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METHODOLOGY

Psychometric properties of the Specific Thalassemia Quality of Life Instrument for adults

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Background: No specific questionnaire has been developed to assess the health-related quality of life of thalassemia patients. Thus, the main objective of this study was to develop, according to psychometric standards, a self-administered Specific Thalassemia Quality of Life Instrument (STQOLI) for adult patients.

Methods: First, a qualitative phase was conducted to generate items and identify domains using the critical analysis incident technique and a literature review. A list of easily comprehensible, non-redundant items was defined using the Delphi technique and a pilot study on ten thalassemia patients. This phase involved both patients and experts. The second step was a quantitative validation phase comprising a study of 128 thalassemia patients in a single hospital. It was designed to select items, identify dimensions, and measure reliability and internal and concurrent validity. The psychometric and scaling properties of the proposed 41-item Specific Thalassemia Quality of Life Instrument were then assessed among patients recruited from the Thalassemia Unit at the General Hospital of Nikaia, Greece.

Results: The final questionnaire had 41 items comprising four main domains and one global item about general health. The factorial structure was satisfactory (loading > 0.40 on each factor of the four domains for all items). Interscale correlations ranged from 0.06 to 0.78, Cronbach's α-coefficients were 0.78 for the psychosocial domain, 0.77 for the chelation domain, 0.72 for the transfusion domain, 0.81 for the disease and symptoms domain, and 0.840 for the total score of the questionnaire.

Conclusion: The 41-item Specific Thalassemia Quality of Life Instrument seems to be a valid tool for assessing health-related quality of life for patients with thalassemia. More research is needed to explore the universal properties of the questionnaire.

Keywords: quality of life, thalassemia, measurement, chelation, transfusion, validation

Introduction

Thalassemia is an inherited blood disease. It is a serious public health problem throughout the Mediterranean region, Middle East, and Indian subcontinent, as well as in Southeast Asia.[1]

Advances in biomedical science and technology have resulted in dramatic improvements in the health care of this condition. With enhanced survival, health-related quality of life (HRQOL) issues have become more prominent.[2] β-thalassemia is the most common form of hemolytic anemia[3] and, each year, approximately 60,000 babies with thalassemia are born worldwide.[4] With the availability of better transfusion regimens, iron chelation therapy, proper management of complications, and good supportive care, it is now possible for patients with thalassemia to have a near normal life span with a good HRQOL.[3]

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The impact of thalassemia major (TM) and thalassemia intermedia (TI) and their associated complications on quality of life (QoL) are largely unknown. Due to the fact that patients with TM have good survival rates because of the development of new treatments and better clinical management,[5–9] we need to explore issues relating to QoL further.

Increased patient survival is accompanied by significant ongoing health care needs related to the chronic condition.[10] Simply surviving is not sufficient; the quality of survival has emerged as a fundamental focus of comprehensive health care.[11] Determining the degree of health impairment as perceived by the patient is essential information needed to recommend suitable therapy; therefore, HRQOL should now be considered an important index of effective health care in thalassemia. However, there is very little published work on the evaluation of QoL in patients with thalassemia.[12] A PubMed search between 1990 and 2012, using the terms thalassemia AND quality of life AND/OR health-related, identified only 20 articles concerning QoL in thalassemia patients.[13–32] One study used a semi-structured interview to access the psychosocial adjustment of adolescents and young adults,[13] another explored the social integration of older thalassemic patients,[14] and a third studied the impact of neocyte transfusion in the management of thalassemia.[15]

A pilot study on QoL, as reflected by the psychosocial adjustment of children with TM undergoing iron chelation treatment, used the PedsQL 4.0 Generic Core Scales.[16] The same measure was used in two additional articles in children[17,18] and the Dartmouth Primary Care Cooperative Information Chart System questionnaire was used in another study.[19]

There was a cross-sectional study on adult patients with transfusion- and iron chelation-independent TI and TM[20] and three studies in young adults using the Short Form 36 (SF-36).[21–23] SF-36 is the most utilized measurement, but it is not specific for thalassemia patients. Two out of the 20 studies used interviews to assess QoL in patients under different chelation treatments[24,25] and one was a review of the life of thalassemia patients.[26]

Among the remaining articles, two studies concerned parents,[27,28] two studies were brief reports,[29,30] one study was an international survey of patients with TM and their views about sustaining life-long desferrioxamine use,[31] and the last article described the burden of TM and its treatment in terms of prevalence of iron-overload-related complications, direct and indirect costs, and patient physical and social well-being with a survey.[32] Results from the literature review revealed that there were no specific QoL instruments.[35]

While a generic HRQOL instrument must be multidimensional, consisting, at a minimum, of the physical, psychological (including emotional and cognitive), and social health dimensions delineated by the World Health Organization,[33,34] disease-specific measures may enhance measurement sensitivity for health domains germane to a particular chronic condition.

The lack of research relating to QoL in this population may be due in part to the lack of tools available to accurately measure HRQOL in patients with thalassemia. There are currently no thalassemia-specific scales for measuring QoL, and it has long been established that generic questionnaires may be insensitive to the unique experience of a patient with thalassemia.[11] Similarly, it has been demonstrated that QoL may vary among different chelation treatments.[36] In light of these considerations, there is a clear need to develop and validate a disease-specific QoL inventory for patients with thalassemia. Without access to a valid tool for measuring and comparing levels of QoL in this population and for tracking patient acceptance of therapies, there is little hope for developing better treatment modalities that will allow better management of the disease. Thus, a project to develop and validate a measure of HRQOL for thalassemia was undertaken.

Our hypotheses were generated based on patient and expert interviews to develop a disease-specific instrument. The main objective of our study was to develop a Specific Thalassemia Quality of Life Instrument (STQOLI) in order to assess HRQOL in these patients, according to psychometric standards, which could be used to compare patient QoL over time and thus in a longitudinal comparison.[37] The questionnaire needed to be brief, understandable, and easy to complete for outpatients aged 18 years or older in Thalassemia Transfusion Units. It was designed to be self-administered. The final version, originally in Greek, is being adapted in English for the purposes of this paper.

The translation strategy was based on minimal criteria developed by the Scientific Advisory Committee of the Medical Outcomes Trust.[38] Translation was performed using the multiple forward and backward translation protocol recommended by Guillemin et al.[39] Following these, two independent bilingual health professionals translated the questionnaire into English (forward translation). The mother tongue of all translators was the Greek language and their level of English was advanced. A reconciliation meeting was conducted to obtain a consensus version. Then, one native Greek speaker who was blinded to the original version retranslated the re-conciliated English version into the source

language (back translation), which is the recommended procedure for creating semantic equivalence.[40] The back translation was revised by the authors, formulating the revised English version of the STQOLI. The results of the qualitative research that comprised the development phase of the STQOLI are presented here.

Methods

Questionnaire development

Phase I: drafting and pre-piloting of the questionnaire

The method we followed used the basic principles for survey design, suggested by de Vaus.[41] This required the definition of a conceptual basis of the questionnaire before designing the specific questions. To archive this, a qualitative phase was conducted to generate items and identify domains using critical incident technique (CIT) analysis[42] and a literature review.

In health care research, CIT analysis can be a good resource for identifying the experiences of a patient in the health care setting, exploring the dimensions of patient–provider interactions, and determining patient responses to illnesses and treatments.

The advantages of CIT analysis are that it is a flexible method that can be used to improve multi-user systems. Data are collected from the respondent's perspective and in his or her own words. It does not force respondents into any given framework. It identifies even rare events that might be missed by other methods that focus only on common and everyday events. CIT analysis is useful when problems occur, but the cause and severity of such problems are unknown. It is inexpensive and provides rich information. It emphasizes the features that will make a system particularly vulnerable, offers major benefits (eg, safety), and can be applied using questionnaires or interviews.

A health psychologist conducted eight individual semi-structured interviews with recent outpatients using CIT analysis.[42] Subjects were asked to detail specific factors, which according to them had an influence on their QoL. Each interview lasted 30 minutes on average. All the different wordings of a given idea were written on a form. Interviews were transcribed and items were generated from the verbatim statements (n = 40 items).

The incidents were identified from the transcriptions and categorized by the research team. With each case, new categories and subcategories were derived from the data. This process of developing categories grounded in the data follows the principles laid down by Flanagan.[42] This will form the basis of a classification of factors influencing QoL in patients with thalassemia.

Participants

Patients were recruited by the specialists who worked in the Transfusion Unit of the General Hospital of Nikaia. In order to complete the targeted sample, three patients were recruited from the list of appointments for laboratory tests, and five were recruited from the daily transfusion list. Participants had to be over 18 years old, have a definite diagnosis of transfusion-dependent thalassemia, and be able to understand and speak Greek fluently. They were asked to provide written consent for their participation in the study. Patients with psychotic or psychiatric diseases were excluded from the study. To ensure a broad spectrum of patients, the population was to include different patients with different marital status and different levels of education.

