden of disease.

Methods

Our study involved patients enrolled in the Thalassemia Longitudinal Cohort (TLC), part of the Thalassemia Clinical Research Network (TCRN). The TCRN is an NIH/NHLBI funded research network composed of 6 core centers in the US, Canada, and the UK and their associated satellite sites. Patients with thalassemia who required regular medical monitoring and were followed at TCRN and satellite sites were recruited to become part of the TLC study. The goal of the TLC is to measure the prevalence and incidence of complications of thalassemia and their treatment (11). The core data for TLC included a medical history interview, medical record review, blood collection, and questionnaires on quality of life, nutritional status, and medication adherence done for each participant at baseline and at yearly follow-up visits.

Demographics (age, race, gender, country of enrollment) and medical data (ferritin, method of chelation, and frequency of transfusions) were collected through self-report and medical chart review. Race was dichotomized into Asian vs. non-Asian because of the small number of patients of 'other' race. Country was used as a three-level predictor and was also dichotomized into US/Canada vs. UK given the similarity in results among North American patients. We divided chelator choice into deferoxamine (DFO) only, oral chelator only, combination chelator, and no chelation. Patients on no chelation where excluded from some analyses that focused on chelator choice.

Because there is no universally agreed upon definition of disease severity beyond diagnosis and transfusion status, we used several proxy measures to get a more nuanced picture of disease burden. Measures we examined included ferritin, transfusion status, self-reported problems related to chelation, and number of disease or treatment related complications. Ferritin levels were obtained from the patient's medical record and used as a continuous variable but log transformed for analysis because of the skew of the data. Transfusion status was defined by the number of transfusions received in the past year; non-transfused (no transfusions) or transfused (including intermittently transfused patients requiring 1-7 transfusions and regularly transfused at least 8 transfusions per year).

A complication summary score was created for each patient by summing the 'yes' responses to a list of 14 potential complications in the questionnaire, for a possible score of 0 to 14. If data on a complication was missing, it was counted as zero. Potential complications included cardiac complications (congestive heart failure, ventricular arrhythmia, low cardiac T2* by MRI), endocrine complications (diabetes type I, diabetes type II, growth hormone deficiency, hypothyroidism, hypoparathyroidism, hypogonadotropic hypogonadism), liver disease (cirrhosis), and transfusion related complications and infections (alloimmumization, active hepatitis C, chronic active hepatitis B, HIV). The list of complications included in the questionnaire was developed by group consensus among the site PIs for the study, all of whom are experienced clinicians caring for thalassemia patients. The summary score does not take into account the fact that some complications are more significant than others, however the number of patients with each complication was too small to analyze each one individually.

To evaluate adherence to chelation patients were asked 'in the past month have you had problems' "remembering"," preparing" or "taking" their chelator. Patients on deferoxamine were also asked how often they had problems "sticking yourself" and "wearing the pump". Answers were on a 5-point Likert scale where 1=never, 2=rarely, 3=sometimes, 4=often and 5= a lot. Therefore a higher score indicated more problems with that aspect of adherence. Patients were also asked to rank how often they "felt successful" taking their chelator on the same 5-point Likert scale as above; in that case a higher score was better, indicating more success with chelation. For the final question about compliance, patients were asked to rate how many side effects they felt they had from their chelator. Each question was examined separately, and as part of a total score, to determine which aspect of chelation contributed the most to adherence difficulties and HRQOL

HRQOL was assessed by self-report with the Medical Outcomes Study 36-Item Short Form Health Survey version 2 (SF-36v2) for all patients over age 14. This is a generic measure of health related functional status and well-being, which has been well-validated in many different populations and disease states. It generates 8 subscale scores; physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. These domains are combined into two summary scores; a physical component summary (PCS) and mental component summary (MCS). Possible scores for each domain range from 0 (worst) to 100 (best), and can be normalized to a mean of 50 and standard deviation of 10 (12). Published norms for the US population by age and gender were used for comparison. Other reported values for patients with thalassemia were obtained from published studies (4, 5, 9, 10, 13-15). There were a total of 276 patients over age 14 in the TLC. Twelve were excluded for not having the SF-36 filled out completely, which resulted in a total sample of 264.

Mean values and standard deviation for subscales and component summaries of the SF-36 are presented. Comparisons between the US subset of the study population and US norms were done using t-test. Comparison was also made with age and gender matched norms to determine if the effects on age and gender in TLC patients were different than that seen in the general population.

In order to determine which differences were clinically as well as statistically significant we used measures of effect size and minimal clinically important difference (MCID). Effect size was calculated for each SF-36 subscale by dividing the difference between TLC scores and the US norm by the US standard deviation. Clinically significant effects was defined as an effect size>0.2, where 0.2-0.49 = ‘small’, 0.50–0.79 = ‘moderate’ and >0.80 = ‘large’(7, 8). A difference in at least 2 points on the normalized (mean of 50) SF-36 scores was used as an approximation of a clinically relevant MCID.

Descriptive statistics were calculated for demographic variables (age, gender, race, country), transfusion status (transfused versus non-transfused), chelation choice (deferoxamine, oral chelator, combination therapy or no chelation), complications (as a continuous measure), ferritin (log transformed) and measures of adherence, as well as the SF-36 component scores and summary scores. Because of the differences noted in the UK patients, analyses were re-run with North American patients only. Bivariate analysis was done on each of the above mentioned variables with the SF-36 scores to determine associations and for consideration of inclusion in the final multivariate model.

