

# EQ-5D-3L Health State Utility Values in Transfusion-dependent thalassemia Patients in Malaysia: A Cross-sectional Assessment

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## Research

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## Abstract

**Purpose:** There is a gap of information describing the health state utility values (HSUVs) of Transfusion-dependent Thalassemia (TDT) patients in Malaysia. These values are useful in the assessment of health-related quality of life (HRQoL), economic evaluations and provide guidance to disease management decisions. The objective of this study was to estimate and derive HSUVs associated with the treatment and complications of TDT patients in Malaysia using the EQ-5D-3L instrument.

**Methods:** A cross-sectional survey using the EQ-5D-3L instrument was conducted between May to September 2018 across various public hospitals in Malaysia. Using a multi-stage sampling, patients diagnosed with TDT and receiving iron chelating therapy were sampled. The findings on the EQ-5D-3L survey were converted into utility values using local tariff values. A two-part model was used to examine and derive health state utility values associated with the treatment and complications of iron overload in TDT.

**Results:** A total of 585 patients were surveyed. The unadjusted mean (SD) EQ-5D-3L utility value for TDT patients were 0.893 (0.167) while mean (SD) EQ VAS score was 81.22 (16.92). Patients who had more than two iron overload complications had a significant decline in HRQoL. Patients who were on oral monotherapy had a higher utility value of 0.9180 compared to other regimen combinations.

**Conclusion:** Lower EQ-5D-3L utility values were associated with patients who developed iron overload complications and were on multiple iron chelating agents. Emphasizing compliance to iron chelating therapy to prevent the development of complications is crucial in the effort to preserve the HRQoL of TDT patients.

## Background:

Thalassemia is the most prevalent hereditary hematologic disorder worldwide, with a 4.83% carrier rate<sup>1,2</sup>. In Malaysia, there is an estimated carrier rate of 3.5-4.0%<sup>3</sup> and an estimated annual birth rate of 2.1/1000<sup>4</sup>. As of August 2018, the Malaysian Thalassemia Registry reports that there are 7,984 thalassemia patients in the country and the numbers have increased since 2009<sup>5,6</sup>. Transfusion-dependent thalassemia (TDT) is an inherited blood disease characterized by the absence or decreased synthesis of one or more globin chains in the haemoglobin molecule, leading to chronic anaemia. Treatment for this condition involves a combination of blood transfusion to correct the anaemia, followed by iron chelating therapy to remove the excess iron resulting from the transfusion<sup>7</sup>.

The diagnosis of TDT has shown to affect a patient's health-related quality of life (HRQoL)<sup>8</sup> and should be considered as an important index when evaluating treatment outcomes as it can be used to inform patient management and policy decisions<sup>9</sup>. Several studies have been conducted in Malaysia to assess the HRQoL of TDT patients. In 2006, a cross sectional study compared the HRQoL of TDT children with healthy controls using the PedsQL 4.0 generic core scale. The study found that the diagnosis of TDT negatively impacts the HRQoL of children compared to their healthy counterparts<sup>10</sup>. Patients undergo physical changes such as the development of thalassemia facies and stunted growth. The recurrent blood transfusion increases their risk of developing iron overload complications such as cardiac complications and diabetes, adding on to the disease burden<sup>7</sup>. The long-term use of medications, frequent hospital visits and fatigue brought about by the chronic anaemia disrupts their ability to function and can cause emotional distress<sup>11</sup>. Another study conducted between 2008 and 2009 using the same instrument found that predictors for a poor HRQoL in TDT children and adolescents included the absence of blood transfusion and iron chelation therapy<sup>12</sup>. A 2009 study conducted with Medical Outcomes Study Short Form 36-item (MOS SF-36) survey instrument aimed to measure the HRQoL of paediatric TDT patients on subcutaneous deferoxamine. The study found the use of optimum dosage deferoxamine reduces the risk of developing iron overload complications and provides a better quality of life to patients<sup>13</sup>. In 2013, another study focused on comparing the HRQoL scores of patients who self-reported and caregivers who proxy-reported using the PedsQL™. Caregivers who proxy-reported were found to underestimate the HRQoL of TDT patients. In addition, the caregivers' HRQoL were summarized based on the number of reported problems on each dimension of the EQ-5D<sup>14</sup>.

