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Original Article

Health-Related Quality of Life in Thai Children with Thalassemia as Evaluated by PedsQL and EQ-5D-Y: A Single-Center Experience

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Abstract. ***Background:*** **Thalassemia remains a challenging chronic disease in Thailand, but national prenatal screening, along with better treatment and management, may have improved health-related quality of life *(*HRQoL*)* for pediatric patients. We aimed to measure the HRQoL of transfusion-dependent *(*TDT*)* and non-transfusion dependent *(*NTDT*)* of these pediatric patients at our institute.**

Methods: **We included all patients 2 – 18 years old, with TDT and NTDT, using the Pediatric Quality of Life Inventory 4.0 Generic Core Scales *(*PedsQL*)* and the EuroQol Group's Five Dimensions for Youth *(*EQ-5D-Y*)* instruments. Patients and caregivers responded as appropriate for age.**

Results: **Mean PedsQL total summary scores *(*TSS*)* *(*SD*)* of child self-reports and parent proxy-reports were 81.00 *(*10.94*)* and 78.84 *(*16.72*)* from 150 participants. Mean EQ-5D-Y VAS *(*SD*)* for children was 89.27 *(*11.56*)* and 86.72 *(*10.62*)* for parent proxies. The most problematic EQ-5D-Y dimension was "having pain or discomfort". These scores had significant correlations between the child and parental proxy perspectives, as well as between the PedsQL and EQ-5D-Y. An age of 8 - 12 years and oral chelation therapy predicted lower self-reported PedsQL TSS. Parental proxy-report predictors for reduced PedsQL TSS and EQ-5D-Y VAS were primary school education for children, parental proxy secondary school education, Universal Coverage insurance, and TDT.**

Conclusion: **HRQoL scores of our pediatric thalassemia patients had improved from the previous decade, and these findings may represent our better standard of care. Some sociodemographic and clinical characteristics may present negative impacts on HRQoL. More exploration is needed to understand predictors and further improve HRQoL, especially for TDT patients.**

Keywords: EQ-5D-Y; PedsQL; Predictor; Quality of life; Thalassemia.

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Introduction. Thalassemia is an inherited hemoglobin disorder in which alpha and beta-globin genetic mutations decrease globin synthesis. It is highly prevalent in Africa, the Mediterranean region, the Middle East, the Indian subcontinent, and Southeast Asia:[1-3] 40-50% of the Thai population likely carries

some sort of thalassemia gene.[4-5] In 1993, the Thai government began screening pregnant women for three severe forms: homozygous β-thalassemia, β-thalassemia/HbE disease, and Hb Bart's hydrops fetalis.[5] Thalassemia has varying severity from asymptomatic/mild anemia (thalassemia minor) to severe (thalassemia major), the latter requiring lifelong blood transfusions. Stem cell transplantation is the sole curative treatment[3] but is reserved for only the most severe cases as it is expensive and requires a direct family donor; thus, blood transfusions and iron chelation remain standard treatments. Between 2013-4, the Thalassemia International Federation (TIF)[6-7] created two classification guidelines for the management of transfusion-dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTDT). While this has resulted in improvements, complications from disease and treatment persist, especially regarding iron overload.

Children and adolescents with chronic illnesses also experience apprehension about physical health, effects on growth and puberty, body image, school absences, and disruption of social activities. Health-related quality of life (HRQoL) is a measure of how well patients can participate in a lifestyle typical for their age.[8-9] Before TIF guidelines implementation, thalassemia patients reported suboptimal HRQoL, associated with disease severity.[10,11] The Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL) is well known and easy to score.[12] Previous research in Thailand demonstrated that healthy children had significantly higher mean HRQoL scores[13] to chronically-ill ones in all PedsQLsubscales. The EuroQol Group's Five Dimensions for Youth (EQ-5D-Y)[14] is another tool to evaluate child and adolescent HRQoL; the questionnaire layout may be more child-friendly. Both instruments have Thai versions with adequate reliability and validity.

While there is a large global body of research on HRQoL for pediatric thalassemia patients, not much has been done in Thailand. In 2015, a Thai study of adolescents with thalassemia reported higher serum ferritin levels, and comorbidities were associated with lower HRQoL.[15] We previously published a report from our hospital (2010) with 2008-9 data,[16] using the PedsQL with 75 pediatric patients and found that family finance and disease severity affected HRQoL outcomes. Somewhat similarly, recent studies from Egypt and Sri Lanka noted comorbidities (short stature, splenectomy, and undernutrition), transfusion dependence, and lower patient and mother educational levels as associated with lower HRQoL scores.[17,18]

As of 2019, our hospital has a broader patient demographic, better-established treatment guidelines, and improved access to pediatric endocrinology and cardiology staff. Our objectives were to assess HRQoL among children and adolescents with thalassemia using both the PedsQL and EQ-5D-Y and examine possible factors affecting HRQoL. We also wanted to determine if improvements occurred in thalassemia management that impacted HRQoL and observe outcome discrepancies for TDT versus NTDT patients.

Methods and Materials.

Participants. The clinical and socioeconomic data of TDT and NTDT patients receiving treatment at our institute, aged 2 - 18 years old, were collected from outpatient records and patient files at the Pediatric Hematology Clinic, Thammasat University Hospital from June 2019 to December 2019. Our study protocol was approved by the Human Ethics Committee of Thammasat University No. 1 Faculty of Medicine; assent and/or informed consent forms were obtained from patients > 7 years old and all parents or guardians. Patients and parents/guardians who did not speak or understand Thai adequately were excluded as were cases with incomplete history or records.

Growth assessment. Anthropometric measurements, including weight, height and body mass index (BMI), were recorded. Z-scores or standard deviation (SD) scores of BMI for age were calculated using WHO Anthro and AnthroPlus software.[19,20] BMI Z-scores (BMIZ) < 2 standard deviations (SD), > 1, and > 2 SD were categorized as underweight, overweight, and obese, respectively.

