Original Article

Correlation of Health-related Quality of Life and Factors Affecting among Different Age Groups in Transfusion-dependent Thalassaemia Patients- A Cross-sectional Study

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ABSTRACT

Introduction: Health-Related Quality of Life (HRQoL) aims to measure a person's views on the impact of their disease. Children suffering from thalassaemia require frequent blood transfusions throughout their lives because of impaired Haemoglobin (Hb). This may necessitate them to stay in the hospital for a longer transfusion day. School, physical activities, competencies, and family stability are all compromised in some way. Assessing HRQoL in individuals with thalassaemia and identifying variables that contribute to low quality of life is crucial.

Aim: To correlate HRQoL and factors affecting among different age groups in transfusion-dependent thalassaemia patients.

Materials and Methods: A cross-sectional study was conducted at MGM College and Hospital, Navi Mumbai, Maharashtra, India from October 2020 to August 2021, 70 thalassaemia patients aged 8-25 years registered for regular blood transfusions were included in the study and divided into three age groups: Group-I (8-12 years) n=25, II (13-17 years) n=24, and III (18-25 years) n=21. The study was approved by Institutional Ethics Committee. Paediatric Quality of Life (PedsQL™) 4.0 generic core scale questionnaire was used to assess patients' HRQoL. This questionnaire has two parallel reports: child self-reports and parent proxy reports and assess HRQoL across four dimensions: physical, emotional, school, and social functioning. Anthropometric and demographic parameters considered are height, weight and age. Pretransfusion Hb and ferritin levels, Cardiac iron overload, age of first transfusion, frequency of transfusion, annual blood requirement were collected and correlated with HRQoL scores. One-way ANOVA, unpaired student's t-test and Pearson's correlation were applied for statistical analysis and p-value less than 0.05 was considered significant.

Results: Comparison of total mean score of child's self-report between three age groups showed significant difference (p=0.001). In Group-I, the lowest score was for physical functioning (41.9±18) and significantly correlated with pretransfusion Hb, annual blood requirement, and age of first transfusion. In Group-II, the lowest score was for school functioning (54±18) and significantly correlated with pretransfusion Hb, annual blood requirement, cardiac iron loading, and age of first transfusion. In Group-III, the lowest score was for school functioning (50.9±12) and significantly correlated with pretransfusion Hb, ferritin level, age of first transfusion, annual blood requirement, and frequency of transfusion.

Conclusion: The HRQoL scores of thalassaemia patients was low in parent's report as compared to children's report in all four dimensions in all three groups. The predominant factors affecting are pretransfusion Hb level, annual blood requirement, and age of the first transfusion.

INTRODUCTION

Thalassaemia is an autoimmune disease that causes red blood cell destruction due to impaired Hb production [1]. Children suffering from thalassaemia require frequent blood transfusions throughout their lives because of impaired Hb. This may necessitate them to stay in the hospital for a longer transfusion day [2]. From the identification of the first incidence of thalassaemia to date, diagnostic and treatment approaches for this life-threatening condition have altered considerably over time. However, despite how basic it appears, any intervention has the potential to enhance HRQoL in thalassaemia [3].

School, physical activities, competencies, and family stability are all compromised in some way. The consequences of which usually lead to psychological, emotional, and societal devastation [4]. Health difficulties, blood transfusions, and other illnesses can lead to poor physical and psychological health, social dysfunction, and absence from school or failure to continue studying [3]. Several factors impact thalassaemic children's HRQoL.

HRQoL is a wide term that tries to determine a person's perceived impact of their disease and/or therapy on their health and wellbeing [5,6]. "Dr. James Varni developed the PedsQL 4.0 generic core scale to assess the fundamental core functioning for paediatric HRQoL across four domains: physical, emotional, school and social functioning" [7-10]. The PedsQL 4.0 questionnaire has widespread recognition as a technique in healthy and unhealthy paediatric populations due to its accuracy, applicability, and accessibility [7-11].