However, these studies have been limited to the paediatric and adolescent TDT population. Apart from that, the HRQoL instruments used were non-preference-based instruments, making it difficult to use the study outcomes in economic evaluations, as the scores are not 'weighted' and does not have 'value' attached to it. Value is measured in terms of 'preference' for a health state<sup>15</sup>. The generic preference-based EQ-5D-3L instrument was developed by the EuroQol Group for this purpose. It consists of a descriptive system and the EQ-5D visual analogue scale (EQ VAS). The responses on the descriptive system is used to form a unique health state which is subsequently converted into a single index value known as a health state utility value (HSUV). These values are obtained from a standardized valuation exercise obtained from the general population in a country. This ensures that the values represent the societal perspective.

As of date, there is no study that describes the HSUV for the transfusion-dependent thalassemia population in the country. Thus, the objective of this study was to survey the HSUVs and health profiles of both paediatric and adult transfusion-dependent thalassemia (TDT) patients in Malaysia using the EQ-5D-3L instrument. The availability of a validated Malay version of the questionnaire and a country-specific general population tariff in Malaysia makes the use of the EQ-5D-3L instrument ideal<sup>16</sup>. In addition to that, this study aims to derive health state utility values based on the iron chelating agent regimen used and the various iron overload complications associated with the condition. These HSUVs would be key drivers in cost effectiveness analyses as estimates of quality-adjusted life years (QALYs) are obtained by multiplying these utility values with the time spent in the health state.

## Methods:

### Study design and participant recruitment

This cross-sectional study was conducted between May to September 2018 in Malaysia. Participants were selected using multi-stage sampling. In the first stage, Malaysia is divided into five clusters based on its geographical location; the northern states (Penang and Perak), the central states (Selangor, the Federal Territory of Kuala Lumpur and Negeri Sembilan), the southern state (Johore), the east coast states (Pahang, Kelantan and Terengganu) and the east Malaysian states (Sabah and Sarawak). In the second stage, a non-probability sampling was used to sample patients from each region.

The sample size was determined using the population prevalence formula. Based on a population 7,984<sup>5</sup>, 5% precision rate, 95% confidence level and an assumption<sup>17</sup> of 50% disease prevalence, an estimated sample of 367 should be recruited. Recruitment criteria includes patients aged three years and above, a diagnosis of transfusion-dependent thalassemia, has received treatment of iron chelating therapy for at least six months and a proficiency in English or the Malay language to complete the surveys. Patients who defaulted treatment or regular follow up for at least a year, have impaired cognitive function, a diagnosis of non-transfusion dependent thalassemia or other hemoglobinopathies were excluded from this study.

## Data collection

One month prior to data collection, a nationwide training of interviewers was conducted. To ensure consistency of data collection, manuals were distributed to the interviewers. Interviewers were given a set of forms consisting of a patient information sheet, informed consent forms for participation, parental consent form, age appropriate assent forms, EQ-5D-3L instrument and data collection form capturing patient's sociodemographic data, and medical history. Study coordinators visited study sites to randomly validate the data collection forms with the medical records to ensure accuracy of the collected data before the end of the data collection period.

Patients were screened and selected by the trained interviewers when they came in for routine follow up based on the inclusion and exclusion criteria. Prior to the face-to-face interview, both the patients & parents (if proxy-reported) were briefed about the objective of the study and assured that information collected would remain confidential. Informed consents and the child's assent were obtained upon agreement to participate. Parents or caregivers were requested to answer the questionnaires on behalf of children aged between 3 to 12 years of age. Adolescents above 12 years old were given the choice to self-report their own quality of life or if they could not, a parent proxy-report was done. Patients aged 18 years and above were expected to self-report their quality of life.