Critical incidents

The eight cases generated 16 incidents (mean: two per case, range: two to five). Ideally, collection of data should have continued until no new categories were generated,[43] but with our small number of cases, the coding was not complete. Nonetheless, the incidents formed natural clusters. The most common factors identified in incidents were "chelation therapy," "transfusion," "complications," and "I feel bad or good" (mean 7; standard deviation [SD] 1) Other factors included, among others, "lack of leisure time," "sleeping problems," "fear for blood units," "sexual problems," "pain from the chelation procedure," "the loss of friends," "fear of the knowledge of the disease in the working environment," and "many complications."

Literature review

The domains that were found to be affected based on the literature review were physical deformity, growth retardation, and delayed puberty due to TM;[11,29,35] physical appearance, eg, bone deformities and short stature, which contribute to a poor self-image;[11,35] severe complications, such as heart failure, cardiac arrhythmia, liver disease, endocrine complications, and infections;[4,31] physical, emotional, social, and school or work functioning;[11,19,23,29,44–46] impact of iron chelation therapy and regular blood transfusions that require frequent visits to the hospital;[47] and pain.[45]

The items were then coded in the four main dimensions that arose from CIT analysis: disease, chelation therapy, transfusion, and psychosocial dimension. The 16 incidents and the 17 factors from the literature review were discussed and were spread in semantic order to build the items to cover all the factors for the four domains. At this phase, a first version of the questionnaire was constructed (60-item version). The first version of the questionnaire to be piloted

included one to three questions about each topic, depending on how complex and relevant the topics seemed.

Phase II: a quantitative phase comprising 2 steps

During the first step, this version was pre-piloted with ten thalassemia patients to establish face validity, during which time they were asked to comment on omissions or irrelevant items. Comments on face validity were received from 13 experts (three hematologists [MD], four nurses, two psychiatrists, two psychologists, and two social workers) who were set up to provide expert input on all stages of development for the questionnaire and to work with a team of questionnaire specialists. Their input consisted of creating a conceptual model, making choices to optimize the questionnaire development process, validating the results at each critical step of development, and providing final decisions on subsequent procedures.

This first step provided a shortened version of the questionnaire (50-item version). This resulted in some rewording and additional questions – for example, "patient satisfaction with the medical and nursing staff." The pilot questionnaire had five attitudinal questions dealing with the following topics that were not answered by the patients: "satisfaction with the staff", "sexual maturity," and "food"; the experts committee decided that they overlapped with other existing items. In order for an item to be excluded from the questionnaire at this step, the majority (eight of 13) of the expert committee had to agree.

Respondents were asked to respond on a five-item Likert scale[46] (extremely influences my QoL, influences my QoL quite a bit, moderately influences my QoL, influences my QoL a little bit, and does not influence my QoL) to each statement. Several questions (12/44) were phrased negatively to prevent "response acquiescence," defined as the tendency to agree rather than disagree.[47]

All patients found the attributes in the questionnaire relevant, and they agreed that the most important characteristics were the four main dimensions that arose from CIT analysis. Participants thought the questionnaire was of proper length, comprehensive, informative, and consistent (data not shown). This added to the experts' opinion that the questionnaire should have four facets that could be measured independently for longitudinal use and a total score for QoL as a tool for research use.

Second, a replication validation phase to corroborate results from the previous steps in a large sample provided the final 41-item questionnaire (available upon request). This second step was a quantitative validation phase comprising a study in a single hospital (General Hospital of Nikaia Greece) of a group of 150 thalassemia patients. Of these patients, 128 (85.3% participation rate) returned their completed questionnaires to the researchers. It was designed to select items, identify dimensions, and measure reliability and internal and concurrent validity.

The sample size was calculated to be representative of the Greek thalassemia population, which is estimated to be 2900 patients, assuming a confidence level of 95% and an accuracy level that would only tolerate a difference of 0.08. The sample size was estimated at 114 patients, but assuming a 10% level of missing data, we aimed to recruit 128 patients.

The inclusion criteria for patients were as follows: (1) having a definite diagnosis of transfusion-dependent thalassemia, and (2) being able to understand the questions on the HRQOL questionnaires. Patients were excluded if they did not speak Greek fluently, had any severe psychiatric illness, and/or were taking part in clinical trials.

Randomization involved a random starting point on a list and then proceeded with the selection of every third element from then onwards. The starting point was not automatically the first on the list, but was instead randomly chosen from within the first to the third elements in the list of patients who had a transfusion appointment or an appointment for clinical tests.

To be consistent with most published relevant work on health measurement scales, we used parametric tests[48] where possible. Reported *P*-values for differences according to gender, age, education, location, and marital status were considered significant at $P < 0.05$. Analyses were performed using SPSS 16.0 (IBM Corporation, Armonk, NY).

Item selection

A first selection of items was made from the descriptive response distribution for each item. The criteria used to guide item selection/deletion were as follows: high rates of nonresponse and "not applicable" response (≥20%), except for items where high rates in this response category were expected, ceiling, and floor effects (≥50%), and unacceptable test–retest reliability (weighted κ-coefficient < 0.60).

Floor and ceiling effects determined whether a disproportionately large percentage of responders were prone to providing either the lowest or highest values. If an item had more than half the answers in the "extremely" or "not at all" categories, the expert committee had to decide the remaining item in the questionnaire.

Out of 50 patients randomly selected as a convenience subsample of the original sample to facilitate evaluation of external (test–retest) reliability for the total score of the measurement, eventually 48 participated (4% dropout). Cronbach's α for this subset at the initial test period was 0.83, and remained the same at the retest period five days after the first assessment (α = 0.83). Correlation between the test and retest mean score of these participants was likewise very high (r = 0.89; $P < 0.001$), suggesting that test–retest reliability was very good for the total score of the STQOLI.

Pragmatic considerations also tempered selection: interest of the item in itself, number of items covering the same domain, and redundancy. Results showed that the proportion of missing responses per item was low. This first selection led to the deduction of ten items.

Validation process

Analyses of the relationship between independent variables and HRQOL were performed to establish those variables associated with HRQOL. Exploratory factor analysis using principal axis factoring with an orthogonal (varimax) rotation was conducted on the sample for each domain independently for sampling reasons.

Procedure

All participants were recruited voluntarily from the Thalassemia Unit at the General Hospital of Nikaia, Greece. The Ethics Committee and the scientific board of the General District Hospital of Nikaia were informed of the purpose of the study and the confidentiality and anonymity of the process and approved the research protocol.

We used systematic sampling, which relies on arranging the target population according to some ordering scheme and then selecting elements at regular intervals through that ordered list. Using this procedure, each element in the population has a known and equal probability of selection. This makes systematic sampling functionally similar to simple random sampling. It is, however, much more efficient (if variance within the systematic sample is more than variance of the population). In our case, it involved a random start and then proceeded with the selection of every k_{th} element from then onwards. In this case, k = population size/sample size. The starting point was not automatically the first in the list, but was instead randomly chosen from within the first to the third element in the list of patients who had a transfusion appointment or an appointment for clinical tests.

After giving written informed consent, patients who took part in the procedure completed a questionnaire on demographic and clinical characteristics along with a battery of tests including STQOLI and the Short Form 12 Patient Questionnaire (SF-12),[49,50] the Greek version of the Depression Anxiety Stress Scale (DASS),[51] Greek Life Orientation Test – Revised (GrLot-R),[52] the Rosenberg Self-Esteem Scale (SES),[53] and the Satisfaction with Life Scale (SWLS).[54]

It was hypothesized that both the Mental Composite Score (MCS) and Physical Composite Score (PCS) would be moderately correlated with the STQOLI total and the four domain scores. Specifically, patients who reported a greater score in the disease and symptoms domain and better global health were also hypothesized to report a higher psychical score in the SF-12, while patients who reported a greater score in the psychosocial domain and better global health were also hypothesized to report a higher mental score in the SF-12. On the other hand, since optimism is a factor affecting QoL, it was hypothesized that GrLOT-R would correlate more highly with the psychosocial domain of the STQOLI and less with the disease and symptoms domain. SES was hypothesized to correlate with the items concerning the effect in body image. Depression, anxiety, and stress were hypothesized to correlate moderately but negatively with the STQOLI total and the four domains scores, since higher scores in the STQOLI factors means better QoL, while the higher a score is in DASS scales, the more symptoms a patient has. Finally it was hypothesized that the SWLS scale would be moderately correlated with the STQOLI total and the four domains scores.

Data analysis

The final questionnaire had 40 items comprising four main domains, plus one global item about the current state of health and general health.

The 40 items in the four domains were as follows:

1. Disease and symptoms, with 12 items;
2. Chelation therapy, with 13 items (five items per os chelation therapy users, five items for subcutaneous chelation therapy users, and three common items);
3. Psychosocial impact, with ten items;
4. Transfusion impact, with five items.