While various HRQoL studies have been successfully done to enhance healthcare in developed countries, similar research and their applicability are lacking in developing countries [4,11]. In recent years, even though clinical management has tremendously improved in developing countries, but little effort has been made to promote patient's quality of life [12]. Hence, Assessing HRQoL in individuals with thalassaemia and identifying factors that contribute to poor quality of life is crucial [13]. Therefore, this study was undertaken to assess HRQoL in thalassaemia patients and correlate it with the factors related to the disease. The hypothesis of this study is that factors like pretransfusion Hb, ferritin level, cardiac iron overloading,

age of first transfusion and annual blood requirement may contribute to low HRQoL scores in thalassaemia patients.

MATERIALS AND METHODS

A cross-sectional study was conducted at MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India from October 2020 to August 2021. The MGM College Ethics Committee, Navi Mumbai granted approval to the study. The ethical clearance number-Ref. MGMIHS/RES./02/2020-2021/68. The aim of the study was explained to all participants and parents and written informed consent of parents and the child's assent were obtained from all of them.

Seventy transfusion-dependent thalassaemia children, adolescents, and young adults aged between 8 to 25 years were included in the study. The convenient sampling method was used to include all the patients registered for blood transfusion in MGM hospital who fulfilled the inclusion criteria during the study period.

Inclusion criteria: Thalassaemia patients between 8-25 years of age who were registered for blood transfusion and were willing to volunteer in the study.

Exclusion criteria: Thalassaemia patients who denied taking part in the study, patients below 8 years and above 25 years and patients with any complications like hypersplenism, cardiac failure, liver failure, etc., were excluded from the study.

Study Procedure

The Paediatric QoL Inventory™ (PedsQL™) 4.0 Generic Core Scale Questionnaire was used to assess HRQoL [7-10].

The participants were divided into three different age groups: I (8-12 years) n=25; II (13-17 years) n=24; and III (18-25 years) n=21. Groups were made on the base of PedsQL™ 4.0 generic core scale. This Questionnaire is different for different age groups.

The appropriate questionnaire was administered for different age groups.

Along with the questionnaire other parameters measured are as follows:

1. Age (years), height (cm), and weight (kg) was among the anthropometric measurements taken. An anthropometric digital weighing scale (MI-120T model, Meditrin instruments, India), was used to record weight. Height was measured using wall mounted height measuring scale. Body Mass Index (BMI) in kg/m^2 was calculated using the formula- weight (kg)/ height (m^2) [14].

2. Haematological parameters: pretransfusion Hb (gm/dL), Ferritin level (ng/mL), and cardiac iron overload (using Cardiac T2* MRI in ms) were investigated.

3. Age of the first transfusion (months), Frequency of transfusion (no./year), and Annual blood requirement (cc/kg/year), were collected from the patient's clinical record.

Questionnaire assessment: Before using the questionnaire, a user agreement was completed with the MAPI Research Institute which has developed the PedsQL™ questionnaire. This questionnaire has two parallel reports: child self-reports and parent proxy reports. The study included child self-report and parent proxy-report of ages 8-12, 13-17, and 18-25 years. PedsQL items inquire about the severity of conditions patients face over one month. For each item, replies are given on a five-point Likert scale from 0 (never a problem) to 4 (almost always a problem). The 23 elements include eight items on physical functioning and five items each on emotional functioning, social functioning, and school functioning, with the overall score. Each scale has been assessed as a number ranging from 100 to 0, with the greater the score, the higher the QoL. The PedsQL questionnaire was to be completed individually by parents and children aged 8 and above for HRQoL assessment [7-10].

STATISTICAL ANALYSIS

Microsoft excel and SPSS software version 16.0 were used to analyse the data. HRQoL scores, for each functioning as well as total scores, for parents as well as child's reports for all three age groups were represented by mean and standard deviation. One-way ANOVA and unpaired student's t-test were applied to study the difference in score. Pearson's correlation was applied to examine the relation between HRQoL and each factor affecting the quality of life. Factors with significant correlation were plotted in a scattered chart. The significance level was considered for the p-value as $p < 0.05$.

RESULTS

[Table/Fig-1] shows the average age, weight, height, and BMI of patients in different age groups. For Group-I: average age (years) was 9.3±1.2, weight (Kg) was 21±3.8, height (cm) was 125±6.3, BMI (kg/m^2) was 13.8±1.9. For Group-II: average age (years) was 14.7±1.3, weight (Kg) was 33±6.3, height (cm) was 150±8.5, BMI (kg/m^2) was 14.5±1.9. For Group-III: Average age (years) was 21.3±2.5, weight (Kg) was 40.1±10, height (cm) was 149±10.6, BMI (kg/m^2) was 17.8±4.4. As per BMI, all patients fall in the underweight category for all age groups.