This study was registered with the National Medical Research Register (NMRR) of Malaysia (NMRR - 17-2614-38966) and was approved by the Medical Research and Ethics Committee (MREC).

## EQ-5D instrument

Both the Malay and English language version of the EQ-5D-3L instruments were used in this study. The instrument was previously validated in Malaysia<sup>18</sup>. The EQ-5D-3L instrument is a preference-based measure of health status consisting of a descriptive system and the EQ-5D visual analogue scale (EQ VAS). The responses on the descriptive system is used to form a unique health state which is subsequently converted into a single index value known as a health state utility value using the Malaysian tariff sets<sup>16</sup>. On the EQ VAS, patients would indicate their self-rated health on a visual analogue scale with 0 being the worst health imaginable, and 100 being the best health imaginable<sup>19</sup>.

## Statistical analysis

Statistical analysis was conducted using STATA version 14<sup>20</sup>. Descriptive statistical analysis including sum, percentage, mean and standard deviation was used to describe the sociodemographic, clinical factors, EQ-5D-3L index and EQ VAS of the patients. A summary of the frequencies of health profiles captured from the data collection would be presented. The EQ-5D-3L health profiles was scored using the Malaysian EQ-5D-3L tariff set derived from a time-trade off multiplicative model<sup>16</sup>. To summarize the responses of the EQ-5D-3L domains, the response was aggregated into 'no reported problems' and 'reported problems' by combining the response of 'some problems' and 'extreme problems'. The data normality of the EQ-5D-3L index and the EQ VAS was determined by observing the histogram and conducting a Shapiro-Wilk test. Statistical significance of differences between means of the utility values and the domain responses of various patient groups were tested using non parametric tests (Mann-Whitney U test or Kruskal-Wallis test) as HRQoL data are expected to be non-normally distributed<sup>21</sup>. The effect size of the differences was estimated relative to the pooled standard deviation of the groups (Cohen's d). Values of (0.2–0.5), (0.5–0.8) and (> 0.8) corresponds to small, moderate and large differences in HRQoL. Marginal effects of the demographic and treatment factors were estimated using STATA's margins command.

The utility values are expected to be skewed, whereby many patients would report perfect health<sup>22</sup>. Hence, a two-part model was used to examine the association between the various groups of transfusion-dependent thalassemia patients and the disutility score (i.e. 1-EQ-5D-3L utility value)<sup>21,23</sup>. The two-part model, which was estimated using STATA's *twopm* command, consists of a logistic regression and a generalized linear model<sup>24</sup>. The logistic regression first models the probability of disutility. The second part of the model utilized a generalized linear model with a gamma distribution and a log link function, as it showed the best fit based on comparisons of Akaike Information Criteria from various models. The analyses were adjusted for sociodemographic factors (age, gender, ethnicity, education level), number of iron overload complications, the specific coexisting complications, and the iron chelating therapy regimen. Results were considered statistically significant for p < 0.05 in all the analysis.

## Results:

The sociodemographic and clinical characteristics of the 585 patients sampled are described in Table 1. There were more females (55.7%) than male (44.3%) patients. The mean (SD) age of the sample was 17.2(5.4) years. Majority of the samples were of the Malay ethnicity. Since young children were also recruited for this study, the source of the HRQoL may have been reported by them self (56.8%) or proxy (43.2%). In both the self-reported and proxy reported groups, majority of the patients had received a primary or secondary education with 71.7% and 62.5% respectively. The mean (SD) age of initiating blood transfusion was 5.4 (7.9) years old while the mean (SD) number of transfusion years was 11.3 (8.9). A total of 56.6% of patients had no iron overload complications while

the remaining 43.4% of patients reported the presence of at least one complication. Out of those who reported complications related to the liver. Majority of the patients were on monotherapy treatment (66.0%). The oral route of administration (56.6%) was the most common route of administration. Only 13.0% of the sampled population had any history of a serious adverse event with iron chelating therapy.