Current QoL was assessed by patient response in each domain. Both overall QoL and subscales were measured with a scale from 0 to 100, with higher values indicating better quality for each scale. Satisfaction with chelation therapy was assessed with two items that were excluded from the final STQOLI for reasons outlined in the Results section. The questionnaire also contained sociodemographic variables,

including age, sex, educational level, professional status, and marital status.

General characteristics of the patients are presented in terms of percentage, mean, and SD. For HRQOL, both total STQOLI score and summary scores were presented in terms of mean and SD. HRQOL scores based on self-reporting both for the new questionnaire and the rest of the scales are presented in Table 1.

The normality of the items of all measures was investigated and found to be within the level recommended for confirmatory and exploratory factor analysis with maximum-likelihood estimation (skewness\2, kurtosis\7)[55] and still within acceptable values for normality.[56]

The psychometric properties of the STQOLI were analyzed as follows: (a) principal component analysis with an orthogonal (Varimax) rotation was utilized to assess the internal structure of the measure; (b) internal consistency reliability of the instrument was assessed using Cronbach's α coefficient,[57] and corrected item-total correlations; and (c) convergent validity was assessed by examining the relationships using a Pearson's product-moment correlation between the STQOLI and SF-12, which was used for analysis with this group of patients to compare the physical and mental composite score with the four new domains of STQOLI. This was decided since the developers have consequently suggested that a 12-item sub-set of the original 36 items of the SF-36 can be used to construct a shorter health survey, which can produce PCS and MCS without substantial loss of information.[49,50]

The Greek versions of DASS, [51] the GrLOT-R,[52] SES,[53] and the SWLS[54] were also administered to test the convergent and discriminant validity.

The primary purpose of the exploratory factor analysis (EFA) is to arrive at a more parsimonious conceptual understanding of a set of measured variables by determining the number and nature of common factors needed to account for the pattern. Assuming that identifying latent variables that account for the correlations among measured variables is the goal of the research project, a researcher must then decide if an exploratory or confirmatory approach will be used. Both (EFA) and confirmatory factor analysis (CFA) are based on the common factor model, and both seek to represent the structure of correlations among measured variables using a relatively small set of latent variables.

However, EFA is primarily a data-driven approach. No a priori number of common factors is specified and few restrictions are placed on the patterns of relations between the common factors and the measured variables (ie, the factor loadings). EFA provides procedures for determining an appropriate number of factors and the pattern of factor loadings primarily from the data. In situations like ours, in which research was conducted for the first time, and in which a researcher has relatively little theoretical or empirical basis to make strong assumptions about how many common factors exist or what specific measured variables these common factors are likely to influence, EFA is probably a more sensible approach than CFA. EFA is likely to be more desirable in these situations because the number of plausible alternative models might be so large that it would be impractical to specify and test each one in CFA.

Additionally, when a strong basis does not exist for identifying a single model or a few specific competing models, it is quite possible that a researcher might fail to identify a number of plausible models. Therefore, in this context, the data-driven approach of EFA seems preferable.

To evaluate the principal component analysis, clusters of items were observed and interpreted. Criteria for retaining

Table 1 Descriptive summary scores for the quality of life (QoL) factors and the Depression Anxiety Stress Scale (DASS); anxiety, stress, and depression scales; Greek Life Orientation Test-Revised (GrLot-R); Satisfaction with Life Scale (SWLS); Rosenberg Self-Esteem Scale (SES); and age

	Min/max*	Min	Max	x	SD
Age		20	62	37.2	9.5
Disease and symptoms D	0–100	30	84.2	62.9	12.8
Psychosocial D	0–100	36	100	72.4	14.8
Transfusion D	0–100	24	96	68.4	17.4
Chelation therapy D	0–100	46	99.9	77.3	11.7
STQOLI total score	0–100	46	89.4	71.4	10.8
Chelation satisfaction	0–100	20	100	76.3	18.2
Limitation from disease and complications	0–100	31	100	72.6	16.7
Effect in daily activities	0–100	20	100	77.2	21.1
Mental health	0–100	20	100	73.3	20.5
Chronicity effect	0–100	5	100	77.9	18.9
Effect in sexual life	0–100	6.7	100	74.3	25.8
Effect in body image	0–100	6.7	100	67.3	22.8
Pain and fatigue	0–100	20	100	79.6	18.4
PCS12	0–100	23.5	63.4	46.4	10.7
MCS12	0–100	17.7	62.2	46.4	11.1
Optimism (GrLOT-R)	0–24	6	24	14.8	3.8
Depression (DASS)	0–42	00	34	6.8	8.5
Anxiety (DASS)	0–42	00	32	6.1	7.1
Stress (DASS)	0–42	00	41	10.8	8.6
Rosenberg self-esteem scale (SES)	10–40	14	37	27.8	3.2
Satisfaction with life scale (SWLS)	5–35	5	35	21.7	7.5

Notes: *The possible minimum and maximum for each measure. Valid n = 128.
Abbreviations: D, domain; Min, minimum; Max, maximum; x, mean; MCS, mental composite score; PCS, physical composite score; SD, standard deviation.

extracted component(s) included the following: (a) eigenvalue of one or greater;[58] (b) percentage of variance accounted for by the retained component(s); and (c) scree plot.[59] Item-component correlations of 0.4 and above were retained. Alpha-coefficients of 0.70 or higher and corrected item-total correlations higher than 0.40 were deemed to indicate good reliability.[60,61]

Other measurements

DASS-42[62,63] is a quantitative measure of distress on the basis of three subscales of depression, anxiety (eg, symptoms of psychological arousal), and stress (eg, cognitive, subjective symptoms of anxiety). We used the Greek validated tool of DASS-42.[51] Each subscale has 14 questions that respondents answered according to a Likert-type scale ranging between 0 ("does not apply to me at all") to 3 ("applies to me very much, or most of the time").

The LOT[64] was developed to assess individual differences in generalized optimism versus pessimism. This measure, and its successor the LOT-R, have been used in a good deal of research on the behavioral, affective, and health consequences of this personality variable. The revised scale was constructed in order to eliminate two items from the original scale, which dealt more with coping style than with positive expectations for future outcomes. The correlation between the revised scale and the original scale is 0.95. The GrLOT-R is a very brief measure that is easy to use. Its brevity makes it ideal for use in projects in which many measures are being used. It should be noted that this is a research instrument, not intended for clinical applications. There are no "cut-offs" for optimism or pessimism and it is used as a continuous dimension of variability.[52]

The Rosenberg SES is a ten-item self-report measure of global self-esteem. It consists of ten statements related to overall feelings of self-worth or self-acceptance. The items are answered on a four-point scale ranging from "strongly agree" to "strongly disagree." The SES has also been administered as an interview.[53]

The SWLS is a measure of life satisfaction developed by Diener et al.[54] Life satisfaction is one factor in the more general construct of subjective well-being. Theory and research from fields outside rehabilitation have suggested that subjective well-being has at least three components: positive affective appraisal, negative affective appraisal, and life satisfaction. Life satisfaction is distinguished from affective appraisal in that it is more cognitively than emotionally driven. Life satisfaction can be assessed specific to a particular domain of life (eg, work, family) or globally. The SWLS is a global measure of life satisfaction. The SWLS consists of five items that are completed by the individual whose life satisfaction is being measured.

Results

Descriptive statistics

Out of the 150 patients who could participate, 128 returned the battery to the researchers (85.3% participation rate). The sample consisted of 34 males (26.6%) and 94 females (73.4%). Their age ranged from 20 to 62 years, with a mean of 37.2. Twenty-five (19.5%) had one to three children (mean 1.3), and 38 of the 128 (29.9%) patients smoked three to 30 cigarettes per day (mean 14.5). Finally, 40 patients (32.8%) had had a splenectomy. The mean and SD of the STQOLI and the subscales of the four domains along with the other measurements and the new factors that were revealed from the factor analysis are shown in Table 1. The domains and subdomains of the STQOLI are not mutually exclusive. In other words, if a patient reported low in the disease and symptoms domain and in the psychosocial domain, the patient would be counted in both categories. That is the reason why we have a 0–100 score both for the four main domains of the questionnaire and the subdomains.

As can be seen in Table 1, PCS12 (mean = 46.4; SD = 10.7) and MCS12 (mean = 46.4; SD = 11.1) were both lower from the normative data of the healthy Greek population (50 ± 10 for both scores).[65]

Validation

Reliability analysis

Cronbach's α and "α if item deleted" were calculated. Since α depends on the length of the scale (the number of questions) and the correlation of the items on the scale (actual reliability), the Spearman-Brown formula, where k is the number of items of the subscale divided by the number of items of the overall scale,[66,67] was used to estimate expected subscale alphas:

$$\alpha_{subscale} = k_{\alpha scale}/(1 + (k - 1)\alpha_{scale}).$$

For reliability, the observed scale α should be >0.70 to be acceptable, >0.80 to be good, and >0.90 to be excellent, and observed subscale α values greater than expected.[68]

The average inter item correlations (coefficient α-values) for the total scale were 0.840 and from 0.711 to 0.781 for the rest of the subdomains. α-levels did not exceed Kline's criterion of 0.7 for internal consistency in any domain[68] and were all higher than the expected α (Table 2).