*Measurement of HRQoL.*The validated Thai versions of the PedsQL and the EQ-5D-Y questionnaires were used to assess pediatric HRQoL. The corresponding user agreement was signed with MAPI Research Institute, Lyon, France, prior to using the PedsQL, and our research was registered at the EuroQol Research Foundation for the EQ-5D-Y. Questionnaires were either completed independently by parent proxies or patients as possible; for very young patients, the questions were given as an interview and forms filled out by research assistants.

The PedsQL has forms for different stages of development per age groups: 2 – 4, 5 - 7, 8 - 12, and 13 – 18 years.[8,9,12] All forms have four sections on physical health (8 items), emotional wellbeing (5), social interaction (5), and/or school (5). All this makes up an 8-item physical health summary score (PHS) and a 15-item psychosocial health summary score (PCHS). Parallel child self-reports and parental proxy-reports were filled out for each age group, except for children 2 - 4 years old, which had only parental proxies. Possible responses to each item were coded 0 to 4, i.e., never to almost always. The child self-report form for the 5 – 7 years old group has a three-point scale instead of five: not at all, sometimes, and a lot. For children 2 – 4 years old not attending kindergarten, daycare, etc., the school section was omitted; if these children were

attending some form of school, parent proxies had to complete only three items in this section.

The EQ-5D-Y is a two-part tool to be completed by all parents/guardians as well as children aged 8 -15 years old. We extended this tool to the age of 18 years, as recommended by the original developer, in order to have only one EQ-5D version in this study.[14,21] The first section has five questions on "mobility" "looking after myself" "doing usual activities" "having pain or discomfort," and "feeling worried, sad or unhappy". There are three possible answers to each question: no problem, some/moderate problem/s, a lot of/severe problem/s. In the last section of the EQ-5D-Y, participants indicate the current level of health on a visual analog scale (VAS) from 0 to 100, 100 being highest or best.

Statistical analysis. Data were expressed as mean (SD; the standard deviation of the mean), range, or percentage (%). Differences in variables between groups were analyzed by t-test, Mann-Whitney U test, or ANOVA for continuous variables and by Chi-square or Fisher's Exact tests for categorical variables as appropriate. Internal reliability was assessed with Cronbach's alpha for summary and total scores of the PedsQL and EQ-5D-Y. We used Pearson's or Spearman's rank correlation coefficients as appropriate to examine the strength of the relations between preference values. Univariate or multivariate stepwise linear regression analysis was undertaken to identify independent predictors of HRQoL. All analyses incorporated Microsoft Excel 2019 and SPSS for Windows (Statistical Package for the Social Sciences version 17.0, SPSS Inc., Chicago, IL, USA). All *p*-values were two-tailed: $p < 0.05$ was considered statistically significant.

Results. We had 150 patients with TDT and NTDT. All children and their guardians (including 94 mothers, 35 fathers, 15 grandmothers, one grandfather, and five other relatives) completed the PedsQL and EQ-5D-Y as appropriate. All children > 8 years old completed the EQ-5D-Y (85 participants); 121 children > 5 years responded to the PedsQL, as expected.

Patient characteristics. The demographic and clinical characteristics of all children are given in **Table 1**. There was a mean age of 9.1 years (SD 4.3, range 2-18.8 years), with 81 males (54%). Most had normal nutritional status, i.e., normal BMIZ, and were studying in primary school. Within the total, 3 had β thalassemia major, 42 with β thalassemia/Hb E, 56 with Hb H disease (with/without Hb Constant Spring [CS]/Hb Pakse [PS]), 25 with AE Bart's disease (with/without Hb CS/Hb PS), 2 with EF Bart's disease (with/without Hb CS), 16 with homozygous Hb E disease, and 6 having homozygous Hb CS disease.

Table 1. Patient characteristics.

	Total	N (%)
Mean age in years (SD)	150	9.1 (4.3)
Gender	150	
- **Male**		81 (54)
- **female**		69 (46)
BMIZ	150	
- **Underweight**		11 (7.3)
- **Normal**		118 (78.7)
- **Overweight**		10 (6.7)
- **Obese**		11 (7.3)
Education level	150	
- **Not attending school**		10 (6.7)
- **Kindergarten**		30 (20)
- **Primary school**		69 (46)
- **Secondary school**		33 (22)
- **Post-secondary education**		8 (5.3)
Household income (THB per month)	150	
- **<25,000**		41 (27.3)
- **≥25,000-50,000**		64 (42.7)
- **>50,000-75,000**		19 (12.7)
- **>75,000**		26 (17.3)
Type of payment	150	
- **Self-payment**		81 (54)
- **Universal Health Coverage Scheme (UC)**		42 (28)
- **Civil Servant Medical Benefit Scheme (CSMBS)/Reimbursement**		27 (18)
Transfusion dependency	150	
- **NTDT**		121 (80.7)
- **TDT**		29 (19.3)
Age at diagnosis (years)	150	
- **Mean (SD)**		3.3 (2.9)
- **<2**		60 (40)
- **≥2**		90 (60)
Age at first blood transfusion (years)	83	
- **Mean (SD)**		3.6 (2.8)
- **<4**		51 (61.4)
- **≥4**		32 (38.6)
Average hemoglobin (g/dL)	150	9.0 (1)
Iron chelation treatment	150	
- **Yes**		29 (19.3)
- **No**		121 (80.7)
Age at starting iron chelation (years)	29	6.6 (3.9)
Serum ferritin level (ng/mL)	148	
- **Mean (SD)**		408.9 (744.5)
- **<1000**		127 (85.8)
- **>1000-2500**		16 (10.8)
- **>2500**		5 (3.4)
Complications	150	
- **Yes**		21 (14)
- **No**		129 (86)
Comorbidities	150	
- **Yes**		31 (20.7)
- **No**		119 (79.3)

Values are expressed as frequency (percentage), mean (standard deviation: SD). Note: BMIZ, Z-score of body mass index; NTDT, transfusion-dependent thalassemia; TDT, non-transfusion dependent thalassemia; THB, Thai baht.