Table 1  
Patients sociodemographic and clinical characteristics (N=585)

Characteristics	Mean	Standard Deviation
	N	%
<b>Age (years)</b>	17.2	5.4
<b>Age at first transfusion (years)</b>	5.4	7.9
<b>Number of years receiving blood transfusion,</b>	11.3	8.9
<b>Source of survey</b>		
Self-reported	332	56.8
Proxy-reported	253	43.2
<b>Gender</b>		
Male	259	44.3
Female	326	55.7
<b>Ethnicity</b>		
Malay	403	68.9
Chinese	94	16.1
Kadazan-Dusun	58	9.9
Others	30	5.1
<b>Education Level of Proxy's who completed Proxy-Report (n= 251)</b>		
No Formal Education	10	4
Primary or Secondary Education	180	71.7
Tertiary Education	61	24.3
<b>Education Level of Patients who completed Self-Report (n= 331)</b>		
No Formal Education	3	0.9
Primary or Secondary Education	207	62.5
Tertiary Education	121	36.6
<b>Presence of Iron Overload (IOL) Complication</b>		
No Complication	331	56.6
One Complication	164	28
Two Complications	66	11.3
Three or more Complications	24	4.1
<b>Cardiac Disease</b>	39	15.3*
<b>Diabetes</b>	20	7.9*
<b>Hypothyroid</b>	25	9.8*
<b>Hypogonadism</b>	90	35.4*
<b>Hypoparathyroidism</b>	52	20.5*
<b>Liver Disease</b>	124	48.8*
<b>Iron Chelation Therapy</b>		
Desferrioxamine (Subcutaneous (SC) Drug)	68	11.6
Deferasirox (Oral (PO) Drug)	245	41.9
Deferiprone (Oral (PO) Drug)	73	12.5
Desferrioxamine + Deferiprone (SC + PO Drug)	154	26.3
Desferrioxamine + Deferasirox (SC + PO Drug)	32	5.8
Deferiprone + Deferasirox (Both Oral Drugs)	13	2.2

<b>Number of Iron Chelating Agents</b>		
Monotherapy	386	66
Dual Therapy	199	34
<b>Route of Iron Chelating Administration</b>		
Subcutaneous	68	11.6
Oral	331	56.6
Subcutaneous + Oral	186	31.8
<b>History of Serious Adverse Event with Iron Chelation Therapy</b>		
Yes	76	13
No	509	87

N, number; SD, standard deviation; IOL, Iron Overload Complication; SC, Subcutaneous; PO, Oral

\*Percentage calculated based on the total number of people who has complication

Table 2 summarizes the EQ-5D-3L utility values and EQ VAS scores by sociodemographic and clinical factors while Figure 1 illustrates the frequencies of EQ-5D-3L utility values based on the number of iron overload complications reported. Mean (SD) EQ-5D-3L utility value for the entire sample was 0.893 (0.167) while the mean (SD) EQ VAS score was 81.22 (16.92). Table 3 summarizes the domain responses by sociodemographic and clinical factors while Figure 2 visualizes the health profiles of the patients. The pain/discomfort (20.2%) and the anxiety/depression (13.5%) domain had a higher percentage of reported problems compared to the other domains (Table 3 and Figure 2). Out of the 243 possible health profiles with the EQ-5D-3L, 32 health profiles were reported, with 67.35% of patients reporting a health state of 11111, followed by 10.09% reporting a health state of 11121 (Additional File Table 1). The range of utility scores in the sample was limited between 0.4454 to 1.000.