Parameters	Group-I (n=25)	Group-II (n=24)	Group-III (n=21)
Age (years)	9.3±1.2	14.7±1.3	21.3±2.5
Weight (Kg)	21±3.8	33±6.3	40.1±10
Height (cm)	125±6.3	150±8.5	149±10.6
BMI (Kg/m²)	13.8±1.9	14.5±1.9	17.8±4.4

[Table/Fig-1]: Mean±SD for age, weight, height, and BMI of patients.
BMI: Body mass index

[Table/Fig-2] shows clinical and haematological characteristics of patients which affects their quality of life. Pretransfusion Hb level (gm/dL) was found to be low in all age groups (Group-I was 6.9±1.2, Group-II was 7±1.4 and Group-III was 6.7±1.2). Ferritin level (ng/mL) was high in all age groups (Group-I was 2604±1000, Group-II was 2587±13 and Group-III was 2197±1204). Not much cardiac iron loading was found through cardiac T2* MRI (ms) (Group-I was 34.8±18, Group-II was 23.8±21 and Group-III was 32.5±21). Mean age of 1st transfusion (months) for Group-I was 10.8±13, Group-II was 18±13 and Group-III was 26.2±30. Mean annual blood required (cc/kg/year) by Group-I was 261±59, Group-II was 255±77 and Group-III was 243±65. Frequency of transfusion per year for Group-I was 14±1.3, Group-II was 14±0.9 and Group-III was 13.7±1.6.

Parameters	Group-I (n=25)	Group-II (n=24)	Group-III (n=21)
Pretransfusion Hb (gm/dL)	6.9±1.2	7±1.4	6.7±1.2
Ferritin (ng/mL)	2604±1000	2587±13	2197±1204
Cardiac iron loading {Cardiac T2*MRI (ms)}	34.8±18	23.8±21	32.5±21
Age of 1st transfusion (months)	10.8±13	18±13	26.2±30
Annual blood requirement (cc/kg/year)	261±59	255±77	243±65
Frequency of transfusion (year)	14±1.3	14±.9	13.7±1.6

[Table/Fig-2]: Mean±SD of clinical and haematological parameters.
Hb: Haemoglobin; Cardiac T2* MRI- Cardiac T2* Magnetic resonance imaging

[Table/Fig-3] shows Comparison of HRQoL of the total mean score of child's self-report between three age groups. Group-I (43.9±14.5) has a significantly lower quality of life than the other two groups (II: 60±10.9 and III: 55.7±14.2).

HRQoL[#]	Group-I (n=25)	Group-II (n=24)	Group-III (n=21)	p-value
Child's self-report	43.9±14.5	60±10.9	55.7±14.2	0.001**

[Table/Fig-3]: Comparison of the total mean score of HRQoL of the child's report using One-way ANOVA with p-value.
*level of significance; #Health related Quality of Life

[Table/Fig-4] shows comparison of total mean score of a child's report with a parent's report between three groups with a significant difference in Group-II (p-0.001) and Group-III (p-0.05) but a non significant difference in Group-I (p-0.9).

HRQoL#	Child's self-report	Parents report	p-value
Group-I (n=25)	43.9±14.5	43.8±10	0.9
Group-II (n=24)	60±10.9	46.2±5.6	0.001**
Group-III (n=21)	55.7±14.2	48±12.5	0.05*

[Table/Fig-4]: Comparison of the total mean score of HRQoL of child's report with parent's report using independent t-test with p-value.
*level of significance; #HRQoL

[Table/Fig-5] shows scoring of individual dimensions of physical, emotional, social, and school functioning scores between three groups. In Group-I, the lowest score was shown for physical functioning in both child (41.9±18) as well as parent report (38±7.9). In Group-II, in the child's report, school functioning had the lowest score (54±18), while social functioning received the lowest score (41.3±8) in the parent's report. In Group-III, both child (50.9±12), as well as parent reports (50.9±12), had the lowest scores for school functioning. Comparison of each domains of child's report between groups shows significant difference (p-values for physical-0.003, emotional-0.05, social-0.001 and school-0.1) and the lowest score was found to be in Group-I in all domains. For parent's report, the lowest score was found for physical (p-0.007) and school (p-value-0.3) domain in Group-I and for emotional (p- 0.4) and social (p-0.001) domain in Group-II.

