Author's response to reviews

Title: Health related quality of life in Middle-Eastern children with beta-thalassemia

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Author's response to reviews: see over
To the Editor

Dear Editor,

We herewith submit a revised version of our manuscript. The title has been changed and now reads: Health related quality of life in Middle Eastern children with beta-thalassemia”. Also the Abstract has been changed according to the Editor’s suggestions. The introduction to the Abstract has been changed to comply with the minor point raised by Reviewer 2. We have carefully addressed all the issues raised by the Reviewers and the replies are given in a point by point fashion on separate pages below.

All Authors have read and approved the final revised version of the manuscript. We hope that in its revised form our paper may be considered worthy of publication.

My very best regards

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Reply to the Editor: For clarity we have added the following sentence to the Methods Section: “The study was approved by the local ethics committee in Cagliari (Authorization n° 58/2006).”

Other changes not specifically requested: Under Authors’ information we decided to delete the sentence “FE is Secretary of the EORTC (European Organisation for Research and Treatment of Cancer) Quality of Life Unit.” because it is not strictly related to the type of study performed here.

All changes in the manuscript have been highlighted in blue bold type (inserted text). Text that has been eliminated has been crossed out and highlighted in red type.

The Abstract has been replaced with the version proposed by the Editor. The first sentence of the Abstract has been changed according to the comment made by Reviewer 2.
Replies to the Reviewers' comments:

Reviewer #1: We thank the Reviewer for his encouraging and constructive review.

Issues that need to be addressed:
1- The authors refer to several studies on the quality of life in children with thalassaemia in the introduction. More details about the studies should be included, given that they differ with this study with respect to both participants' characteristics and time of examination. Such details may help convincing the reader about the contribution given by the present study.

We strongly agree with this observation. Therefore, we have deleted the paragraph immediately above the Conclusions Section: “have reported a reduction in physical, social and school functioning ranging between 10% and 24%, regardless of age, gender, ethnicity or household income [13]. The lowest mean score was often observed for the school domain [13,16,18]. Age at onset of anemia, age at first transfusion, irregular iron chelation therapy and lower pre-transfusion hemoglobin levels were factors significantly affecting HRQoL [16].” and have replaced it with the following text:

“Only a few studies have used PedsQL 4.0 to assess HRQoL in thalassemia patients. Details are given in Table 4. Overall, PedsQL domain scores were collected from 600 patients and 76 parents. Ismail et al. [13] reported the data obtained on a cohort of 78 Malaysian patients (mean age 11.9 years) and compared the scores to those of 235 healthy controls. The results showed a 10% to 24% reduction in the physical, social and school functioning domains of the patients, regardless of age, gender, ethnicity and household income. The authors recommended that the Ministry of Health continue to support these patients with the supply of free desferal. Cheuk et al. [14] conducted a comparative study in Hong Kong to evaluate the differences in HRQoL between 25 transfusion dependent thalassemia patients and 15 patients who underwent hematopoietic stem cell transplantation. PEDsQL scores of the first group were not significantly different from those of the transplanted patients, indicating that conventionally treated patients adapt relatively well to the burden of chronic illness and treatment. Clarke et al. [15] focused on mothers’ reports of 22 thalassemia children (aged on average 10 years) waiting for hematopoietic stem cell transplantation. The results showed a significant compromise in HRQoL in spite of the fact that the children displayed behaviour comparable to that of the general population. Thavorncharoensap et al [16] evaluated PEDsQL scores in 315 thalassemia children and adolescents in Thailand. Again, the school functioning subscale scored the lowest, with a mean of 67.9 (69.4 in our report). Age at onset of anemia, age at first transfusion, irregular iron chelation therapy and low pre-transfusion hemoglobin levels were factors significantly affecting HRQoL. The authors suggested the introduction of suitable programs aimed at providing psychosocial support and a link between the patient, school officials, the family and the physician. Surapolchai et al [17] conducted a study on 75 thalassemia children in Thailand and were the first to assess HRQoL from both the patients’ and parents’ perspective. Child self-reports were negatively influenced by low family income and an onset age of anemia below 2 years, whereas the negative predictor of total HRQoL score in parent proxy-reports was the frequency of red blood transfusions. Finally, Garaibeh et al [18] compared the outcomes of PEDsQL obtained on a sample of 128 Jordanian thalassemic children aged 8-18 years with those of 83 healthy children. The patients had significantly lower HRQoL mean scores in all dimensions compared to their healthy counterparts. The lowest mean score was reported for the school domain (46.7):
healthcare providers, counsellors and school teachers have an important role in helping children to overcome this problem. Many aspects of these previous reports underline the effectiveness of the approach applied in the present study which offers a unique perspective of HRQoL by evaluating both child-self and parent-proxy reports.”