Table 2  
Summary of EQ-5D-3L utility values & EQ VAS

Factors	N	%	EQ-5D-3L Utility Values		EQ VAS			
			Mean (SD)	Effect size	p-value <sup>t</sup>	Mean (SD)	Effect size	p-value <sup>t</sup>
Total Sample	585	100	0.893(0.167)	-	-	81.22 (16.92)	-	-
<b>Source of survey</b>								
Self-reported	332	56.8	0.8869 (0.1646)	0.080	0.219	78.08 (18.19)	0.439	<0.001*
Proxy-reported	253	43.2	0.9 (0.1689)			85.36 (14.10)		
<b>Gender</b>								
Male	259	44.3	0.9113 (0.1567)	-0.202	0.0113*	82.29 (15.53)	-0.114	0.450
Female	326	55.7	0.8778 (0.1727)			80.37 (17.93)		
<b>Category</b>								
Child ( $\leq$ 18 years old)	364	62.2	0.8976 (0.1632)	0.079	0.371	84.97 (15.16)	0.611	<0.001*
Adult	221	37.8	0.8844 (0.1718)			75.04 (17.86)		
<b>Presence of Iron Overload Complication</b>								
Absent	331	56.6	0.9111 (0.1527)	0.257	0.002*	83.31 (16.61)	0.288	0.0001*
Present	254	43.4	0.8686 (0.1803)			78.49 (16.70)		
Cardiac	39	6.7	0.8211 (0.2000)	0.463	0.0067*	80.38 (15.36)	0.053	0.519
Diabetes	20	3.4	0.8136 (0.2125)	0.495	0.054	74.15 (19.95)	0.433	0.062
Hypothyroid	25	4.3	0.8498 (0.2074)	0.269	0.301	74.56 (20.81)	0.412	0.113
Hypogonadism	90	15.4	0.8488 (0.1966)	0.313	0.0088*	77.6 (18.94)	0.254	0.070
Hypoparathyroidism	52	8.9	0.8883 (0.1717)	0.029	0.887	77.21 (17.33)	0.260	0.054
Liver	124	21.2	0.8387 (0.1789)	0.417	<0.001*	77.8 (16.91)	0.257	0.0033*
<b>Route of iron chelating therapy</b>								
Subcutaneous (SC) Only	68	11.6	0.8769 (0.187)	Reference Group	0.0156 <sup>Y</sup>	78.45 (15.68)	Reference Group	0.0001 <sup>Y</sup>
Oral (PO) Only	331	56.6	0.9108 (0.1514)	0.215		83.82 (15.41)	0.347	
SC + PO	186	31.8	0.8660 (0.1805)	0.060		77.60 (19.06)	0.047	
<b>Number of iron chelating agents</b>								
Monotherapy	386	66.0	0.9081 (0.1533)	0.274	0.0045*	82.95 (15.52)	0.299	0.0025*
Dual Therapy	199	34.0	0.8627 (0.1862)			77.90 (18.95)		
<b>History of Serious Adverse Event with iron chelating therapy</b>								
Yes	76	13.0	0.8814 (0.1808)	0.078	0.585	78.16 (17.52)	0.208	0.068
No	509	87.0	0.8943 (0.1644)			81.67 (16.80)		

Values of scores are presented as Mean (SD; Standard Deviation);

Values of scores are presented as Mean (SD; Standard Deviation);

N, number; SC, subcutaneous; PO, oral; VAS, Visual Analogue Scale

*p*-value<sup>t</sup>, using Mann Whitney U Test; *p*-value<sup>Y</sup>, using Kruskal Wallis Test; \* indicates significance at *p*-value < 0.05

Effect Size (Cohen's d) Interpreted as d = 0.2-0.5 (Small), d = 0.5-0.8 (Moderate) and d > 0.8 (Large)

Based on the EQ-5D-3L utility values, statistical significance from Mann-Whitney and Kruskall-Wallis test found the variables of gender (effect size = 0.202), the presence of iron overload (effect size = 0.257), route of iron chelating therapy (effect size = 0.215 for oral and 0.06 for combination therapy compared to subcutaneous) and the number of iron chelating agents used (effect size = 0.274) to be statistically significant. However, the effect sizes of these variables were only small, with a coefficient that ranged less than 0.5, with the number of chelating agents used having the largest effect size.