HRQoL#	Group-I (n=25)	Group-II (n=24)	Group-III (n=21)	p-value
Child's self-report				
Physical	41.9±18	58.8±13	60.5±19	0.003**
Emotional	43.8±16	59±16	52.7±27	0.05*
Social	47.8±15	70.3±15	71.3±15	0.001**
School	44±17	54±18	50.9±12	0.1
Parents report				
Physical	38±7.9	48.6±12	52.7±14	0.007**
Emotional	49.8±24	44±10	54.5±27	0.4
Social	48.8±13	41.3±8	69.5±18	0.001**
School	43.4±18	51±21	50.9±12	0.3

[Table/Fig-5]: Mean±SD for scoring of each dimension for child's self-report and parent proxy report using one-way ANOVA with p-value.
*level of significance; #HRQoL

[Table/Fig-6] shows the correlation of HRQoL of the total mean score of child self-report and parameters which affect the quality of life. In Group-I, there was a weak positive correlation with Cardiac T2* MRI (iron loading) and a strong positive correlation with the pretransfusion Hb and age of the first transfusion. Ferritin showed moderate negative, annual blood requirement showed strong negative, and frequency of transfusion showed a weak negative

Factors	Group-I (n=25)	Group-II (n=24)	Group-III (n=21)
Pretransfusion Hb	r=0.43 (p-value=0.03)*	r=0.52 (p-value=0.04)*	r=0.87 (p-value=0.001)**
Ferritin	r=-0.29 (p-value=0.15)	r=-0.30 (p-value=0.2)	r=-0.72 (p-value=0.007)**
Cardiac T2* MRI	r=0.09 (p-value=0.6)	r=0.50 (p-value=0.05)*	r=0.33 (p-value=0.1)
Age of 1st transfusion	r=0.67 (p-value=0.002)**	r=0.67 (p-value=0.005)**	r=0.77 (p-value=0.001)**
Annual blood requirement	r=-0.40 (p-value=0.04)*	r=-0.50 (p-value=0.05)*	r=-0.77 (p-value=0.001)**
Frequency of transfusion	r=-0.17 (p-value=0.4)	r=-0.46 (p-value=0. 07)	r=-0.80 (p-value=0.006)**

[Table/Fig-6]: Correlation of HRQoL of child's self-report total mean score and factors affecting using Pearson Correlation (R) with p-value.
level of significance; Hb: Haemoglobin; Cardiac T2 MRI: Cardiac T2* Magnetic resonance imaging
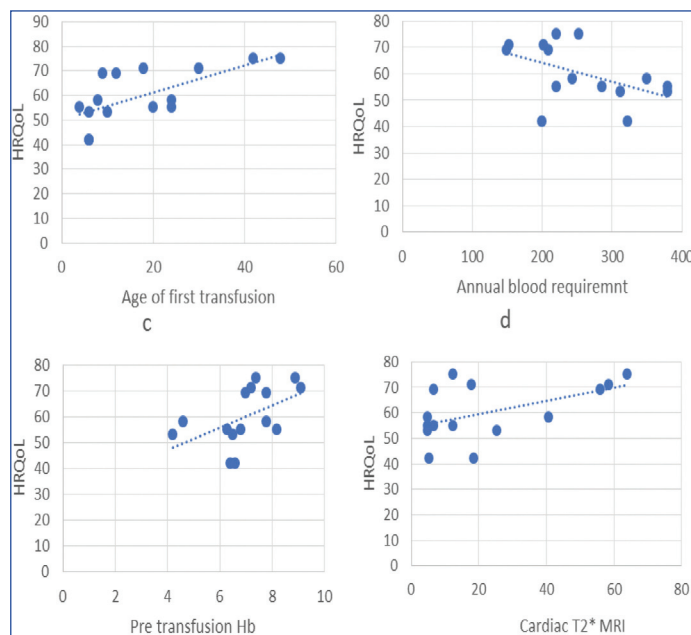
correlation. In Group-II, pretransfusion Hb, Cardiac T2* MRI (iron loading), and age of the first transfusion show a strong positive correlation. Annual blood requirement and frequency of transfusion showed a strong negative correlation and Ferritin moderate negative correlation. In Group-III, pretransfusion Hb, and age of the first transfusion show a strong positive correlation and Cardiac T2* MRI (iron loading) showed a moderate positive correlation. Annual blood requirement, Ferritin and frequency of transfusion showed a strong negative correlation.