Table 2 Cronbach's α for the total score of Specific Thalassemia Quality of Life Instrument (STQOLI) and the four subscales

Domains of STQOLI	Cronbach's α	Expected Cronbach's α	Corrected item total correlations	Factors from EFA	Total variance explained**	Number of items
Disease and symptom[a]	0.813	0.692	0.141–0.604	3	57.312	12
Chelation therapy impact[a]	0.767	0.679	0.110–0.701	3	80.377	13
Transfusion impact[a]	0.723	0.324	0.308–0.553	2	69.048	5
Psychosocial impact[a]	0.782	0.612	0.277–0.644	3	65.516	10
Total score[a]	0.840		0.290–0.955			40
Chelation satisfaction	0.808		0.678	1	83.896	2
Chelation impact ICP*	0.972	0.324	0.903–0.949	1st		5
Limitation from disease and complications*	0.823	0.391	0.461–0.695	2nd		7
Chelation impact ICT	0.812	0.311	0.576–0.692	3rd		4
Effect in daily activities*	0.835	0.297	0.594–0.710	4th		3
Mental health*	0.829	0.297	0.654–0.711	5th		3
Chronic effect*	0.740	0.311	0.340–0.628	6th		4
Effect in sexual life*	0.727	0.297	0.524–0.569	7th		3
Pain and fatigue*	0.633	0.297	0.409–0.491	8th		3
Effect from transfusion*	0.632	0.297	0.385–0.509	9th		3
Effect in body image*	0.570	0.297	0.315–0.408	10th		3
Splenectomy and somnolence*	0.544	0.268	0.374	11th		2

Notes: [a]The four quality of life domains; EFA was run independently for each due to the fact that each domain had items measuring different surface attributes. *The eleven factors revealed from the EFA in the total scale (40 items). **The variance explained is for the factor analysis for each domain independently.
Abbreviations: EFA, exploratory factor analysis; ICP, ion chelation pump; ICT, iron chelation tablets.

The fact that Cronbach's α-coefficient for the total number of items was 0.84 indicates that the total scale has high internal consistency. We also observed that it was not necessary to delete any more of the items to improve the reliability score of the test since factor analysis had no items with complex structure that needed to be removed because they could not be categorized to a factor. Furthermore, based on the results from the first factor analysis, which indicated that each section included two to three factors accounting for more than 50% of variance, we found that even though none of the factors showed $\alpha < 0.70$, some items showed suboptimal item-total correlation (either <0.2 or >0.5). The two items that were removed from the questionnaire were q4 and q5, which referred to satisfaction from the chelation therapy. Since Cronbach's α was sufficiently improved when items were removed, the omission of items from the scale was justified. Another two items that had a low inter-item correlation were q38 ($r = 0.100$) and q36 ($r = 0.079$). However, Cronbach's α did not improve sufficiently when these items were removed and thus omission of these items from the scale was not justified. Finally, the experts' committee decided that both items were important for the questionnaire and were kept in the questionnaire. Items that were loading poorly on both factors were erased. This led to the second factor analysis of the 40 items, in which eleven factors led to satisfactory item-total correlation. The results of the internal consistency for the factors of each domain and the eleven factors of the second factor analysis of the 40 items along with item-total correlations are presented in Table 3.

Validity

Content validity

Content validity, ie, whether the instrument provides adequate coverage of the topic, was addressed by the interviews that were conducted both with patients and experts in the first phase of this research. However, EFA was used to analyze interrelations among the items of the questionnaire. Due to the large number of questions, the exploratory factor analysis was the best way to recognize and explain the dimensions of the four domains. Thus, principal component analysis with orthogonal Varimax rotation was conducted to assess the internal structure of the measure.

Before performing the factor analysis, we checked whether the assumptions regarding the normality of the distribution were satisfied. Skewness and kurtosis were used as indicators of the normality among single variables.[69,70]

In this analysis, skewness and kurtosis were used as indicators of normality among single variables; one item (q36) was transformed because it did not satisfy the assumptions of normality. After that, we applied parametric statistics, consistent with published relevant work.[56] To investigate the internal structure of the STQOLI (construct validity), five criteria were applied to determine how many factors should be retained for each subdomain: (a) the point of inflexion

Table 3 Exploratory factor analysis (EFA) with varimax rotation for the 40 items and the second EFA for the chelation satisfaction items

Factor interpretation	Item		EFA 1										
			Component										
			1	2	3	4	5	6	7	8	9	10	11
Chelation impact ICP	q51	The ICP troubles me (CID)	0.961										
	q6	I lose valuable time to prepare the ICP (CID)	0.955										
	q8	QoL is affected by the time required by the iron chelation therapy with ICP (CID)	0.945										
	q7	I cannot sleep well because of the ICP (CID)	0.926										
	q15	My social relationships are affected by the ICP (CID)	0.924										
Disease effect in mobility and social relations	q41	Disease complications affect QoL (DSD)		0.732									
	q40	I feel tired because of the disease (DSD)		0.731									
	q20	The disease limits my professional activities (work or school) (DSD)		0.616									
	q19	I cannot go out with my friends as much as I would like to because of the disease (PSD)		0.588									
	q30	I suffer from arthralgias (DSD)		0.544									
	q49	I feel hopeless and depressed (PSD)		0.521									
	q31	I have osteoporosis problems because of the disease (DSD)		0.503									
Chelation impact ICT	q12	The amount of tablets for iron chelation troubles me (CID)			0.811								
	q14	The way of administration of ICT affects my nutrition (CID)			0.772								
	q9	The per os chelation therapy causes me other side-effects (CID)			0.746								
	q16	The time schedule of the intake of ICT affects my social life (CID)			0.728								
Daily activity time	q46	The time that I miss for the transfusion affects my life (TID)				0.861							
	q47	The time that I miss for the tests affects the quality of my life (DSD)				0.775							
	q45	The distance between my home and the thalassemia center creates a problem in my daily life (TID)				0.703							
Psychological quality	q50	I am energetic (PSD)					0.875						
	q2	My emotional status restricts my everyday life (PSD)					0.788						
	q48	I feel calm and peaceful (PSD)					0.747						
Effect of chronicity	q35	I have arrhythmias because of the disease (DSD)						0.709					
	q23	Some features in my appearance have been changed, a fact that bothers me (PSD)						0.617					

(*Continued*)

Table 3 (*Continued*)

Factor interpretation	Item		EFA 1										
			Component										
			1	2	3	4	5	6	7	8	9	10	11
	q32	I have cardiological problems because of the disease (DSD)						0.608					
	q13	The disease affects my ability to eat or drink whatever I want (DSD)						0.498					
Effect in sexual life	q38	My sexual life is affected negatively because of the iron chelation therapy (CID)							0.757				
	q39	My sexual life is affected negatively because of the disease (DSD)							0.740				
	q37	I entered puberty late due to the disease, which affects me negatively (PSD)							0.684				
Pain and fatigue	q33	I feel fatigue when I have low hemoglobin (DSD)								0.752			
	q28	The intake of iron chelation drugs causes me painful abdominal discomforts (CID)								0.648			
	q29	Iron chelation procedure is painful to me (CID)								0.513			
Transfusion impact	q44	I experience reactions from the blood transfusion, which affects the general state of my health (TID)									0.306		
	q43	The lack of blood units for my transfusion regime affects my emotional status negatively (TID)									0.872		
	q42	The origin of the blood (if it is substantially checked) that I will receive causes me anxiety and fear (TID)									0.532		
Body image	q24	I prefer that others not know about my disease (PSD)										0.728	
	q17	I am treated differently (negatively) in my workplace when they are aware about my disease (PSD)										0.582	
	q25	The body imprints (eg, black spots in the belly from the iron chelation machine or the color on the skin) makes me feel uncomfortable (PSD)										0.416	
	q36	Splenectomy that affects me (DSD)											0.787
	q34	I feel somnolence because of the iron chelation (CID)											−0.529
		Eigenvalue (cumulative %)	4.910	3.518	3.105	3.043	2.715	2.340	2.332	2.285	1.804	1.712	1.510
			12.276	21.070	28.832	36.440	43.227	49.078	54.909	60.623	65.132	69.412	73.188

Factor interpretation	Item	EFA 2	Component
			1
Satisfaction with chelation therapy	q4	I respond to the iron chelation therapy	0.929
	q5	The current iron chelation therapy is effective	0.929
		Eigenvalue (cumulative %)	1.727
			86.359

Notes: Extraction method, principal component analysis. Rotation method: varimax with Kaiser normalization. (a) Rotation converged in 24 iterations. (b) 1 component extracted.