Almost 20% (19.3%) were TDT (three with β thalassemia major, 21 with β thalassemia/Hb E, 2 with Hb H disease, 3 with AE Bart's disease (with/without Hb CS/Hb PS), all receiving iron chelation therapy regularly. Around 55% (55.17%) of the patients (16/29) were receiving deferiprone (DFP), only one patient receiving deferasirox (DFX), and 12/29 were receiving combination therapy: eight with deferoxamine (DFO)+DFP and four with DFO+DFX.

The mean age (SD) at diagnosis, at first blood transfusion, and at starting iron chelation was 3.3 (2.9) years (range 0.1- 15 years), 3.6 (2.8) years (range 0.1 - 15 years), and 6.6 (3.9) years (range 2-17.7 years), respectively. Only 21 patients (14%) had complications, mostly endocrinal diseases, including vitamin D deficiency (14 patients), adrenal insufficiency (three), and short stature or growth failure (three). Hypogonadism, hypothyroidism, or hypoparathyroidism was not found in our participants. We screened for pulmonary hypertension only in TDT, NTDT with iron overload, and splenectomy patients due to hospital protocol; we had no cases of pulmonary hypertension. There was one case of gallstones. In the 20.7% of total patients with some sort of comorbidity, 45.2% suffered from allergic diseases, including seven cases of allergic rhinitis, four cases of asthma, and three cases of asthma with allergic rhinitis (data not shown).

HRQoL scores comparisons and correlations. The reliability of the PedsQL and EQ-5D-Y was very acceptable with Cronbach's alpha values > 0.7 (0.925 and 0.863, respectively). All mean (SD) scores for PedsQL and EQ-5D-Y self-reports, as well as proxy-reports, are seen in **Table 2**.

Quality of life scores were shown to have significant correlations between child self and parental proxy reports for both PedsQL and EQ-5D-Y. For mean PedsQL scores (SD), children's self-reports were slightly higher than parental proxies for two categories: total summary score (TSS) and PHS; only PHS was significantly different (p = 0.030), the others not being statistically significant. PCHS child and parental proxy reports were practically identical. EQ-5D-Y VAS showed a statistically significant correlation with the PedsQL TSS of both self-reports and proxy-reports: (r = 0.344, p = 0.001 and r = 0.271, p = 0.001, respectively). In addition, the EQ-5D-Y dimensions revealed statistically significant correlations with the PedsQL of both self-reports and proxy-reports. Significant relationships were found between the EQ-5D-Y dimensions of "mobility" "looking after myself" and "doing usual activities" with PedsQL PHS scores (r = -0.220 and -0.171; -0.477 and -0.138; -0.401 and -0.183: for self- and proxy-reports, respectively). Moderate correlations were also seen between the EQ-5D-Y dimensions of "having pain or discomfort" and "feeling worried, sad or unhappy" with the PedsQL PCHS scores (r = -0.271 and -0.254; -0.381 and -0.274: for self- and proxy-report, respectively). Please see **Supplementary Table 1**.

HRQoL scores and related factors. PedsQL child self-report and parent proxy-report scores along with patient demographic and clinical characteristics are in **Table 3** and **4**. Age group and type of payment demonstrated significant differences within self-reported TSS (p = 0.005 and 0.035). For parental proxy reports, child education level, parental marital status, household income, parent proxy education, and type of payment revealed significant differences in TSS (p = 0.027, 0.040, 0.009, 0.005 and < 0.001, respectively) in **Table 3**. Being TDT or NTDT, average Hb, and having iron-chelation therapy were all significantly related to self-reported TSS (p = 0.006, 0.017, and 0.014, respectively), as indicated in **Table 4**. In addition, transfusion dependency, average Hb, ferritin level and iron-chelation therapy were also associated with parental proxy TSS (p = < 0.001, 0.047, < 0.001, and < 0.001, respectively); these patients typically had lower self-assessed HRQoL scores.

Figure 1 shows proxy and self-report EQ-5D-Y dimensions. Having some or many problems in "suffering pain or discomfort" (49.4% child report and

Table 2. Quality of life scores: comparisons and correlations among child self-reports and parent proxy-reports.

Scales	Child self-report Mean (SD)	Parent proxy-report Mean (SD)	Correlation coefficient (r) (p)	Comparison (p)
PedsQL (N=121) - Total summary score	81.00 (10.94)	78.84 (16.72)	0.456 (<0.001*)	0.203
- Physical health summary score	84.43 (12.31)	80.06 (20.26)	0.384 (<0.001*)	0.030*
- Psychosocial health summary score	77.56 (12.63)	77.61 (15.85)	0.416 (<0.001*)	0.976
• **Emotional function**	75.79 (16.99)	79.40 (17.10)	0.360 (<0.001*)	0.084
• **Social function**	87.07 (15.20)	84.87 (17.91)	0.428 (<0.001*)	0.275
• **School function**	69.83 (15.95)	67.79 (20.83)	0.406 (<0.001*)	0.359
EQ-5D-Y (N=85) - EQ-5D VAS	89.27 (11.56)	86.72 (10.62)	0.334 (0.001*)	0.070

Values are expressed as mean (standard deviation: SD) and Pearson's or Spearman's rank correlation coefficient, r. Statistical method used: Pearson's or Spearman's rank correlation coefficient; and Mann-Whitney U, independent sample t-test as appropriate; p < 0.05 was considered statistically significant. Note: VAS, visual analog scale.

Table 3. PedsQL scores from child self-reports and parent proxy-reports by demographic characteristics.