Moreover, we have added a Table (Table 4) reporting data collected in previous studies assessing QoL in thalassemia using PedsQL 4.0:

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample and nationality</th>
<th>Physical Functioning Mean (SD)</th>
<th>Emotional Functioning Mean (SD)</th>
<th>Social Functioning Mean (SD)</th>
<th>School Functioning Mean (SD)</th>
<th>Psychosocial Summary Score Mean (SD)</th>
<th>Total Summary Score Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Parents</td>
<td>Patients</td>
<td>Parents</td>
<td>Patients</td>
<td>Parents</td>
<td>Patients</td>
</tr>
<tr>
<td>Ismail et al. 2006 [13]</td>
<td>78</td>
<td>Malaysia</td>
<td>69.1 (16.4)</td>
<td>NR</td>
<td>68.1 (17.2)</td>
<td>NR</td>
<td>74.3 (18.7)</td>
</tr>
<tr>
<td>Cheuk et al. 2008 [14]</td>
<td>25</td>
<td>Hong Kong</td>
<td>66.7 (16.0)</td>
<td>NR</td>
<td>60.8 (17.1)</td>
<td>NR</td>
<td>82.5 (17.7)</td>
</tr>
<tr>
<td>Clarke et al. 2009 [15]</td>
<td>22</td>
<td>UK</td>
<td>NR</td>
<td>66.5 (21.8)</td>
<td>NR</td>
<td>73.6 (22.7)</td>
<td>NR</td>
</tr>
<tr>
<td>Thovornchansup et al. 2010 [16]</td>
<td>315</td>
<td>Thailand</td>
<td>78.2 (14.8)</td>
<td>NR</td>
<td>75.9 (16.6)</td>
<td>NR</td>
<td>83.7 (14.7)</td>
</tr>
<tr>
<td>Sarangolela et al. 2010 [17]</td>
<td>54</td>
<td>Thailand</td>
<td>79.6 (2.3)</td>
<td>NR</td>
<td>72.2 (2.6)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Garaibhe et al. 2011 [18]</td>
<td>128</td>
<td>Jordan</td>
<td>54.2 (15.1)</td>
<td>NR</td>
<td>62.4 (23.3)</td>
<td>NR</td>
<td>73.3 (20.9)</td>
</tr>
<tr>
<td>This report 2012</td>
<td>60</td>
<td>Middle East</td>
<td>68.4 (27.2)</td>
<td>67.1 (28.0)</td>
<td>76.9 (24.6)</td>
<td>71.7 (25.3)</td>
<td>76.4 (20.6)</td>
</tr>
</tbody>
</table>

2- A bit more information about the medical aspects and burdensome nature of the illness, I feel, would help.

As suggested by the Reviewer, at the end of the second paragraph of the Background section we have added the following text to complete the information given (page 4):

“Overall, the psychosocial burden affects many aspects of the patient's life such as education, free-time, physical activities, skills, capabilities and family adjustment, the effects of which often result in anxiety, isolation and depression.”

3- I was wondering why the authors did not recruit a control group of healthy subjects.

We compared the PEDs QoL scores with those assessed in healthy people and reported in the questionnaire manual. However, we have included a sentence within the paragraph concerning the limitations of the study (last paragraph of the text) to further address the comment raised by the Reviewer:

“Further research with a longitudinal study design and the recruitment of a healthy control group is warranted.”