Abbreviations: CID, chelation impact domain; ICP, iron chelation pump; ICT, iron chelation tablets; DSD, disease and symptoms domain; PSD, psychosocial domain; QoL, quality of life; TID, transfusion impact domain.

displayed by the scree plot; (b) the "eigenvalues >1.0" criterion; (c) The "proportion of variance accounted for an approximate additional 5% of the variance" criterion; (d) the interpretability criteria, which is that a given component should contain at least three variables with significant (>0.40) loadings; variables loading on the same component should share the same conceptual meaning; and variables loading on different components should appear to measure different constructs; and (e) for the best solution in terms of interpretability and theoretical sensibility, solutions with up to two factors more and two factors less were also investigated.

Questions whose deletion increased the overall α and those that loaded < 0.40 or loaded to two factors or were unexpectedly grouped in a factor were thoroughly examined.

Factor analysis for each domain independently

In the disease and symptoms domain, analysis identified three factors accounting for 57.14% of the variance. The first factor consisted of items q40, q41, q30, and q31, which included the limitations from the disease. The second factor consisted of items q32, q35, q33, q20, and q13, which referred to problems from the disease complications, while the third consisted of items q36 and q39. In the chelation impact domain, analysis identified three factors accounting for 80.38% of the variance. The first factor was loaded with items q51, q6, q8, q7, and q15, which referred to chelation therapy with a pump, the second with items q14, q9, q16, q12, and q28, which referred to oral chelation therapy and the third with q38, q29, and q34, which included the common questions for both therapies. In the psychosocial impact domain, analysis identified three factors accounting for 58.92% of the variance where the first factor was loaded with items q2, q50, q49, and q48, which referred to mental health, the second with q23, q37, q19, and q25, which referred to psychological impact due to the disease, and the third with items q17 and q24, which referred to the social effect due to the disease. Finally, the transfusion impact domain analysis identified two factors accounting for 69.52% of the variance where q41 and q40 were loaded in the first factor, explaining the psychological effect from the transfusion, and q43, q42, and q44 in the second factor, explaining the impact of transfusion in QoL.

Factor analysis for the 40 items

Factors loadings after rotation are reported in Table 3. The analysis identified eleven factors accounting for 73.2% of the variance. The first factor was composed of all the items in the chelation therapy with a pump factor of the first EFA (q51, q6, q8, q7, and q15). The second factor was composed of four items from the disease limitations factor (q40, q41, q30, q31, and q20) and two items from the psychosocial domain referring to limitation in daily activities (q19) and feeling depressed (q49). The third factor was composed of four items of the oral chelation therapy domain (q12, q14, q9, and q16), while the fourth factor had the items from the transfusion factor (q46 and q45) and an item from the disease domain (q47), all referring to problems caused by time limitation. The fifth factor was composed of all the items in the mental health factor (q2, q50, and q48). The sixth factor consisted of all the items referring to the chronic problems caused by the disease (q35, q23, q32, and q13). The seventh factor contained three items (q38, q39, and q37) referring to sexual life. The eighth factor contained three items referring to pain and fatigue (q33, q28, and q29), while the ninth factor consisted of three items from the transfusion impact domain referring to the effect of blood transfusions. The tenth factor had two social items from the psychosocial impact domain (q24, q17) and an item referring to body image, which affects social relationships with others due to body imprints. Finally, the eleventh factor had only two items: one referring to the chronic problem of splenectomy (q36), and an item about sleep (q34).

Construct validity

Scale and subscale intercorrelations

The total STQOLI and SF-12 total scores (PCS12 and MCS12) correlated strongly and positively (r = 0.551 and 0.354; $P < 0.001$) (Table 4), suggesting a substantial association between HRQOL in thalassemia (STQOLI) and generalized mental and physical HRQOL as it is measured with SF-12, although the coefficient indicates that the measures do not overlap completely.

Interscale correlations ranged from 0.141 to 0.701 for all domains (Table 2). The four domain scores correlated significantly and moderately with each other (r = 0.301–0.645; $P < 0.001$) (Table 4). All domain scores were strongly related to the STQOLI total score ($r_{CID} = 0.655$, $r_{DSP} = 0.870$, $r_{PSD} = 0.761$, and $r_{TID} = 0.781$; $P < 0.001$, respectively), a result that agrees with Kline,[68] according to whom "maximum validity … is obtained where test items do not all correlate with each other, but where each correlates positively with the criterion. Such a test would have only low internal-consistency reliability."

All the other factors were correlated significantly and moderately with each other and the main domains

Table 4 Pearson product-moment correlations for Specific Thalassemia Quality of Life Instrument (STQOLI) and the other measurements

	CID	DSD	PSD	TID	STQOLI total score	Limitation	Effect in everyday activities	Mental health	Effect of chronicity	Effect in sexual life
CID	1									
DSD	**0.476****	1								
PSD	**0.429****	**0.645****	1							
TID	**0.301****	**0.551****	**0.409****	1						
STQOLI total score	**0.655****	**0.870****	**0.761****	**0.781****	1					
Limitation[1]	**0.331****	**0.846****	**0.606****	**0.529****	**0.726****	1				
Everyday activities	**0.329****	**0.585****	**0.483****	**0.757****	**0.692****	**0.502****	1			
Mental health	**0.261****	**0.387****	**0.764****	**0.236***	**0.507****	**0.398****	**0.215***	1		
Effect of chronicity	**0.514****	**0.777****	**0.610****	**0.372****	**0.687****	**0.542****	**0.377****	**0.380****	1	
Effect in sexual life	**0.350****	**0.562****	**0.501****	**0.158**	**0.499****	**0.315****	**0.213***	**0.266****	**0.413****	1
Effect in body image	**0.319****	**0.381****	**0.778****	**0.331****	**0.554****	**0.363****	**0.503****	**0.340****	**0.345****	**0.196***
Pain and fatigue	**0.682****	**0.596****	**0.458****	**0.497****	**0.743****	**0.451****	**0.443****	**0.261****	**0.516****	**0.269****
Chelation satisfaction	**0.375****	**0.236***	**0.418****	0.062	0.188	**0.225***	0.140	**0.273****	**0.220***	**0.176**
PCS12	0.158	**0.670****	**0.416****	**0.519****	**0.551****	**0.691****	**0.514****	**0.257****	**0.348****	**0.191***
MCS12	0.116	**0.208***	**0.626****	0.184	**0.354****	**0.354****	0.043	**0.840****	**0.286****	0.100
Optimism	**0.312****	**0.378****	**0.524****	0.145	**0.354****	**0.373****	**0.203***	**0.382****	**0.277****	**0.265****
Depression	**–0.395****	**–0.360****	**–0.680****	**–0.261****	**–0.455****	**–0.328****	**–0.255****	**–0.789****	**–0.336****	**–0.274****
Anxiety	**–0.295****	**–0.247***	**–0.631****	**–0.293****	**–0.404****	**–0.311****	–0.179	**–0.662****	**–0.284****	**–0.280****
Stress	**–0.214***	**–0.248****	**–0.664****	**–0.295****	**–0.437****	**–0.293****	**–0.237***	**–0.732****	**–0.254****	**–0.238***
Self esteem	0.065	0.051	0.107	0.039	0.068	0.006	0.103	**0.195***	–0.064	–0.069
Life satisfuction	**0.228***	**0.436****	**0.639****	0.174	**0.458****	**0.419****	**0.242****	**0.599****	**0.355****	**0.262****
Age	–0.162	**–0.390****	**–0.217***	**–0.365****	**–0.270***	**–0.477****	**–0.331****	**–0.237***	**–0.389****	–0.122

Notes: [1]From disease and complications; *correlation is significant at the 0.05 level (2-tailed); **correlation is significant at the 0.01 level (2-tailed). Significant correlations are in bold. Light grey zone: interscale correlations for the subdomains of STQOLI. Dark grey zone: interscale correlations for the factor revealed from EFA the 40 items of the STQOLI.

Abbreviations: CID, Chelation impact domain; DSD, Disease and symptoms domain; MCS, Mental composite score; PCS, Physical composite score; PSD, Psychosocial domain QoL, Quality of life; TID, Transfusion impact domain.

(r = 0.213 to 0.777; $P < 0.05$) with the exception of the transfusion impact domain that had no significant correlation with the effect in the sexual life factor (r = 0.158; nonsignificant).

Convergent and discriminant validity

In order to examine the convergent validity of the total score of STQOLI and each domain independently, we also administered DASS, GrLOT-R, SES, and SWLS. Correlations between theoretically similar measures should be "high," while correlations between theoretically dissimilar measures should be "low."

To establish discriminant validity, you need to show that measures that should not be related are in reality not related.[70]

The strong and statistically significant correlation between MCS and the psychosocial impact domain (r = 0.626; $P < 0.001$) and PCS with the disease and symptoms domain (r = 0.670; $P < 0.001$) (Table 4) show that the new measurement has a good convergent validity in the first two domains.