Based on the EQ VAS, the Mann-Whitney and Kruskal-Wallis test found the source of survey (effect size = 0.439), category of child or adult (effect size = 0.611), the presence of iron overload (effect size = 0.288), route of iron chelating therapy (effect size = 0.347 for oral and 0.047 for combination therapy compared to subcutaneous) and the number of iron chelating agents used (effect size = 0.299) to be statistically significant. The effect size of the child or adult category was the largest with a value of 0.611.

Table 3 summarizes the domain responses by sociodemographic and clinical factors based on aggregates of "no problem reported" and "problem reported". Based on the number of iron overload complications, Figure 1 illustrates the distribution of EQ-5D-3L utility values based on its range. Figure 2 illustrates the pain/discomfort domain had the highest frequency of reported problems, with most problems being moderate. Using Chi-square test, the aggregated domain responses were tested for statistical significance. On the mobility domain, the adult or child category, gender, presence of iron overload complications, route and the number of iron chelating agents used were significant. On the self-care domain, the child or adult category and route of iron chelating agent significant. On the usual activity domain, the presence of iron overload complications, route and the number of iron chelating agents used were significant. On the pain/discomfort domain, the presence of iron overload complications and the route of iron chelation administration was significant. On the anxiety/depression domain, the gender, presence of iron overload complications, route and the number of iron chelating agents used was significant.

The marginal effects of the various sociodemographic and clinical factors on the disutility score were analysed using the two-part model and presented in Table 4. Gender, education, length of transfusion, presence of iron overload complications and number of iron chelating agents used were found to be significant predictors for the disutility score. When comparing the EQ-5D-3L utility values of patients with complications to patients without complications in the two-part model, the HRQoL declining effect becomes significant when there are at least two coexisting complications. Patients who used dual iron chelating agents had lower utility scores by 0.15 points when compared to those who were on monotherapy.

Table 5 presents the health state utility values for the different types of iron chelating agents and specific iron overload complications which were generated using a two-part model, controlling for gender and the presence of iron overload complications in the model. The analysis was conducted using the full sample (n=585) and a restricted sample (n=429). In the restricted sample, patients who reported perfect health but had iron overload complications were excluded from the analysis. We hypothesized that patients who had iron overload complications would not be able to achieve perfect health and hence wanted to examine what the health state utility values would be without that cohort. Using the full sample, patients who had diabetes had the lowest utility value of 0.815 compared to other iron overload complications. However, when the restricted sample was used, patients with hypothyroid had the lowest utility value of 0.838. In both sample analysis, patients who were on oral monotherapy had a higher utility value compared to other routes of administration.