4- The subjects originally came from countries of the Middle East (i.e. Kurdistan, Palestine, Libya, Iraq and Syria) and therefore spoke different languages; so I was wondering if the PedsQS was validated in original language (all questionnaire in arabic language?) of these countries.

As reported in the Methods section, the questionnaires were completed in a validated version of the Arabic language (back translation method). This was the language spoken by all patients and their families. To better clarify these aspects, the following sentences have been added to the Methods Section: “The arabic version of this questionnaire was validated by Garaibhe et al. in 2011 on
a cohort of 128 Jordan thalassemia patients [18] (Table 4). Our cohort of patients and parents all spoke the Arabic language.”

5. Even if the Pediatric Quality of Life Inventory is a good questionnaire to investigate the quality of life and it is “sensitive to cognitive development”, the authors did not complete a real cognitive or psychological evaluation with normative scale, which would have been helpful in order to avoid confounding factor (i.e. cognitive, psychological or psychiatric problems in parents or children) that could have influenced the results. Please include and discuss this aspect among the limitations of the study.

We agree with the Reviewer and have added the following text to the Conclusions (top of page 12): “A limitation of the present study was that although the PedsQL questionnaire is sensitive to cognitive development, we did not perform a complete cognitive or psychological evaluation based on normative scale scores, which would have been helpful in order to avoid confounding factors (i.e. cognitive, psychological or psychiatric problems in parents or children).”

6- The authors stated that when they compared the level of agreement between child self and parent proxy-ratings, it was found that parents tended to slightly underestimate their child’s HRQoL. I was wondering if there were differences according to gender, age and socioeconomic status to try to better explain this result or if differences were also found in different populations (i.e. in Italian patients or in the patients of other Countries of Middle East).

Currently there is no data in the literature to make comparisons with the populations mentioned. Indeed, further study is required. However, we have further addressed this issue and the following text has been added:

Last line of the Results Section: “Multivariate analysis did not reveal any associations with age or gender in either patients or their parents.”

In the first paragraph of the Conclusions: “By increasing the awareness and knowledge levels of the parents, we can help sick children in developing countries to get the best care locally and to thus improve HRQoL.”

7- A psychosocial support to reduce emotional distress, to improve the compliance to chelation, and to strengthen coping strategies for a better integration in daily life has indeed been indicated. For instance, Aydinok and al. (2005) suggested that the frequency of psychopathology is higher in thalassaemics in comparison with normal population. For this reason, thalassaemic patients and their parents need a lifelong psychological support for prevention of mental health issues. In the conclusion section the authors should suggest therapy strategies (i.e. cognitive-behavioral therapy, Mazzone et al. 2009) that other reports showed to have a good effect on the compliance to chelation therapy.

We thank the Reviewer for this constructive comment. We fully agree and have added the following text to the Conclusions Section: “Thalassaemia patients and their parents require lifelong psychological support for prevention of mental health issues. Several effective psychological strategies are available. Cognitive-Behavioural Family Therapy (CBFT) can be an effective psychological approach to children with beta-thalassaemia major, capable of increasing compliance to treatment, lessening the emotional burden of disease and improving the quality of life of caregivers. [23]”

Moreover, the following bibliographical Reference has been added:
Reviewer #2: We thank the Reviewer for his useful comments and suggestions:

Major revision:

1- The authors should specify the inclusion and exclusion criteria used to recruit the subjects. Did you include only beta-thalassemia major?

We agree with this observation and have added the following sentence to the Methods Section: “Only patients under the age of 18 years with a genetically confirmed diagnosis of beta-thalassemia were included in the study.”

2- The authors should state clearly when and how the PedsQL was administered to the patients and their parents (at the hospitals while waiting for treatment or after receiving treatment? For those who came to Italy to receive stem cell transplantation, PedsQL was given before or after receiving the transplant? This is considered importance as it may affect the level of HRQOL you measured in the study).

Indeed this is an important point which has now been clarified in the text (Near the Beginning of the Methods Section): “Questionnaires were administered in the Thalassemia Center of the Hevi Pediatric Hospital (Duhok, Iraq) immediately before transfusing patients and at the Binaghi Hospital (Italy) and San Raffaele Hospital (Italy) one month before bone marrow transplantation.”