In favor of the questionnaire's good convergent validity was also the one-way between groups analysis of variance (ANOVA), which was conducted to explore the relationship between the four domains of the new questionnaire and the five categories of general health as it was described by the patients (exceptional, very good, good, fair, and bad), since we found a statistically significant difference in almost all the categories of general health compared to the quality domains of STQOLI. ANOVA revealed overall significant differences between the four groups on general health, with $P < 0.001$ for the disease and symptoms domain, the transfusion domain, the psychosocial impact domain, and for the total STQOLI, and $P < 0.05$ for the chelation impact domain (Table 5).

Post hoc analyses with the Dunnett-t test after Bonferroni correction revealed that patients with fair health experienced significantly lower quality in the disease and symptoms domain than patients with good (mean difference = –12.11; $P < 0.05$), very good (mean difference = –26.08; $P < 0.001$), and exceptional health (mean difference = –28.56; $P < 0.001$). They also experienced significantly lower quality in the

Table 4 (*Continued*)

Effect on body image	Pain and fatigue	Chelation satisfaction	PCS 12	MCS 12	Optimism	Depression	Anxiety	Stress	Self esteem	Life satisfaction	Age
1											
0.380**	1										
0.264**	0.187	1									
0.212*	**0.321****	**0.410****	1								
0.201*	0.118	**0.206***	0.044	1							
0.424**	**0.320****	**0.259****	**0.344****	**0.322****	1						
–0.431**	**–0.365****	**–0.305****	**–0.302****	**–0.702****	–0.338**	1					
–0.420**	**–0.312****	**–0.426****	**–0.353****	**–0.603****	**–0.276****	**0.769****	1				
–0.422**	**–0.284****	**–0.315****	**–0.298****	**–0.662****	**–0.309****	**0.753****	**0.809****	1			
0.204*	0.195	0.057	0.030	0.082	**0.214***	**–0.366****	–0.034	–0.141	1		
0.383**	**0.375****	**0.299****	**0.406****	**0.463****	**0.578****	**–0.507****	**–0.390****	**–0.468****	**0.268****	1	
–0.112	–0.143	0.011	–0.139	**–0.289****	–0.042	**0.296****	**0.233***	0.073	0.028	–0.068	1

transfusion domain than patients with very good ($P < 0.05$) and exceptional health ($P < 0.05$). Similar findings were obtained for the psychosocial domain where patients with fair health experienced significantly lower quality than patients with very good ($P < 0.05$) and exceptional ($P < 0.001$) health. Finally, in the total STQOLI, patients with fair health had significantly lower scores than patients with very good (mean difference = –15.82; $P < 0.05$) and exceptional (mean difference = –19.21; $P < 0.05$) health. The Bonferroni correction revealed a significant difference in the mean scores between patients with moderate health and patients with very good ($P < 0.05$) and exceptional health ($P < 0.05$).

Depression, anxiety, and stress had a significant and strong negative correlation with the psychosocial domain

Table 5 One-way ANOVA between general health and the domains of Specific Thalassemia Quality of Life Instrument (STQOLI)

General health	Disease and symptoms mean (SD)	Transfusion impact mean (SD)	Psychosocial impact mean (SD)	Chelation impact mean (SD)	Total STQOLI mean (SD)
Bad	*	*	*	*	*
Fair	40.6 (12.3)	51.2 (11.8)	58 (15.6)	68.8 (7.3)	57.4 (13.3)
Good	52.7 (10.4)	61.5 (15.1)	59.9 (11.2)	71.2 (11.8)	62.8 (6.2)
Very good	66.6 (9.1)	69.1 (17.9)	76.6 (11.3)	79.2 (10.3)	73.2 (9.3)
Exceptional	69.1 (12.5)	77.3 (14.5)	79.8 (15.8)	81 (12.5)	76.6 (11.6)
Total	36.9 (12.7)	68.4 (17.4)	72.3 (14.8)	77.3 (11.7)	71.4 (10.8)
P-value	**0.001**	**0.001**	**0.000**	**0.05**	**0.001**
F	22.17	5.79	17.59	4.61	10.23

Notes: Statistically significant differences $P < 0.001$, $P < 0.01$, and $P < 0.05$ according to one-way analysis of variance are in bold; *no patient chose the "Bad" general health option, hence it was omitted from the analysis.
Abbreviations: ANOVA, analysis of variance; SD, standard deviation.

($r_{depression} = -0.680$, $r_{anxiety} = -0.631$, and $r_{stress} = -0.664$; $P = 0.001$) as expected, and moderate correlation with the other subdomains of the STQOLI (Table 4). Life satisfaction was correlated significantly with all subdomains, something that was expected since QoL is a relevant construct with life satisfaction.

Self-esteem, which is a characteristic of personality, had no correlation with the STQOLI domains, but a small correlation with the effect in body image factor (r = 0.205; $P < 0.05$), something that was in favor of discriminant validity for the new questionnaire, since QoL is a completely different construct than self-esteem.

Optimism, on the other hand, was significantly and strongly correlated with the psychosocial factor (r = 0.524; $P = 0.001$), something that was expected since dispositional optimism has been found to be a significant predictor of mental health,[71] while it had a weak correlation with the rest of the domains.

Sex, education, and location comparisons

Bivariate analyses (*t*-test, ANOVA, and Pearson's and Spearman's correlation coefficients as appropriate) were then performed to evaluate the relationships between independent variables and HRQOL, as it was measured with the four domains of the new measurement. The *t*-test for independent samples was employed to compare means. The equality of variances required for the *t*-test was established by Levene's test. Where the variances differed, the test statistic *t* and the error probability *P* were assessed based on the corrected degrees of freedom. The level of significance was set at $P = 0.05$.

Males reported statistically significantly lower QoL in the disease and symptoms domain ($t = -2.588$; $P < 0.05$) and in the psychosocial domain ($P < 0.05$) compared to women (Table 6). Patients that had had a splenectomy reported statistically significantly lower QoL in the disease and symptoms domain ($t = -3.226$; $P < 0.05$) than patients without a splenectomy (Table 6). Results showed no significant differences ($P > 0.05$) in terms of place of residence, marital status, and education in the four subdomains of the questionnaire (Table 6).

Significant overall differences were observed in the chelation therapy domain ($P < 0.05$) between the three categories of chelation therapy, which is in agreement with the literature.[72] Post hoc analyses with the Dunnett-t test after Bonferroni correction revealed that patients under subcutaneous chelation therapy experienced significantly lower quality in the chelation impact domain than patients under oral (mean difference = −16.11; $P < 0.05$) and combination therapy (mean difference = −16.57; $P < 0.05$) (Figure 1).

Finally, ANOVA was used to identify significant differences in quality of life between the three different age categories of the sample. Analysis showed significant overall differences in the disease and symptoms domain F ([2118] = 13.219, $P < 0.001$) between the three age groups (18–35, 36–50, and 50-plus) as in the transfusion domain F ([2118] = 7.455, $P < 0.05$). Post hoc analyses with the Dunnett's *t*-test after Bonferroni correction revealed that patients >50 years of age experienced significantly lower QoL, both in the disease and symptoms domain ($P < 0.001$), as well as in the transfusion domain ($P < 0.05$) (Table 6).

Interpretation of the measurement

The scores for each domain were calculated by adding the answers to all the items in each domain. A linear transformation was then carried out, so that the scoring scale for each domain was standardized between 0 and 100, with a score of 100 indicating the highest level of QoL. The present QoL was assessed by patient response in each domain. The sum of every domain was transformed in a 0–100 scale in order to be easily compared with global measurements and especially with SF-12, where scores were calculated using norm-based scoring (mean 50; SD 10)[73] and reported for physical and mental dimensions on a 0–100 scale, from worst to best QoL (SF-36 and SF-12).[47,64]

We assumed that 10% of the total score for each subscale means that QoL is affected, and a score < 50 means that QoL is severely affected in each domain, since we set 100 to be the score for perfect QoL, for both the total score of the questionnaire and the four subscales, as is measured in most of the QoL measures. Overall QoL, as it was valued with the total score of the STQOLI measurement, was affected (<90%) in 97.9% of patients and severely affected (<50%) in only 3.2% of patients.

QoL assessed in each domain showed the following results: In the disease and symptom domain, 81% had QoL < 90% (the total score was <90) and 6.4 had <50. In the chelation therapy domain, 94.7% had a score < 90 and 28.1% had a score < 50, while in the psychosocial domain, the respective percentages were 85.9% and 8.1% and were 98.6% and 27.4% in the transfusion domain.