Table 3  
Summary of dimension responses

Demographics	Mobility n (%)			Self-care n (%)			Usual activity n (%)			Pain/discomfort n (%)		
	No Problem	Reported Problem	p-value <sup>a</sup>	No Problem	Reported Problem	p-value <sup>a</sup>	No Problem	Reported Problem	p-value <sup>a</sup>	No Problem	Reported Problem	p-value <sup>a</sup>
Total Sample (n=585)	552(94.4)	33(5.6)	-	561(95.9)	24(4.1)	-	538(92.0)	47(8.0)	-	467(79.8)	118(20.2)	-
Category			0.005*			0.029*			0.309			0.1
Child (<18 yo)	351(96.4)	13(3.6)		344(94.5)	20(5.5)		338(92.9)	26(7.1)		297(81.6)	67(18.4)	
Adult (>18 yo)	201(90.9)	20(9.1)		217(98.2)	4(1.8)		200(90.5)	21(9.5)		170(76.9)	51(23.1)	
Gender			0.017*			0.564			0.39			0.0
Male	251(96.9)	8(3.1)		247(95.4)	12(4.6)		241(93.1)	18(6.9)		215(83.0)	44(17.0)	
Female	301(92.4)	25(7.6)		314(96.3)	12(3.7)		297(91.1)	29(8.9)		252(77.4)	74(22.6)	
Presence IOL			0.04*			0.86			0.020*			0.0
Yes	234(92.1)	20(7.9)		244(96.2)	10(3.8)		226(89.0)	2(11.0)		188(74.0)	66(26.0)	
No	318(96.1)	13(3.9)		317(95.8)	14(4.2)		312(94.3)	19(5.7)		279(84.3)	52(15.7)	
ICT Route			0.006 <sup>b</sup> *			0.425 <sup>b</sup>			0.028 <sup>b</sup> *			0.2
SC	63(92.7)	5(7.3)		67(98.5)	1(1.5)		63(92.7)	5(7.3)		51(75.0)	17(25.0)	
PO	321(97.0)	10(3.0)		318(96.1)	13(3.9)		312(94.3)	19(5.7)		272(82.2)	59(17.8)	
SC + PO	168(90.3)	18(9.7)		176(94.6)	10(5.4)		163(87.6)	23(12.4)		144(77.4)	42(22.6)	
No of ICT Agents			0.001*			0.212			<0.001*			0.1
Monotherapy	373(96.6)	13(3.4)		373(96.6)	13(3.4)		367(95.1)	19(4.9)		315(81.7)	71(18.3)	
Dual Therapy	179(90.0)	20(10.0)		188(94.5)	11(5.5)		171(85.9)	28(14.1)		152(76.4)	47(23.6)	
History of SAE			0.048*			0.999			0.027*			0.9
Yes	68(89.5)	8(10.5)		73(96.0)	3(4.0)		65(85.5)	11(14.5)		61(80.3)	15(19.7)	
No	484(95.1)	25(4.9)		488(95.9)	21(4.1)		473(92.9)	36(7.1)		406(79.8)	103(20.2)	

Values of scores are presented as n(%), number(percentages);IOL, Iron Overload Complications; ICT, Iron Chelating Therapy; SC, subcutaneous; PO, oral; SAE, Severe Adverse Effects&nbsp;p-value<sup>a</sup>, using Mann Whitney U Test; p-value<sup>b</sup>, using Kruskal Wallis Test;\* indicates significance at p-value < 0.05

Table 4: Marginal effects estimated with two-part model for the association between sociodemographic and clinical factors with EQ-5D-3L disutility score (i.e. 1 – EQ-5D-3L utility value)

Table 4  
Marginal effects estimated with two-part model for the association between sociodemographic and clinical factors with EQ-5D-3L disutility score (i.e. 1 - EQ-5D-3L utility value)