3- The rationale for each cut off points used in the analysis should be given to the reader (i.e. regular transfusion = pre-transfusion hemoglobin >= 9, ferritin values > 1,300 µg/dl, irregular iron chelation therapy = less than once a week.

This information has been added at the end of the Statistical analysis section. The paragraph has been changed as follows: “Different responses of boys and girls to items within a domain, as well as ferritin levels above 1300 mg/dl (Yes/No), Hepatomegaly (Yes/No), transfusion and iron chelation frequency (regular/slightly irregular/irregular), were analyzed using the Mann-Whitney test. Cut-off points were based on standard clinical guidelines. Ferritin values above 1300 µg/dl clearly suggest liver iron overload (Table 1).”

4- Please briefly describe how you selected the variables for multivariate analysis. Since the dependent variable (Y), the total score, is normally distributed. Please mention about the statistical method you use, whether the Y is the Log(total score) or else? The detail should be given in table 2.

We have amended the text under the Statistical Analysis Section to explain how the multivariable linear regression models were derived. Specifically, we have amended the manuscript so that it is also clear that the “Y” outcome is the total score (which was approximately normally distributed). The sentence now reads: “Multivariable linear regression models using the PedsQL score as the outcome (which was normally distributed) and the patient characteristics as predictors were constructed using Bayesian model averaging [22].”

Moreover, we have added a new bibliographical Reference to complete the explanation:
5- Are there any differences between patients receiving care at Italy and Middle East countries?

We have added the following sentence to the Results Section (before the subheading Child self and parent proxy-reports of HRQoL):

“No differences were observed between patients who received supportive care in the Middle East and those treated in Italy before transplantation.”

6 and 7- Please further discuss and compare the scores obtained from each domain (i.e. Is the total score considered low as compared to normal child in Middle East countries? What is the most affected domain?) and also compare the findings with other previous studies. Please further discuss the factors found to be associated with HRQOL in your study and compared with those of the other previous studies. For example, this study indicated that the delay in the start of iron chelation therapy is the factor that affects HRQOL, however, age at first transfusion, ferritin level as well as pre-transfusion hemoglobin are not associated with HRQOL. Please explain the possible reasons.

The first observation was also raised by Reviewer #1, point 1. We fully agree with both the Reviewers and detailed discussion has been added to the text. Please see our answer above (reply to Reviewer #1) showing the text and table added to the manuscript.

To address the second observation concerning the relationship between HRQoL and iron chelation we have added the following text in the discussion section: “Delayed iron chelation can lead to excessive accumulation of iron in body organs. Health issues arise especially when excess iron is stored in the heart, liver or pancreas.”

8- The differences between child and parent’s score mostly are from emotional domain. Could you explain why? Also, please compared with other previous studies that also compare the differences between parent and child in thalassemia or in other diseases?

We hypothesized in the discussion that "It would appear that parents tend to consider HRQoL of their children more compromised in domains dealing with interpersonal relationships, rather than those concerning physical impairment. A possible explanation may be that parents of thalassemia children unconsciously project their pessimistic feelings onto their child’s functioning."

Moreover, the following text has been added to the discussion section: “Thavorncharoensap et al [16] evaluated PEDsQL scores in 315 thalassemia children and adolescents in Thailand. Again, the school functioning subscale scored the lowest, with a mean of 67.9 (69.4 in our report). Age at onset of anemia, age at first transfusion, irregular iron chelation therapy and low pre-transfusion hemoglobin levels were factors significantly affecting HRQoL. The authors suggested the introduction of suitable programs aimed at providing psychosocial support and a link between the patient, school officials, the family and the physician.”

and to the conclusions (with an additional bibliographical reference): Thalassaemia patients and their parents require lifelong psychological support for prevention of mental health issues. Several effective psychological strategies are available. Cognitive-Behavioural Family Therapy (CBFT) can be an effective psychological approach to children with beta-
thalassaemia major, capable of increasing compliance to treatment, lessening the emotional burden of disease and improving the quality of life of caregivers. [23]