Characteristics	Child self-report (n = 121)			Parent proxy-report (n = 150)		
	TSS Mean (SD)	PHS Mean (SD)	PCHS Mean (SD)	TSS Mean (SD)	PHS Mean (SD)	PCHS Mean (SD)
Age (years) (n=150)						
- **2-4 (n=29)**	NA	NA	NA	84.39 (14.58)	86.31 (18.29)	82.45 (14.81)
- **5-7 (n=38)**	83.86 (8.01)	88.87 (8.71)	78.86 (10.41)	77.45 (17.52)	79.36 (22.19)	75.53 (15.20)
- **8-12 (n=50)**	77.17 (12.73)	80.00 (14.91)	74.33 (13.81)	75.38 (17.20)	76.56 (20.12)	74.20 (16.79)
- **13-18 (n=33)**	83.49 (9.38)	86.01 (9.13)	80.96 (12.26)	80.81 (15.98)	80.68 (19.35)	80.94 (14.94)
***p*-value**	0.005*	0.002*	0.047*	0.108	0.229	0.066
Gender (n=150)						
- **Male (n=81)**	79.79 (12.11)	83.22 (13.35)	76.36 (13.60)	79.06 (17.06)	81.14 (20.35)	76.97 (16.10)
- **Female (n=69)**	82.39 (9.33)	85.83 (10.94)	78.96 (11.36)	78.59 (16.44)	78.81 (20.24)	78.37 (15.63)
***p*-value**	0.193	0.246	0.261	0.864	0.485	0.594
BMIZ (n=150)						
- **Underweight (n=11)**	77.73 (7.82)	78.49 (7.07)	76.97 (11.15)	71.28 (16.03)	70.74 (21.84)	71.82 (13.59)
- **Normal (n=118)**	81.19 (11.51)	84.99 (13.08)	77.39 (12.89)	79.92 (16.97)	81.20 (20.18)	78.63 (16.04)
- **Overweight/obese (n=21)**	81.99 (9.62)	85.17 (9.96)	78.80 (12.68)	76.75 (15.07)	78.57 (19.50)	74.92 (15.55)
***p*-value**	0.565	0.246	0.900	0.217	0.246	0.279
Education level						
- Not attending school/kindergarten (n=40)	86.48 (6.28)	89.77 (10.18)	83.18 (5.70)	83.90 (13.90)	85.86 (18.01)	81.94 (14.33)
- Primary school (n=69)	79.12 (12.11)	83.68 (13.69)	74.57 (13.28)	75.20 (18.29)	76.45 (21.92)	73.94 (16.59)
- Secondary school/ post-secondary education (n=41)	82.67 (9.10)	84.25 (10.07)	81.10 (11.54)	80.04 (15.31)	80.49 (18.43)	79.58 (14.88)
***p*-value**	0.055	0.313	0.009*	0.027*	0.063	0.025*
Household income (THB per month) (n=150)						
- **≤50,000 (n=105)**	80.18 (11.34)	84.04 (12.94)	75.41 (15.35)	76.68 (17.37)	77.20 (21.31)	76.15 (15.76)
- **>50,000 (n=45)**	82.86 (9.89)	85.31 (10.87)	80.40 (11.37)	83.89 (14.01)	86.74 (15.85)	81.04 (15.69)
***p*-value**	0.216	0.603	0.100	0.009*	0.003*	0.083
Parental marital status (n=150)						
- **Marriage (n=117)**	80.99 (10.88)	84.36 (11.69)	77.62 (12.87)	80.52 (15.71)	82.08 (18.68)	78.96 (15.65)
- **Divorce (n=33)**	81.01 (11.35)	84.63 (14.42)	77.38 (12.02)	72.87 (18.97)	72.92 (24.08)	72.83 (15.86)
***p*-value**	0.906	0.911	0.861	0.040*	0.049*	0.049*
Parent proxy (parent or guardian) educational level (n=150)						
- **Primary school (n=23)**	80.89 (13.16)	83.53 (15.81)	78.25 (14.00)	81.81 (14.19)	85.33 (16.00)	78.28 (14.93)
- **Secondary school (n=49)**	81.31 (9.79)	85.24 (11.56)	77.37 (11.83)	72.52 (17.42)	71.56 (22.28)	73.48 (15.44)
- **Post-secondary education (n=78)**	80.82 (11.02)	84.20 (11.59)	77.44 (12.85)	81.94 (16.02)	83.86 (18.52)	80.01 (16.03)
***p*-value**	0.976	0.860	0.963	0.005*	0.001*	0.075
Type of payment (n=150)						
- **Self-payment (n=81)**	81.44 (8.73)	83.99 (10.23)	77.65 (13.93)	78.42 (15.06)	80.79 (18.72)	76.05 (14.59)
- **Universal Health Coverage Scheme (UC) (n=42)**	77.84 (13.90)	82.70 (15.80)	72.98 (16.01)	73.06 (19.13)	73.21 (22.85)	72.90 (17.21)
- **Civil Servant Medical Benefit Scheme (CSMBS)/ Reimbursement (n=27)**	85.37 (9.43)	88.84 (10.06)	81.90 (11.07)	89.10 (12.81)	88.54 (17.27)	89.65 (11.09)
***p*-value**	0.035*	0.172	0.016*	<0.001*	0.007*	<0.001*

Values are expressed as mean **(**standard deviation; SD**)**; Statistical method used**:** Mann-Whitney U, Independent sample t-test or One-way ANOVA, as appropriate; *****$p < 0.05$ was considered statistically significant**.** Note**:** NA, not applicable; PCHS, psychosocial health summary; PHS, physical health summary score; THB, Thai baht; TSS, total summary score.

61.3% parental proxy) and "feeling worried, sad or unhappy" (40% child and 27.3% parental proxy) was reported more often than for "doing usual activities" (21.2% child and 18% parental proxy) and "mobility" (15.3% and 13.3%). "Looking after myself" seemed to pose the least difficulty: 7.1% and 12%. Mobility was the sole area with more problems for TDT patients versus NTDT from parental proxy perspectives (p =

Table 4. PedsQL scores from child self-reports and parent proxy-reports by clinical characteristics.