Discussion

QoL is strongly related to an individual's perception of his or her life situation. Therefore, different people will have different perceptions of the effect of thalassemia in their lives. When assessing HRQOL, one should consider

Table 6 One-way ANOVA and *t*-test for the categorical variables of the sample

	N	Disease and symptoms domain Mean (SD)	Transfusion Impact domain Mean (SD)	Psychosocial impact domain Mean (SD)	Chelation impact domain Mean (SD)	Total STQOLI Mean (SD)
Sex						
Males	34	58.1 (11.2)	70.6 (16.3)	67.7 (13.8)	76.2 (11.4)	69.2 (9.9)
Females	94	64.8 (12.9)	67.5 (17.9)	71.1 (17.8)	65.8 ± 17.5	72.4 (11.1)
P-value		0.011	NS	0.38	NS	NS
Education						
Elementary	16	68.3 (11)	54.3 (20.3)	71.0 (10.9)	64.4 (17.4)	65.1 (8.8)
High school/senior high school	45	74.8 (10)	62.6 (15.7)	73.5 (13.1)	64.1 (16.1)	69.4 (8.9)
Pre-graduate	58	77.6 (15.2)	64.3 (17.1)	74.0 (16.1)	62.6 (19)	70.8 (12.4)
Postgraduate	7	82.6 (15.8)	68.6 (10.9)	83.1 (12.3)	68.6 (17.5)	74.9 (11.1)
Total	126	75.7 (13.4)	62.6 (17)	73.9 (14.4)	63.6 (17.5)	69.9 (10.9)
P-value		NS	NS	NS	NS	NS
Place of residence						
Inside Athens	102	75.4 (13.5)	61.6 (16.8)	72.7 (14.5)	63 (17.4)	68.9 (10.7)
Outside Athens	22	75.8 (13.1)	64.4 (20.1)	78.9 (13.6)	70.2 (18.6)	74.9 (11.6)
P-value		NS	NS	NS	NS	NS
Marital status						
Single	71	75.8 (14.1)	63.4 (16.8)	74.4 (14.1)	61.5 (16.4)	69.6 (10.9)
Married	48	75.6 (12.7)	60.5 (18)	74.6 (13.9)	66.5 (19.8)	69.9 (11.8)
Divorced	9	74.9 (12.2)	60 (18.3)	65.0 (17.2)	68.7 (11.7)	69.8 (3.9)
Total	128	75.7 (13.3)	62.1 (17.2)	73.8 (14.4)	64.0 (17.6)	69.7 (10.9)
P-value		NS	NS	NS	NS	NS
Chelation treatment						
Subcutaneous	7	65.3 (9.3)	77.7 (12.8)	72.3 (9.9)	61.4 (20.4)	65.6 (13.7)
Per os	59	64.3 (12.7)	70.3 (17.9)	72.3 (15.8)	77.5 (8.2)	72.4 (10.9)
Combination	60	61.2 (13.2)	65.3 (16.9)	73.3 (14.2)	77.9 (13.4)	70.8 (10.6)
Total	126	62.9 (12.8)	68.4 (17.4)	72.8 (14.6)	77.3 (11.7)	71.4 (10.8)
P-value		NS	NS	NS	0.17	NS
Yes	39	57.8 (12.5)	64.9 (17.4)	71.1 (16)	77.9 (12.8)	68.4 (12.1)
Splenectomy						
No	80	65.5 (12.2)	69.8 (17.4)	73.5 (14.2)	76.9 (11.2)	72.7 (10)
P-value		0.002	NS	NS	NS	NS
Age						
18–35	35	68.1 (9.8)	72.2 (16.9)	72.9 (12.8)	77.5 (13.1)	72.4 (9.9)
36–50	70	62.3 (13.3)	67.1 (16.3)	72.8 (16.8)	76.3 (11.9)	71.1 (11.5)
50+	23	50.2 (12.1)	53 (20)	65 (6.3)	80.6 (8.7)	65.6 (10.5)
Total	128	63.1 (12.9)	67.3 (17.2)	72.1 (15.1)	76.9 (12.1)	71.2 (11)
P-value		0.001	0.015	NS	NS	NS

Notes: Student's *t*-test or analysis of variance with the Dunnett method after Bonferroni correction for multiple comparisons was performed.
Abbreviations: ANOVA, analysis of variance; NS, not significant for *P*-values > 0.05; SD, standard deviation; STQOLI, Specific Thalassemia Quality of Life Instrument.

the patient's views of his or her own health and well-being in the areas of physical, psychological, and social functioning.[74]

An assessment of an individual's HRQOL incorporates his or her appraisal of both the effects of his or her clinical diagnosis, as well as treatment side effects, and can provide important information for optimizing medical treatment, such as chelation therapy.[75–78] Therefore, accurate HRQOL assessment can assist in making patients' priorities explicit to both patients and their health professionals, and can signify an important factor in guiding care decisions.

Current measures evaluate patients' HRQOL across a number of domains; however, they do not explicitly evaluate patients' priorities or preferences, and thus may be unable to precisely identify priorities in care. Further, patients' HRQOL domain preferences may change over time, depending on treatment progression, as can happen in chelation therapy with per os treatment, and life situations, and can differ as a function of demographic and disease characteristics. The ability to more precisely and efficiently assess patients' HRQOL in a clinical setting is therefore vital in providing broad and individualized medical care, and thus

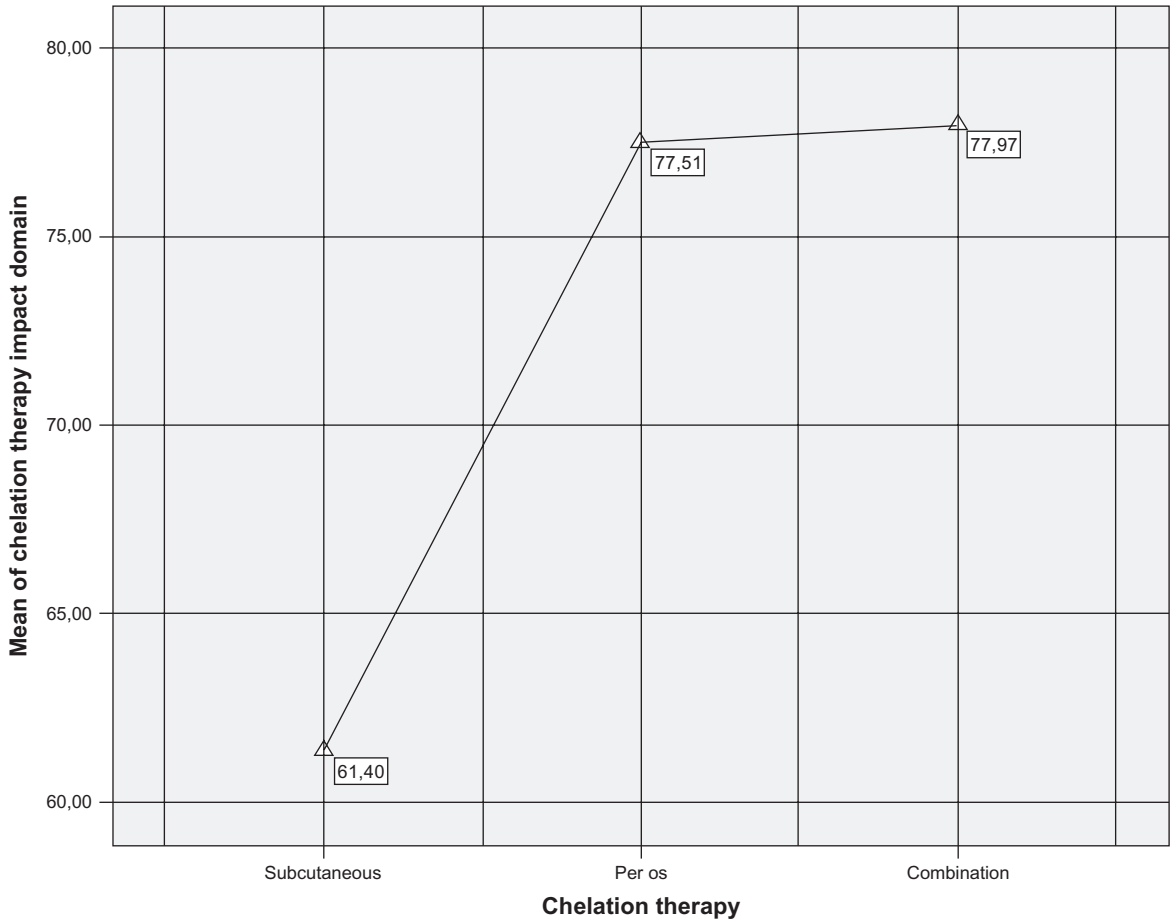

Figure 1 Differences in the chelation impact domain between the three chelation therapies from ANOVA.
Abbreviation: ANOVA, analysis of variance.

emphasizes the importance of assessing the accuracy and validity of current measures.

Numerous measures have been developed to assess patients' HRQOL,[65,75,79,80] but most of them are generic and are not designed for the needs of thalassemia patients. Since there is no specific instrument for measuring QoL in thalassemia, this study's goal was to develop and validate the new STQOLI questionnaire by attempting to assess domain preferences as they relate to the current situation of the patient.

This study supports the reliability and validity of the Greek version of the STQOLI. The validation was based on data provided by 128 patients, using exploratory factor analysis. The results show that construct validity, internal consistency, and concurrent validity of the Greek version of the STQOLI, and their corresponding subscales were generally supported by our population. Thus, the 41-item STQOLI seems to be a valid tool in assessing HRQOL for patients with thalassemia.