Additional bibliographical Reference:

9- Please mention the limitation of your study
We agree with the Reviewer and, accordingly, have added the following text towards the end of the Conclusions: A limitation of the present study was that although the PedsQL questionnaire is sensitive to cognitive development, we did not perform a complete cognitive or psychological evaluation based on normative scale scores, which would have been helpful in order to avoid confounding factors (i.e. cognitive, psychological or psychiatric problems in parents or children). Another limitation of the study was that HRQoL measurements were obtained in a cross-sectional manner. Further research with a longitudinal study design and the recruitment of a healthy control group is warranted.

Minor revisions:

1- For the abstract: The background makes the reader think that this article will discuss about the disease in Mediterranean countries but it is not.

We agree and have changed the Abstract as follows:

Abstract

Background: Thalassemia is a common disorder worldwide with a predominant incidence in Mediterranean countries, North Africa, the Middle East, India, Central Asia, and Southeast Asia. Whilst substantial progress has been made towards the improvement of Health related quality of life (HRQoL) in western countries, scarce evidence-based data exists on HRQoL of thalassemia children and adolescents living in developing countries.

Patients and Methods: We studied 60 thalassemia children from Middle Eastern countries with a median age of 10 years (range 5 to 17 years). HRQoL was assessed with the Pediatric Quality of Life Inventory (PedsQL) 4.0. The Questionnaire was completed at baseline by all patients and their parents. The agreement between child-self and parent-proxy HRQoL reports and the relationship between HRQoL profiles and socio-demographic and clinical factors were investigated.

Results: The scores of parents were generally lower than those of their children for Emotional Functioning (mean 75 vs 85; p=0.002), Psychosocial Health Summary (mean 70.3 vs 79.1; p=0.015) and the Total Summary Score (mean 74.3 vs 77.7 p=0.047). HRQoL was not associated with ferritin levels, hepatomegaly or frequency of transfusions or iron chelation therapy. Multivariate analysis showed that a delayed start of iron chelation had a negative impact on total PedsQL scores of both children (p=0.046) and their parents (p=0.007).

Conclusions: The PedsQL 4.0 is a useful tool for the measurement of HRQoL in pediatric thalassemia patients. This study shows that delayed start of iron chelation has a negative impact on children's HRQoL.
2- Please describe the psychometric property of PedsQL (Arabic language) and mentioned whether it was used in previous studies?

As mentioned in the Methods section, we used the validated arabic version of PedsQL 4.0 for our patients and their parents who all spoke the Arabic language. The original version of the PedsQL Generic Core Scales is well known for reliability, validity, responsiveness and practicality in both physically healthy pediatric populations and in pediatric patients with acute and/or chronic health conditions. In fact, internal consistency reliability of the PedsQL 4.0 Generic Core Scale approaches 0.90 for self-reports (Varni et al. 2001).

The arabic version was validated by Garaibhe et al in 2011 on a cohort of 128 Jordan thalassemia patients (Reference 18 and Table 4 of our manuscript). These authors found that the Cronbach’s alpha reliability for internal consistency for the Arabic translated version of PedsQL was 0.89 for the total scale and 0.65 for the physical, 0.76 for the emotional, 0.77 for the social and 0.89 for the school functioning domains. To better clarify these aspects, the following sentences have been added to the Methods Section: “The arabic version of this questionnaire was validated by Garaibhe et al. in 2011 on a cohort of 128 Jordan thalassemia patients [18] (Table 4). Our cohort of patients and parents all spoke the Arabic language.”

3- In table 2: please proper label the heading of the table (Is it the Beta coefficient that was reported?)

We thank the Reviewer for this comment: Yes, Table 2 is indeed the regression coefficient (beta) from the regression model. We have amended Table 2 accordingly.

4- Unit abbreviation: Please check with the journal’s requirement.
The units have been checked i.e. ug/dl has been replaced with the appropriate symbol: µg/dl
We have also checked that it conforms to journal style (title page: the uillstops and colons at the end of the affiliations have been taken out. Moreover, shaded boxes in tables have been taken out.