Characteristics	Child self-report (n = 121)			Parent proxy-report (n = 150)		
	TSS Mean (SD)	PHS Mean (SD)	PCHS Mean (SD)	TSS Mean (SD)	PHS Mean (SD)	PCHS Mean (SD)
Transfusion dependency (n=150)						
- **NTDT (n=121)**	82.43 (9.23)	85.63 (10.50)	79.24 (10.48)	81.85 (15.06)	83.50 (18.32)	80.21 (14.77)
- **TDT (n=29)**	75.99 (14.64)	80.24 (16.78)	71.73 (17.25)	66.27 (17.71)	65.73 (21.96)	66.80 (15.87)
***p*-value**	0.006*	0.124	0.039*	<0.001*	<0.001*	<0.001*
Age at diagnosis (years) (n=150)						
- **<2 (n=60)**	78.78 (13.38)	82.03 (14.89)	75.53 (14.46)	80.29 (15.42)	80.99 (19.88)	79.58 (14.11)
- **≥2 (n=90)**	82.26 (9.13)	85.79 (10.42)	78.72 (11.39)	77.88 (17.56)	79.45 (20.60)	76.30 (16.86)
***p*-value**	0.130	0.106	0.182	0.388	0.649	0.199
Age at first blood transfusion (years) (n=83)						
- **<4 (n=51)**	77.55 (13.22)	82.20 (15.09)	72.91 (15.04)	73.98 (18.14)	74.88 (22.02)	73.08 (16.78)
- **≥4 (n=32)**	82.05 (8.32)	84.82 (9.89)	79.28 (10.00)	80.43 (17.15)	80.76 (19.10)	80.09 (16.48)
***p*-value**	0.104	0.406	0.033*	0.112	0.216	0.066
Average hemoglobin (g/dL) (n=150)						
- **7-9 (n=90)**	79.76 (10.57)	83.65 (11.89)	75.86 (12.84)	76.72 (17.53)	77.33 (20.78)	76.11 (16.59)
- **>9-10.5 (n=47)**	80.62 (11.32)	83.64 (13.26)	77.60 (12.14)	80.24 (15.91)	82.45 (20.22)	78.04 (14.97)
- **>10.5 (n=13)**	89.03 (9.30)	90.87 (11.01)	87.18 (8.26)	88.44 (9.04)	90.39 (11.58)	86.50 (10.70)
***p*-value**	0.017*	0.136	0.011*	0.047*	0.058	0.084
Serum ferritin level (ng/mL) (n=148)						
- **<1,000 (n=127)**	81.90 (9.34)	85.25 (10.63)	78.55 (10.98)	81.01 (15.60)	82.43 (19.00)	79.59 (15.16)
- **≥1,000 (n=21)**	75.59 (16.50)	79.77 (18.53)	71.40 (18.54)	66.03 (17.62)	65.92 (22.12)	66.14 (15.24)
***p*-value**	0.121	0.226	0.119	<0.001*	<0.001*	<0.001*
Iron chelation treatment (n=150)						
- **None (n=121)**	82.43 (9.24)	85.50 (10.62)	79.36 (10.39)	81.82 (14.91)	83.47 (18.08)	80.16 (14.74)
- **Oral chelation (n=17)**	74.20 (15.44)	78.71 (14.97)	69.69 (19.34)	63.60 (19.45)	62.50 (22.13)	64.71 (18.45)
- **Combined iron chelation (n=12)**	78.58 (13.65)	83.52 (19.22)	73.64 (14.20)	70.38 (16.66)	70.57 (24.12)	70.19 (12.20)
***p*-value**	0.014*	0.121	0.009*	<0.001*	<0.001*	<0.001*
Complications						
- **Yes (n=21)**	82.61 (9.32)	83.64 (10.27)	81.53 (11.31)	81.45 (15.38)	82.89 (16.67)	80.00 (15.79)
- **No (n=129)**	80.67 (11.25)	84.58 (12.71)	76.01 (14.81)	78.42 (16.95)	79.60 (20.81)	77.23 (15.88)
***p*-value**	0.471	0.756	0.119	0.443	0.493	0.459
Comorbidities						
- **Yes (n=31)**	81.43 (12.20)	85.29 (13.41)	77.56 (13.08)	74.32 (17.33)	74.80 (20.33)	73.83 (17.13)
- **No (n=119)**	80.88 (10.64)	84.19 (12.05)	77.56 (12.57)	80.02 (16.43)	81.43 (20.10)	78.60 (15.42)
***p*-value**	0.820	0.688	0.999	0.091	0.105	0.137

Values are expressed as mean **(**standard deviation; SD**)**; Statistical method used**:** Mann-Whitney U, independent sample t-test or one-way ANOVA, as appropriate; *****p < 0.05 was considered statistically significant. Note**:** NA, not applicable; NTDT, transfusion-dependent thalassemia; PCHS, psychosocial health summary; PHS, physical health summary score; TDT, non-transfusion dependent thalassemia; TSS, total summary score.

0.004) (data not shown). Significant differences were seen in parental proxy reports for EQ-5D-Y VAS regarding the type of payment and serum ferritin levels. Those using any reimbursement and patients with lower ferritin levels had higher EQ-5D-Y VAS compared to those with self-payment or under UC coverage with higher ferritin levels (p = 0.026 and 0.031) (data not shown).

Linear regression analysis for predictors of HRQoL scores. Using a forward stepwise linear regression method for our final model, age group and iron chelation treatment were independently associated with child self-report PedsQL TSS (R2 = 0.118, p = 0.001) (**Table 5A**). An age of 8-12 years negatively predicted PedsQL TSS versus one of 5 - 7 years (p = 0.011). Oral chelation therapy reduced PedsQL TSS significantly as compared to those having no iron chelation (p = 0.005). The same regression model examined factors affecting PedsQL TSS for parental proxy-reports: **Table 5B**.

This TSS was predicted by children's education, proxy education, type of payment, and TDT (R = 0.239, p < 0.001). Primary school children appeared to experience negative impacts, according to their parents/guardians, as opposed to those not attending school or in kindergarten (p = 0.029). Parent proxies