Multivariate analysis was done including factors that were significant on bivariate screen (age, gender, country, complications, chelator choice, side effects, ferritin, transfusion status). Race was kept in the model despite not being significant on univariate screen because it was felt that it was important to include in this population. Since the only measure of adherence with a significant association with SF-36 scores was ‘side-effect’, it was the only adherence measure included in the final model. The final multivariate model included gender, race (Asian vs non-Asian), chelator choice (only for patients on chelator), self-reported frequency of side effects from chelation, country, number of complications (as a

continuous measure), ferritin (in log scale) and transfusion status (transfused versus not-transfused).

Statistical analyses were performed with SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, USA). QualityMetric Health Outcomes™ Scoring Software 2.0 (QualityMetric Inc., Lincoln, RI, USA) was used to score the SF36 data.

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Appendix 1

The following institutions and researchers contributed to the Thalassemia Clinical Research Network Thalassemia Longitudinal Cohort data reported in this paper.

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Center: New England Research Institutes, Sonja McKinlay, PhD, Principal Investigator, Lisa Virzi, RN, MS, MBA, Project Director, Felicia Trachtenberg, PhD, Senior Statistician.

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Table 1

Patient Demographics

Variable	TLC n=264
Gender	
Male	127 (48%)
Female	137 (52%)
Age (years)	Mean = 29 (14-58)
14-17	40 (15%)
18-24	72 (27%)
25-34	72 (27%)
35-44	57 (22%)
45-54	20 (7.6%)
55-64	3 (1%)
Race	
White	144 (56%)
Asian	104 (40%)
Other	11 (4%)
Chelator	
None	22 (8.4%)
Deferoxamine (DFO, Desferal)	57 (22%)
Deferasirox (DFX, Exjade)	136 (52%)
Deferiprone (L1)	9 (3.4%)
DFO/L1	21 (8%)
DFO/Exjade	17 (6.5%)
Thalassemia Diagnosis	
B-thal regularly transfused[1]	204 (78%)
B-thal intermittently transfused[2]	24 (9%)
B-thal non-transfused[3]	2 (0.8%)
HbH CS	4(1.5%)
EB-thal regularly transfused[1]	20 (7.6%)
EB-thal intermittently transfused[2]	6 (2.3%)
EB-thal non-transfused[3]	1 (0.4%)
alpha-thal	2 (0.8%)
Transfusion Status[4]	
Transfused	224 (87%)
Non-Transfused	33 (13%)
Location	

Variable	TLC n=264
US	193 (73%)
Canada	36 (14%)
UK	35 (13%)
Ferritin	Median 1371 (range 67-23,712)
Number of Secondary Complications	mean 1.7 (range 0-8)
0	90 (34%)
1	60 (23%)
2	39 (15%)
3	38 (14%)
4	15 (5.7%)
5	14 (5.3%)
6	5 (1.9%)
7	2 (0.76%)
8	1 (0.38%)

[1] at least 8 transfusions in the past year

[2] 1-7 transfusions in the past year

[3] no transfusions in the past year

[4] in the past year

Table 2

Comparison between TLC SF-36 Scores and US norms

SF-36 measure	US norm	TLC (n=264)	p-value*	Effect size#	US patients only	p-value	Effect size#
Physical Functioning	50	48.18*	0.004	0.18	49.32	0.35	0.068
Role-Physical	50	47.33*	<0.0001	**0.27 (small)**	48.52*	0.042	0.15
Bodily Pain	50	49.41	0.35	0.059	50.19	0.80	−0.019
General Health	50	41.5*	<0.0001	**0.85 (large)**	41.27*	<0.0001	**0.87 (large)**
Vitality	50	48.89	0.08	0.11	49.65	0.63	0.035
Social Functioning	50	46.79*	<0.0001	**0.32 (small)**	48.01*	0.006	0.20
Role-Emotional	50	46.78*	<0.0001	**0.32 (small)**	48.15*	0.01	0.18
Mental Health	50	49.04	0.12	0.096	49.38	0.40	0.062
Physical Summary	50	46.8*	<0.0001	**0.32 (small)**	47.57*	<0.0001	**0.24 (small)**
Mental Summary	50	47.95*	0.002	0.20	48.73	0.11	0.13

Clinically significant effects defined as: 0.2-0.49 = ‘small’, 0.50-0.79 = ‘moderate’, >0.80 = ‘large’(8)

*one sample T test shows significant difference between population and US norm ($p<0.05$)

#effect size = difference in mean / population SD

Table 3

Magnitude of Effect for Significant Factors Associated with HRQOL ($p<0.05$) from Multivariate Model

	Age (decade)	Asian	Side effects	Country (US ref)	Complications	Female	Transfused
Physical Functioning	**−2.28**	**−2.64**		Canada −1.69 **UK −9.42**		**−2.63**	
Role-Physical	−1.93		−1.63	**Canada −2.14** **UK −9.45**			
Bodily Pain			**−2.97**	Canada 0.79 **UK −8.96**	−1.16		
General Health	**−2.22**		−1.62		−1.17		**5.46**
Vitality	−1.57	**−3.29**	**−2.37**	Canada 0.87 **UK −6.86**	−0.98		
Social Functioning	**−2.25**		**−2.37**	Canada −1.99 **UK −6.58**			
Role-Emotional	−1.92			**Canada −2.05** **UK −10.20**		**−3.13**	
Mental Health			−1.67	Canada 0.59 **UK −4.83**	−1.10		
Physical Summary	**−2.12**		−1.80	Canada −0.09 **UK −8.03**	−0.87		
Mental Summary			−1.79	Canada −0.41 **UK −5.91**			

Highlighted effects (greater than 2 points) may be considered clinically relevant