[Table/Fig-7] shows significant positive correlation between HRQoL and a) Age of the first transfusion (r=0.67, p=0.002); b) Pretransfusion Hb (r=0.43, p=0.03) and negative correlation with; c) Annual blood requirement (r=-0.40, p=0.04) in Group-I.
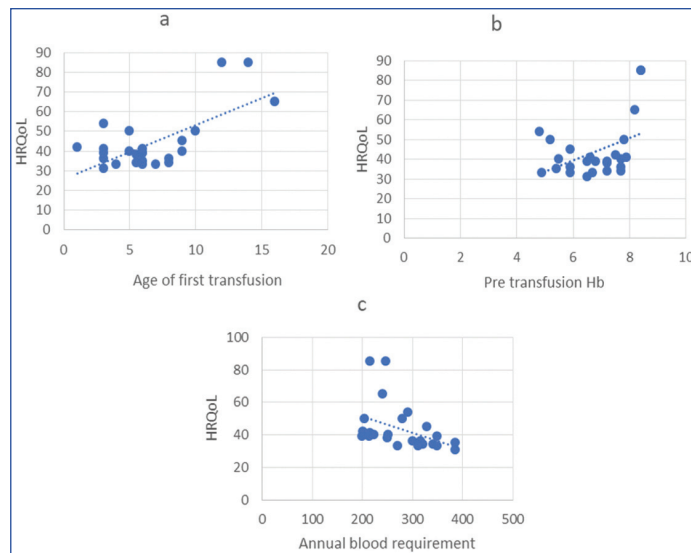
[Table/Fig-7]: Group-I: Significant correlation between HRQoL with: a) Age of first transfusion; b) pre transfusion Hb; and c) Annual blood requirement.
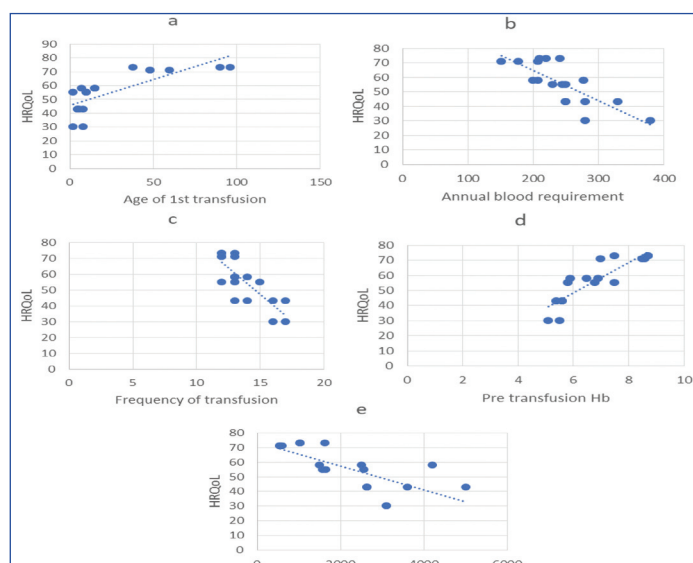HRQoL: Health related quality of life; Hb: Haemoglobin

[Table/Fig-8] shows significant positive correlation between HRQoL; and a) age of the first transfusion (r=0.67, p=0.005), c) Pretransfusion Hb (r=0.52, p=0.04); and d) Cardiac iron loading (r=0.50, p=0.05) and negative correlation with; b) Annual blood requirement (r=-0.50, p=0.05), in Group-II.