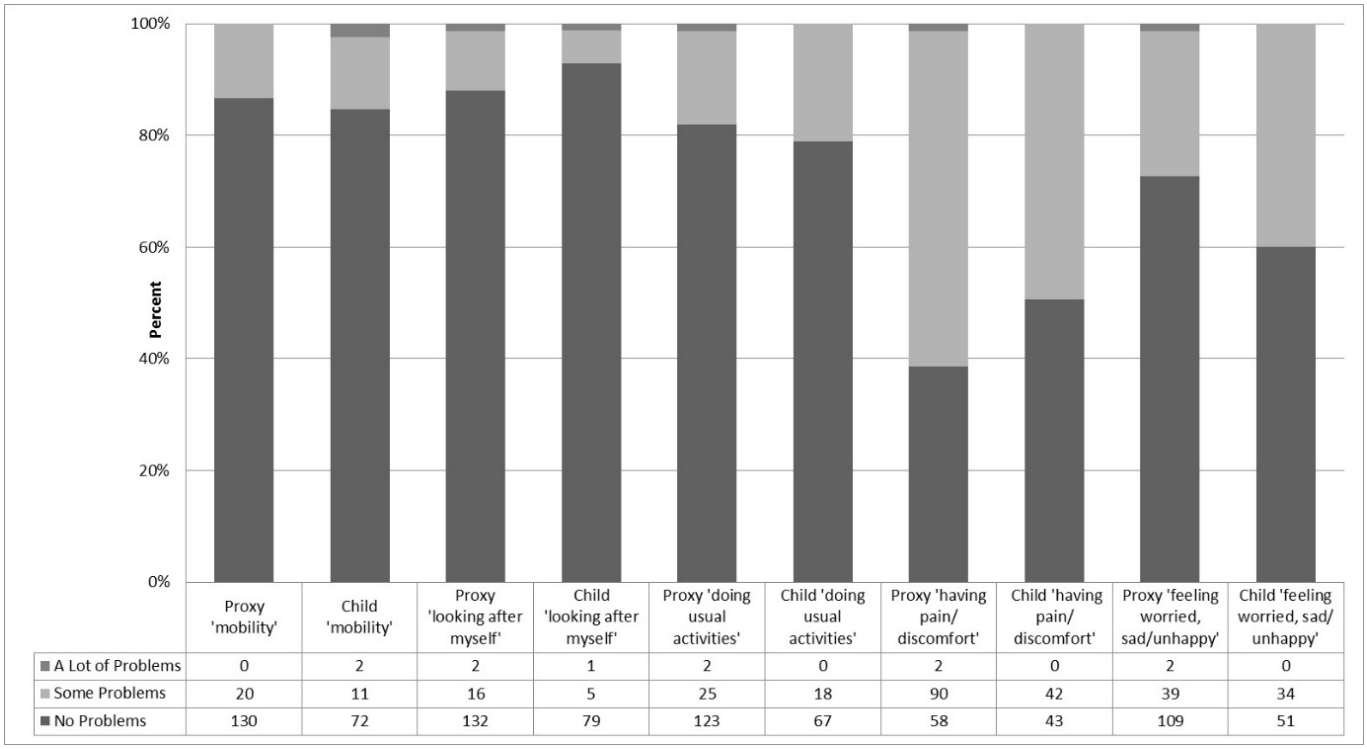

Figure 1. Distribution of EQ-5D-Y dimensions from child self-reports (N = 85) and parent proxy-reports (N = 150).

Table 5. Multivariate linear regression predicting PedsQL TSS scores of child self-report and parent proxy-report and EQ-5D-Y VAS of parent proxy-report.

A. PedsQL TSS scores of child self-reports.					
Characteristics	**Coefficients (β)**	**SE (β)**	***p*-value**	**95%CI**	***p*-value**
Child self-report ($p = 0.001$*)					
Age (years)					0.006*
- **5-7**	-	-	-	-	
- **8-12**	-5.79	2.25	0.011*	-10.24 to -1.33	
- **13-18**	0.93	2.49	0.709	-3.99 to 5.86	
Iron chelation treatment					0.018*
- **None**	-	-	-	-	
- **Oral chelation**	-8.09	2.83	0.005*	-13.69 to -2.48	
- **Combined iron chelation**	-2.32	3.31	0.486	-8.88 to 4.24	

B. PedsQL TSS scores of parent proxy-reports.					
Characteristics	**Coefficients (β)**	**SE (β)**	***p*-value**	**95%CI**	***p*-value**
Parent proxy-report ($p < 0.001$*)					
Child education level					0.040*
- **Not attending school /kindergarten**	-	-	-	-	
- **Primary school**	-6.63	3.00	0.029*	-12.57 to -0.69	
- **Secondary school**	-0.73	3.31	0.826	-7.28 to 5.82	
Proxy education level					0.008*
- **Primary school**	-	-	-	-	
- **Secondary school**	-10.67	3.72	0.005*	-18.02 to -3.31	
- **Post-secondary education**	-4.10	3.64	0.262	-11.29 to 3.09	
Type of payment					0.011*
- **Self-payment**	-	-	-	-	
- **Universal Health Coverage Scheme (UC)**	2.93	3.64	0.385	-3.72 to 9.58	
- **Civil Servant Medical Benefit Scheme (CSMBS)/ Reimbursement**	10.18	3.34	0.003*	3.57 to 16.79	
Transfusion dependency					<0.001*
- **NTDT**	-	-	-	-	
- **TDT**	-14.38	3.67	<0.001*	-21.63 to -7.12	

C. EQ-5D-Y VAS of parent proxy-reports.					
Characteristics	**Coefficients (β)**	**SE (β)**	***p*-value**	**95%CI**	***p*-value**
Parent proxy-report ($p = 0.024$*)					
Type of payment					0.011*
- **Self-payment**	-	-	-	-	
- **Universal Health Coverage Scheme (UC)**	-5.23	1.99	0.009*	-9.15 to -1.30	
- **Civil Servant Medical Benefit Scheme (CSMBS)/ Reimbursement**	0.13	2.32	0.955	-4.46 to 4.71	

Values are expressed as coefficients **(**β**)**, SE **(**standard error**)**, 95**%** CI **(**confidence interval**)**; Statistical method used**:** forward stepwise linear regression; ***p* < 0.05 was considered statistically significant. Note**:** NTDT, transfusion-dependent thalassemia; TDT, non-transfusion dependent thalassemia; TSS, total summary score; VAS, visual analog scale.

with a secondary school education seemed to have lower TSS compared to parents/guardians with less education ($p = 0.005$). Parental proxy reports of TDT patients displayed poorer TSS than those children with NTDT ($p < 0.001$). Interestingly, there was a positive relationship between TSS and medical payment by

Civil Servant Medical Benefit Scheme (CSMBS) or any reimbursement scheme versus self-payment ($p = 0.003$). UC negatively predicted parental proxy EQ-5D-Y VAS in comparison with self-payment ($p = 0.009$) ($R = 0.037$, $p = 0.024$) (**Table 5C**).