The sample size of this study was 128 patients, which is a good number for the factor analysis procedure and the 41-item questionnaire. It is estimated that there are 2900 thalassemia patients in Greece. A general rule of thumb is that one should have at least 50 observations and at least five times as many observations as variables;[81] thus, if we had wanted to apply factor analysis on the whole questionnaire, we would have needed a sample size of 205 patients.

However, as Tucker and MacCallum suggest, research in psychology often includes a number of steps which, though they may not be explicitly stated, can be recognized clearly and which represent integral parts of the research process.[82] The first step is the identification of the domain and population of interest. Given a domain and population of interest, the researcher selects the domain variables that are to be measured. These variables are the surface attributes that may be observed and measured. For example, in our research, in the psychosocial impact domain, we wanted to construct a test to measure distinct kinds of attributes, such as mental health, self-image, and subjective feelings about the disease. In the transfusion domain, we wanted to measure both the impact of transfusion on QoL and the way a patient feels that transfusion is affecting his or her life. Each

of these tests represents a surface attribute. Clearly, in any given domain, it would be possible to identify and measure a vast array of surface attributes. A set of surface attributes measured in a given study will be referred to as a battery of surface attributes.

According to the same authors, factor analysis involves a set of techniques designed to identify order and structure in such data by providing a parsimonious and meaningful explanation for the observed variation and covariation in surface attributes.[82]

Assuming that each surface attribute has internal attributes, meaning the unobservable characteristics of people that differ in extent or to a degree and are more fundamental than surface attributes, we took the decision to first explore each surface attribute with a separate factor analysis to determine the latent variables of each domain. The decision was made since the four domains are not subdomains but are different surface attributes that affect QoL and can be used independently as a single measure or as a part of a battery. A second EFA was then applied in the total questionnaire following the rule of thumb of Stevens[81] based on sample size and keeping loadings higher than 0.448 for the 128 patients.

Item deletion (which is one reason to apply factor analysis) was already decided upon after a first CFA and the evaluation of "Cronbach's-α if item deleted" in the 60 and 50 items, respectively, with the consent of the experts committee.

Nevertheless, both factor analyses in the whole sample and for each attribute independently had the same factor loadings for the chelation therapy, transfusion impact, and disease and symptoms domain. There was a slight difference in the psychosocial factor since the questionnaire as a whole has different questions concerning the psychological effect in transfusion, chelation therapy, social life, and body image. Only item 36, regarding splenectomy, could have been excluded from the questionnaire since it loaded differently in the two EFAs, but according to the experts committee, it was an important item, so it remained in the questionnaire.

In terms of content and face validity, both are optimized by a wide range of individuals involved.[67] The wide number of people involved in the experts committee optimizes content, and the wide number of people involved in content's transformation into a questionnaire and in pilots demonstrates that this content has been successfully transferred in the questionnaire. The fact that all five alternative response options in almost all questions were used supports this conclusion.[83] Three questions with zero or only one answer in the first and last option, as well as all questions with the majority of the answers in the moderate area, were thoroughly examined and the three items referring to interferon and satisfaction with the medical and nursing staff were excluded from the questionnaire.

High reliability is usually a prerequisite for sensitivity,[67] and this condition was met for the total score of the new instrument and the factors with more items. Only three factors out of the eleven that were revealed from the second factor analysis had unacceptable reliability, >0.7, but the items of those factors are inside the main four factors with acceptable reliability and nevertheless were higher than expected (Table 2). Furthermore, the score differences found among splenectomized patients and patients who had not had a splenectomy[84] and between patients with different treatments[72] are a good sign of the instrument's ability to detect existing differences among groups (sensitivity). It is reasonable to accept that these differences really exist as reported in the literature.[72,85]

The fact that female patients perceive their psychosocial and disease domains higher than the male patients may reflect reality rather than bias or simply chance since it has been repeatedly reported that female patients with TM survive longer than males and that the difference is due to the lower rate of cardiac disease in females.[5,85,86] In addition, females tolerate iron toxicity better, possibly as an effect of reduced sensitivity to chronic oxidative stress.[87]

The results that were found both from the ANOVA and the Pearson correlation relating to age differences are also in favor of the discriminant validity of the new measurement since it is common knowledge that the older a patient is, the more complications he or she has from the disease. We can also assume that if a patient is having regular transfusions, he or she eventually gets tired from the continuing procedure since it is known that patients feel more distress from their treatments than from their illness itself.[88]

In terms of interpretation, QoL for each patient was given as a summary score between 0% (worst QoL) and 100% (best possible QoL) and four sub scores for each individual domain in the same order. This concept can be very useful for the serial assessment of QoL among patients with TM and interventions can be designed in various domains that improve QoL in thalassemia patients.

It is known through research that as the clinical burden increases, so does the psychological burden.[54] The results of the present study are consistent with the literature since we found negative significant correlations between STQOLI and depression, anxiety, stress, and age, meaning that the better QoL a patient has, the less anxious, depressed, and stressed

he or she is, and the younger a patient is, the better his or her QoL. Further research is warranted to continue the qualitative and quantitative study of QoL using validated instruments in patients with thalassemia in order to advance our understanding of the issues and to improve patient QoL.

Given that minimal literature was available, we relied on patient and clinician interviews. It is a positive aspect that the clinicians interviewed had experience primarily with iron overload in thalassemia and sickle cell disease.

As previously mentioned, CIT analysis was used to identify important factors in QoL. We have discussed the advantages of this technique, but we must also refer to its disadvantages. A first problem comes from the type of reported incidents. CIT analysis relies on events being remembered by users and also requires the accurate and truthful reporting of these events. Since critical incidents often rely on memory, incidents may be imprecise or may even go unreported. The method also has a built-in bias toward incidents that happened recently, since these are easier to recall. Finally, respondents may not be accustomed or willing to take the time to tell (or write) a complete story when describing a critical incident.

In order to avoid these disadvantages, we also used semi-structured interviews and asked the patients to respond to each factor that we found in the literature review.

This study has several limitations, including a small sample size and a homogeneous patient population (ie, Caucasian patients with TM). Our conclusions can only be applied to patients with TM, which were the largest group of patients studied. Another limitation was the poorly targeted population. Patients on the poor side of the QoL spectrum were missing.

Although the purpose of this questionnaire was to explore QoL in adults and not in children, who are the next target group of our research, patients came from an adult transfusion center and there were no patients between 18 and 19 years old while the research was in progress, a fact that may add a bias in the sample.

Another limitation would be that the questionnaire is geographically bounded; although Greek is the official language of our country, diverse cultures coexist within Greece. Therefore, it would be important to carry out a cross-cultural adaptation before it is used in other countries, and also to validate the adapted questionnaire as if it were a new one.

In the current study, we developed the STQOLI based on experiences among an adult population with a mean age of 28–47 years. However, there may be added value to evaluating the experiences and QoL in thalassemia among pediatric and adolescents populations, and incorporating them into the STQOLI.

Future studies with the STQOLI should examine patients with other types of Cooley disorders and different ethnicities in a larger population because dimensionality examinations of questionnaires are influenced by the study population, and the greater the sample size, the greater the power in detecting misfit.

Additional qualitative research with pediatrics would be warranted, whereas with adolescents, a two-stage process of concept elicitation and CIT analysis may be sufficient. We recommend further qualitative and empirical studies to assess the impact of thalassemia on QOL using this instrument in more patients to explore the global psychometric properties of the questionnaire.

Finally, we should add that QoL assessment involves a class of measurement fundamental to many aspects of health care planning and outcomes research. It is relevant for assessing symptoms, side effects of treatment, disease progression, satisfaction with care, quality of support services, unmet needs, and appraisal of health and health care options, and STQOLI is the first and only (to our knowledge) questionnaire for thalassemia patients that allows the decision of how well the patient feels to be reported by the patient.

Patient self-reporting, as in the STQOLI, is the most desirable, and often, the only way to obtain this critical information. Thus, accurate and meaningful measures of the various dimensions of QoL are vitally important. In addition, patient-reported outcomes have become increasingly important tools for understanding how various conditions affect patients. Both the US Food and Drug Administration and the Committee for Medicinal Products for Human Use of the European Medicines Agency emphasize the value of patient-reported outcome measures in identifying and quantifying a patient's perspective on his or her disease and its treatments. STQOLI is such a tool for thalassemia patients to express their perspectives.

Conclusion

Although there are some limitations to the study, as mentioned above, the results show that construct validity, internal consistency, and concurrent validity of the Greek version of the STQOLI, and its corresponding subscales, were generally supported by our population; thus, the 41-item STQOLI seems to be a valid tool in assessing HRQOL for patients with thalassemia.

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Authors' contributions

GL conceived of the study, coordinated and participated in the design of the study, performed the statistical analyses, and drafted the manuscript. DM, MD, and AE participated in the design. All authors read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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