[Table/Fig-8]: Group-II: Significant correlation between HRQoL with; a) age of first transfusion; b) Annual blood requirement; c) Pretransfusion Hb; and d) Cardiac T2* MRI.
HRQoL: Health related quality of life; Hb: Haemoglobin; Cardiac T2* MRI: Cardiac T2* Magnetic resonance imaging

[Table/Fig-9] shows significant positive correlation between HRQoL; and a) Age of the first transfusion (r=0.77, p=0.001); and

d) Pretransfusion Hb (r=0.87, p=0.001) and negative correlation with b) Annual blood requirement (r=-0.77 p=0.001); c) Frequency of transfusion (r=-0.80 p=0.006); and e) Ferritin level (r=-0.72, p=0.007) in Group-III.

[Table/Fig-9]: Group-III: Significant correlation between HRQoL with: a) Age of first transfusion; b) Annual blood requirement; c) Frequency of transfusion; d) pre transfusion Hb; and e) Ferritin level.
HRQoL: Health related quality of life; Hb: Haemoglobin

DISCUSSION

Thalassaemia's outcome has changed drastically over time, from a life-threatening disease to a chronic condition with impairment [15]. Measuring HRQoL in patients to get a perspective of how they feel about their illness and how it affects their life. Implementing strategic choices targeted not only at extending the life and even at improving the quality of life of these people is critical [11]. Therefore, HRQoL in transfusion-dependent thalassaemia patients was assessed in this study. Further, investigation was done for individual factors that may affect HRQoL of patients. Because the study focused on the patient's perspective, only HRQoL scores from children's self-reports were correlated with different factors. The parent's report was collected and compared to the child's report to see the parent's perspective on their child's disease [16].

Paediatric QoL inventory version 4.0 (PedsQL 4.0) Generic core scales was used to analyse HRQoL in this study, as PedsQL 4.0 questionnaire proved simple to understand and was previously widely utilised in patients with thalassaemia [16,17]. Overall scores of HRQoL were significantly lower in thalassaemia patients according to parent's reports as compared children's report and finding are similar to those of research conducted by Mikael NA and Al-Allawi NA; Mettananda S et al., Thavorncharoensap M et al., Hakeem GLA et al., Baghianimoghadam MH et al., Ismail A et al., which showed low scores in HRQoL in thalassaemia patients compared to normal counterparts [11,13,16-19]. This is unsurprising given the disease's chronic nature, but it is disconcerting because HRQoL scores are still much worse despite major advances in medical care. This shows that advancements in medical care may not significantly impact these patients' quality of life [13]. Few studies conducted by Boonchooduang N et al., Ismail M et al., Sultana R et al., show contradictory findings with higher HRQoL [20-22]. Furthermore, some researchers like Caocci G et al., Varni JW et al., Boonchooduang N et al., Surapolchai P et al., have noted that parent scores were lower than their children's scores [4,10,20,23]. A similar result was found in this study too. This could be related to the parents' increased concern, dissatisfaction, and protective view of their child's well-being, as well as their propensity to overprotect their chronically unwell child [23].

In this study, the child's HRQoL in different age groups showed that in Group-I physical score was the lowest and in Groups II and III the lowest score was for school functioning. Studies by Ismail A et al., Anionwu E and Atkin K, Musallam K et al., Saeed N, Shafie AA et al., had similar findings with lowest score in physical and school domains [19,24-27]. This might be linked to the fact that frequently missing school for routine check-ups, irregular blood transfusions due to unavailability of matched blood as well as tiredness during strenuous exercise due to chronic anaemia had a considerable negative impact on the HRQoL. There is little data on whether patients score low in this element are as a result of anaemia, which contributes to poor academic ability, or frequent hospital visits, which causes absences from school [27]. When child's report of HRQoL was compared to parent's reports, in Group-I and Group-III the report was similar to the child's report but in Group-II social functioning showed the lowest score. As paediatric patients are not aware of their illness but as they grow they had low self-esteem and showed negative thoughts about their life, as well as unhappiness, anger, and hurt in response to their chronic disease which significantly decreases psychosocial well-being [28]. and need psychosocial support as suggested by Aydinok Y et al., and Goldbeck L et al., [29,30].