Discussion. In this single-institution study of HRQoL in Thai children with thalassemia, we compared the unique perspectives of children and their parent proxies from two discrete instruments*:* PedsQL and EQ-5D-Y**.** A wealth of research using PedsQL in pediatric patients with thalassemia[10,15-18] generally shows it to be a reliable and valid tool for healthy and chronically-ill children**.** While the EQ-5D-Y has also been used in chronic illness, we could not find any reports of it for children with thalassemia; our study may be the first**.** Two other studies have examined children with thalassemia using different versions: EQ-5D and EQ-5D-3L.[22,23]

EQ-5D-Y appears to have some favorable attributes*:* the questionnaire is relatively quick and straightforward for participants to complete and appropriately comprehensible for each cognitive-developmental stage**.**[14,24,25] However, we should also note that the EQ-5D-Y does not cover some aspects of child HRQoL, such as some psychometric properties and family relationships, which are covered by other generic instruments like PedsQL**.**[26] In addition, the EQ-5D-Y can be used with confidence in acutely-ill children but has not been as good in chronic disorders or healthy children**.**[27] This study supported that EQ-5D-Y was proper to assess in chronically-ill children, like thalassemia, rapidly.

In place of any existing research with pediatric thalassemia, we compared our patients' EQ-5D-Y dimensions with studies on children having a different chronic illness such as cystic fibrosis in Germany, diabetes mellitus in Spain, and chronic kidney disease in Taiwan**.**[28-30] Our thalassemia patients reported more difficulties in pain*/*discomfort and anxiety*/*depression as compared to their usual activities, mobility, and self-care; this mirrored the previous research**.** It might be assumed that the children experience more psychosocial challenges versus physical hindrances**.** Further research needs to be done using EQ-5D-Y with pediatric thalassemia patients in other settings and certainly over the long term**.**

The study demonstrated both EQ-5D-Y VAS and dimensions had statistically significant correlations with the PedsQL TSS, PHS, and PCHS, particularly of both child and parent proxy reports. Parental proxy scores were also in line with the children's from both PedsQL and EQ-5D-Y and which is consistent with our prior research using PedsQL[16,31,32] solely. In other research,[15,16,33] parent proxy-rated HRQoL scores were typically lower than child-rated ones. Notably, for us, only the PHS for parent proxy-rated PedsQL was significantly lower ($p = 0.030$); our TSS were slightly lower but not significantly. Regarding this lower TSS, we can speculate parent proxies may be more concerned about the current and future effects of their child's physical disability, i.e., financial burdens, social interactions, etc., than these young children are at present. However, for the significantly lower PHS, parents/guardians may be merely relying on what they can observe of their child's suffering. This topic could be useful to explore in future research. Children rated their psychosocial health lower than their physical health in the PedsQL, particularly for the scholarly function; this also matches several past studies.[10,15-18,24] Perhaps this is due to frequent school absences, restrictions within social activities at school, physical pain from medical procedures such as venipuncture, intravenous access for transfusion, or injection, or even lower self-esteem.

We were pleasantly surprised that all of our current parental proxy and self-reported HRQoL scores were noticeably higher when compared to a decade-old report that was written pre-implementation of the TIF guidelines, from our hospital.[16] It is hoped this is a result of consistent improvements in medical care over the last ten years, but it may also reflect a broader social acceptance of chronic illnesses and other external changes. The implementation of the TIF

guidelines toward improving thalassemia care management at our hospital, better subspecialty pediatric care, and greater availability of oral iron chelation drugs may have raised HRQoL scores. Better health care is likely to have resulted in less pain and discomfort for patients and improved social interactions and functions. One important point may be the ability to have subcutaneous administration equipment at home in cases requiring combined iron chelation. Although the procedure remains physically uncomfortable, it may be more convenient for children and parents/guardians to have this take place in the home.

It must be noted that our lower ratio of TDT versus NTDT, 1/5 of the patients in this paper as compared to 1/3 in the past, may have resulted in higher HRQoL than previously. While it may merely be that patients are happier because their disease is less severe, this finding requires further examination as we had twice the number of participants here: 150 versus the 75 before. This lower proportion of TDT may be the longer-term outcomes of the national screening policy for severe types of thalassemia, coupled with the better general social awareness of thalassemia and its effects.

This study examined predictors of HRQoL using stepwise linear regression from both PedsQL and EQ-5D-Y VAS. For the PedsQL, age was significantly associated with HRQoL according to children's self-report data, similar to prior reports.[10,34] Patients 8-12 years old had lower HRQoL, leading to us to see this age group as a negative predictor. As this age group often experiences a transition from preschool to elementary school, they may be worried about their learning ability or school absences. As they grow older, children naturally become more aware of any differences from their peers.

For our patients, iron chelation therapy, particularly oral chelation, significantly and negatively impacted HRQoL. Leafy MS et al.[35] observed all patients experienced burden with chelation, no matter which type. Similarly, Thavorncharoensap et al.[10] stated that iron chelation treatment was associated with poorer HRQOL. Three other studies found that patients using oral chelators, especially deferasirox, had a better quality of life versus those using injectable forms.[22,36,37] However, we must state that these findings may differ from ours due to the particular breakdown of our chelation patients. First of all, only 29/150 of our patients received any kind of chelation therapy (**Table 4**), which is relatively low. Of these 29 patients, 17 used oral chelation, and 12 used combined oral/injection.

Moreover, most of our patients use deferiprone versus deferasirox as it is cheaper and more accessible in Thailand. We imagine that any patients taking oral chelation already are experiencing iron overload and more likely to develop complications related to this; thus, they would have a worse quality of life in relation to more severe disease. Medications' side effects and the burden of compliance would likely be factors to explore further.