5- In statistical analysis: Descriptive measure for PEDsQL… please change to PedsQL
The change has been made as requested.

Reviewer #3: We thank the Reviewer for his constructive criticism:

1- was the relationship between the BMT transplant centers in Italy and the middle east to a single clinic, or multiple clinics? The narrative implies a single middle-east center. It would be useful to know that.

The Centers are all mentioned in the author affiliations. However to ensure that there is no misunderstanding the following sentence has been added to the Methods Section: “Questionnaires were administered in the Thalassemia Center of the Hevi Pediatric Hospital (Duhok, Iraq) immediately before transfusing patients and at the Binaghi Hospital (Italy) and San Raffaele Hospital (Italy) one month before bone marrow transplantation.

2- There is NO discussion of limitations. While this format has become “a requirement” they often do not add anything to the article – especially in this domain (the limitations discussion is, however, extremely relevant for clinical trial publications).

We agree with the Reviewer that this information should be given and have added the following text to the conclusions section: A limitation of the present study was that although the PedsQL questionnaire is sensitive to cognitive development, we did not perform a complete cognitive or psychological evaluation based on normative scale scores, which would have been helpful
in order to avoid confounding factors (i.e. cognitive, psychological or psychiatric problems in parents or children). Another limitation of the study was that HRQoL measurements were obtained in a cross-sectional manner. Further research with a longitudinal study design and the recruitment of a healthy control group is warranted.

3- one suspects that they are building on HRQOL work started under the broader rubric of Novartis phase IV clinical trials with deferasirox (which were actually modeled by the US Thalassemia Clinical Research Network).

Our patients were not included in any Novartis protocol. Moreover, Deferasirox is not available in the countries included in our study). Therefore, this hypothesis can be easily excluded.

4- The authors “promise” in their title a discussion of the sociodemographic factors BUT the analysis of the data does not have any sociodemographic components – except for the basic demographic characteristic of gender.

We agree with the Reviewer and have changed the title accordingly: Health related quality of life in Middle Eastern children with beta-thalassemia

5- The basic data set suggests that there are many sociodemographic characteristics that can be examined. For example, the report addresses 60 patients, 30 patients came to Italy for BMT. How does this group compare to the other 30? One would expect to see differences since the fact that 30 left the mid-east to go to Europe suggests that this group had the resources (?) or had the donor necessary for a BMT.

In the Results section we have added the sentence: “No differences were observed between patients who received supportive care in the Middle East and those treated in Italy before transplantation.”

It is true that all patients who came to Italy had an HLA compatible donor. However, all patients had actually been treated for years in their homeland and so that is probably why this did not make a difference.

6- Are there any differences between the patient’s country for origins? A few countries are mentioned – how many subjects from each country? There is a suggestion of a migration between countries in the middle east – so, are the migrants from urban or rural areas in their home country? What were the reasons for the migration?

As reported in the results, we did not find significant differences regarding the country of origin. The number of subject from each country is mentioned in Table 1. The reasons for migrations is beyond the scope of this paper.

7- Was there a difference in socio-demographic characteristics of the patients that received delayed transfusion?

We did not find any differences in age, sex or country of origin in patients with delayed start of transfusional support.

Reviewer #4: We thank the Reviewer for his comments and have improved the text as follows:

1- type of the study should be added in the first paragraph of method

We agree and have added the type of study as suggested.

From November 2007 to August 2008, we performed a cross-sectional study on a group of 60 thalassemia children and their parents, all originally coming from countries of the Middle East.
2- *Diagnosis of beta thalassemia major should be added in the methods*
Accordingly, we have added the following sentence under Patients and Methods:

“Only patients under the age of 18 years with a genetically confirmed diagnosis of beta-thalassemia were included in the study.”

3- *Type of treatment including adequate iron chelation and blood transfusion in all different centers in this study are the same or different?*
Table 1 splits patients according to the frequency of iron chelation and blood transfusions. The small number of patients does not permit further sub analysis regarding single country clinical behaviour.