Patients with thalassaemia in all three age groups have lower pretransfusion Hb levels, despite regular blood transfusion. pretransfusion Hb levels must be checked regularly to maintain a range between 9-10.5 g/dL [31,32]. This study findings suggest that greater the pretransfusion Hb levels better the HRQoL ratings, also previously reported by Thavorncharoensap M et al., Surapolchai P et al., Elalfy MS et al., [16,23,33]. The studies by Mevada ST et al., and Jafari-Shakib A et al., showed contrary results with better Hb level [34,35]. Low pretransfusion Hb levels could be linked to the fact that minimal Hb levels are linked to a variety of symptoms, including lethargy, overall weakness, and reduced mental alertness, all of which can contribute to a patient's HRQoL being compromised across several domains [16].

There was a negative association between HRQoL scores and serum ferritin levels. Because the association was weak and non significant, no clinical implications in Group-I and Group-II was found, but in Group-III the correlation was significant. Cardiac T2* MRI has a weak positive correlation with HRQoL. More the Cardiac T2* MRI lesser the iron loading. The studies conducted by Borgna-Pignatti C et al., Dubey AP et al., Olivieri NF et al., Telfer PT et al., shows that long-term iron overload and high serum ferritin levels can cause significant morbidity and mortality [31,32,36,37]. This may be because long-term iron overloading is damaging; short-term iron overloading, as indicated by a raised serum ferritin level, did not invent obvious signs or difficulties, and thus did not affect their HRQoL [16]. So, it may be considered as the age advances the complications go on increasing.

In this study, there is a significant correlation with age of first transfusion and annual blood requirement in all three age groups, the possible explanation for the significant correlation of the amount of blood required may be related to low pretransfusion Hb levels. But on the other hand, there have been non significant relation with the frequency of transfusion per year in Group-I and Group-II, as the questionnaire ask questions concerned with well-being about a previous month which might not be considered for a whole year, also suggested by Thavorncharoensap M et al., [16]. In contrast, Group-III showed a significant correlation, advancing in age could be the possibility as discussed above.

Age was an important factor of HRQoL in thalassaemia patients. Although shifting from child to adult brings with it a whole slew of new problems, like a much more active lifestyle, determining

a successful job path, and marriage, it also brings up health issues [25]. Despite all these, adolescent patients showed much greater HRQoL than comparable younger individuals, according to this study. This conclusion seemed comparable with previous studies by Thavorncharoensap M et al., Ismail A et al., Mikelli A et al., Motti F et al., which found that older age group children with thalassaemia had lower levels of depression, indicating better coping and adaptation [16,19,38,39], and poor HRQoL was linked to commencing transfusion at a younger age as seen in the study by Hakeem GLA et al., [17]. This finding was contrast with the finding of Mikael NA and Al-Allawi NA and Shafie AA et al., which shows HRQoL worsens as patients grow older [11,27]. Prolonged exposure to recurrent transfusion has a significant impact on thalassaemia patients' fitness and physical performance [17].

Changes in medical interventions for thalassaemic patients to make them more patient-centered, accessible, thorough, as well as complete might shorten hospitalisation duration and enhance treatment results, particularly patient's HRQoL. Counselling programs should be planned to discuss their illness, lifestyle, and other issues which may help in psychosocial well-being [27].

As blood transfusions are the only preferable way to fight this illness, effective measures for the availability of blood transfusions should be done. Also, maintaining pretransfusion Hb level above 9 g/dL is necessary [31,32]. An iron chelate regimen that minimises the long-term implications of iron overloading is crucial even when there was a non significant association between serum ferritin and HRQoL [40-42], that might improve the patient's HRQoL.

Limitation(s)

The limitation of this study was, that the healthy counterparts were not included in the study so there was no HRQoL score of healthy people to compare and the comparison was based on the literature available. Another limitation is that the results may be limited in the potential to be extended to patients in other geographical locations as the patients were from the same location.

CONCLUSION(S)

The HRQoL scores of thalassaemia patients were low in parent's report as compared to children's report in all four dimensions in all three groups. Age is an important indicator of HRQoL in thalassaemia patients. This study found greater HRQol scores in adolescents then younger individuals. All correlating factors affects quality of life to some extent but predominant factors in all three age groups affecting HRQoL were pretransfusion Hb level, annual blood requirement, and age of first transfusion.

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