Parental proxy-reports for PedsQL outlined some unique and significant associations with HRQoL: child education, proxy education, type of payment, and transfusion dependency. Similar to the self-reports, parents/guardians also believed that primary school children had lower HRQoL. Caregivers may be concerned about both social integration and school performance at this age. Furthermore, our results seemed to show that parental proxy education at the secondary school level was significantly correlated with lower perceived children's HRQoL; university education was as well but not significantly. A subgroup analysis of the impact of parental education on HRQoL (N=129: 94 mothers and 35 fathers) also revealed a concordance in which parents with secondary school completion had the lowest PedsQL TSS (p = 0.037, data not shown). Our datum does not appear to concur with an Egyptian and Iraqi paper that reported high levels of parental education were associated with higher HRQoL outcomes.[18,32,36] It is only speculation at this point, but perhaps caregivers who completed secondary school in Thailand are more anxious about the challenges their children might face, or this might merely be a cultural difference. Thailand people with less education could be more inclined to trust the public health care system, whereas those with more education may be prone to have more doubt as they may have access to alternatives. This tendency should be further explored by an in-depth interview study.

Family economic status appeared to play a significant role in the PedsQL measurement of HRQoL, similar to the previous Thai study.[16] For example, CSMBS/any reimbursement system had positive impacts on parental proxy perspectives. Probably, the type of payment is, in itself, a proxy for familial disposable income and access to financial assets. Besides, CSMBS and the other reimbursement schemes offer a wider variety of treatment choices and convenience. This is especially relevant for the location of treatment, as people under UC are obligated to seek care in the region where they were registered, and sometimes families work and live elsewhere. Indeed, parental proxy reports showed that the Use of UC negatively predicted the EQ-5D-Y VAS, in comparison with self-payment.

Overall, all PedsQL scores, both parental and child proxies, were lower for children who were TDT. Unsurprisingly, parent proxies of children with TDT reported significantly lower TSS than NTDT parent proxies, after using multivariate linear regression. This finding is in line with prior research[10,16,18] and is likely because of disease severity along with the inconvenience and perceived distress during treatment,

as mentioned before. However, another Thai study[15] in teenagers with thalassemia reported no differences in PedsQL scores between TDT and NTDT; this latter paper had a higher amount of TDT patients. The differing scores may be a result of attitude changes with age.

The most critical limitation in our study is the absence of a control group of healthy children. It would be useful to repeat this work incorporating healthy controls with the EQ-5D-Y, to see if the results still stand, along with the PedsQL. The EQ-5D-Y may indeed be appropriate for children with thalassemia; however, this is unknown at this point as we have no other research to compare it with. It certainly would be appropriate to repeat this study in five or ten years and see if scores improve or reduce in line with public policy and health care access. A higher number of participants, along with data from other centers, would also give a clearer picture of HRQoL.

Conclusions. This is the first study attempting to use the EQ-5D-Y with Thai pediatric thalassemia patients, comparing EQ-5D-Y and PedsQL scores from parent proxies and children. Within our limited data, it appears the EQ-5D-Y might be useful for measuring the quality of life in these children. Predictors of lower HRQoL scores, according to self-report, included the age of 8 - 12 years and oral chelation. Parental proxy-report predictors of lower scores were primary school education for children, secondary school parental proxy education, UC healthcare payment, and transfusion dependency. Overall, HRQoL scores were higher from our institution's report ten years ago; this may be due to better management guidelines as well as a better standard of care, including access to more specialists. Further long-term research needs to take place, especially to improve the quality of life for TDT patients.

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Supplementary Table.

Supplementary Table 1. Correlations between PedsQL and EQ-5D-Y dimensions and VAS among child self-reports and parent proxy-reports.

A. Child self-reports.

HRQoL	PedsQL Total summary score	PedsQL Physical health summary score	PedsQL Psychosocial health summary score
EQ-5D-Y Dimension 1: "Mobility"	-0.334 $p = 0.002$*	-0.220 $p = 0.001$*	-0.372 $p < 0.001$*
EQ-5D-Y Dimension 2: "Looking after myself"	-0.443 $p < 0.001$*	-0.477 $p < 0.001$*	-0.313 $p = 0.004$*
EQ-5D-Y Dimension 3 "Doing usual activities"	-0.372 $p < 0.001$*	-0.401 $p < 0.001$*	-0.261 $p = 0.016$*
EQ-5D-Y Dimension 4 "Having pain or discomfort"	-0.256 $p = 0.018$*	-0.228 $p = 0.036$*	-0.227 $p = 0.036$*
EQ-5D-Y Dimension 5 "Feeling worried, sad or unhappy"	-0.404 $p < 0.001$*	-0.337 $p = 0.002$*	-0.381 $p < 0.001$*
EQ-5D-Y VAS	-0.334 $p = 0.001$*	0.253 $p = 0.019$*	0.357 $p = 0.001$*

B. Parent proxy-reports.

HRQoL	PedsQL Total summary score	PedsQL Physical health summary score	PedsQL Psychosocial health summary score
EQ-5D-Y Dimension 1: "Mobility"	-0.194 $p = 0.017$*	-0.171 $p = 0.036$*	-0.191 $p = 0.019$*
EQ-5D-Y Dimension 2: "Looking after myself"	-0.171 $p = 0.036$*	-0.138 $p = 0.092$	-0.185 $p = 0.023$*
EQ-5D-Y Dimension 3 "Doing usual activities"	-0.245 $p = 0.003$*	-0.183 $p = 0.025$*	-0.282 $p < 0.001$*
EQ-5D-Y Dimension 4 "Having pain or discomfort"	-0.249 $p = 0.002$*	-0.213 $p = 0.009$*	-0.254 $p = 0.002$*
EQ-5D-Y Dimension 5 "Feeling worried, sad or unhappy"	-0.276 $p = 0.001$*	-0.242 $p = 0.003$*	-0.274 $p < 0.001$*
EQ-5D-Y VAS	0.271 $p = 0.001$*	0.191 $p = 0.019$*	0.328 $p = 0.001$*

Values are expressed as Pearson's or Spearman's rank correlation coefficient, r. Statistical method used**:** Pearson's or Spearman's rank correlation coefficient as appropriate; $p < 0.05$ was considered statistically significant. Note**:** VAS, visual analog scale.