	Disutility score	Standard Error	z	p-value	95% Lower	95% Upper
<b>Age</b>	0.108493	0.000631	1.8	0.1972	0.0938	0.123185
<10 years old as reference group						
11-20 Years Old	0.11741	0.01611	0.62	0.6068	0.072479	0.162341
21-30 Years Old	0.10731	0.019571	0	0.9995	0.055595	0.159024
31-40 Years Old	0.141119	0.027471	1.23	0.4311	0.07392	0.208317
41-50 Years Old	0.260868	0.054056	2.84	0.0118	0.141564	0.380171
>50 Years Old	0.118334	0.065249	0.17	0.6146	-0.02291	0.259576
<b>Gender</b>						
Female as reference group						
Male	0.07391	0.013637	-2.45	0.0361	0.033758	0.114061
<b>Education Category</b>						
No Formal Education as reference group						
Primary Education	0.082937	0.073266	-0.34	0.0015	-0.07415	0.240028
Tertiary Education	0.071927	0.073862	-0.49	0.0148	-0.08633	0.230186
<b>Age initiated transfusion</b>	0.107706	0.000846	0.41	0.6956	0.092563	0.122849
<b>Years of transfusion</b>	0.109195	0.000745	2.47	0.0486	0.094319	0.124072
<b>Presence of Iron Overload Complications</b>						
IOL Presence	0.149873	0.014075	3.02	0.0087	0.108904	0.190842
<b>Number of coexisting iron overload complications</b>						
No complication as reference group						
1 Complication	0.129972	0.01566	1.44	0.3123	0.086017	0.173927
2 Complications	0.162672	0.023462	2.36	0.0367	0.103426	0.221918
3 or more complications	0.250668	0.045765	3.13	0.0007	0.147709	0.353628
<b>Number of Iron Chelating Agents</b>						
Monotherapy as reference group						
Dual Therapy	0.152716	0.015299	2.96	0.0042	0.109354	0.196079
<b>Route of iron chelating therapy administration</b>						
Subcutaneous route as reference group						
Oral	0.073408	0.022823	-1.49	0.2814	0.015295	0.131522
Combination of oral & subcutaneous	0.118249	0.025031	0.44	0.9078	0.055809	0.180689
<b>Iron chelating agent</b>						
Desferrioxamine (DFO) as reference group						
Deferasirox (DFX)	0.071287	0.023099	-1.56	0.1926	0.012694	0.12988
Deferiprone (DFP)	0.063569	0.027281	-1.61	0.2759	-0.00322	0.130358
DFO + DFP	0.113021	0.025442	0.22	0.9751	0.049836	0.176205
DFO + DFX	0.143411	0.040593	0.89	0.5918	0.050531	0.23629
DFX + DFP	0.168639	0.072966	0.84	0.0718	0.012309	0.324969
<b>History of Serious Adverse Event with Iron Chelating Therapy use</b>						
History of Serious Adverse Event with Iron Chelating Therapy use	0.1203	0.022203	0.58	0.3262	0.063289	0.17731

Table 5  
Health state utility values derived from the two-part model

Health State	Full Sample (n=585)		Restricted Sample (n=429)	
	Utility Value	95% CI	Utility Value	95% CI
TDT with Non-specific Iron Overload Complication	0.852	0.811 0.893	0.905	0.880 0.929
TDT with Cardiac Complication	0.820	0.742 0.897	0.846	0.805 0.887
TDT with Diabetes	0.815	0.711 0.919	0.839	0.788 0.890
TDT with Hypothyroid	0.853	0.761 0.945	0.838	0.787 0.889
TDT with Hypogonadism	0.841	0.785 0.896	0.860	0.827 0.893
TDT with Hypoparathyroidism	0.894	0.832 0.955	0.856	0.815 0.897
TDT with Liver iron overload	0.826	0.778 0.875	0.929	0.907 0.951
TDT with Desferrioxamine (DFO)	0.893	0.880 0.906	0.779	0.707 0.852
TDT with Deferasirox (DFX)	0.915	0.856 0.974	0.854	0.837 0.870
TDT with Deferiprone (DFP)	0.940	0.875 1.005	0.778	0.698 0.859
TDT with DFO + DFP	0.903	0.841 0.964	0.749	0.691 0.808
TDT with DFO + DFX	0.862	0.229 0.953	0.758	0.662 0.854
TDT with DFX + DFP	0.814	0.653 0.975	0.754	0.591 0.917
TDT on subcutaneous (SC) therapy	0.893	0.879 0.906	0.779	0.706 0.852
TDT on oral (PO) therapy	0.918	0.860 0.976	0.949	0.902 0.997
TDT on SC + PO therapy	0.895	0.834 0.957	0.890	0.837 0.942

CI, Confidence Interval; TDT, Transfusion-dependent Thalassemia; DFO, Desferrioxamine; DFX, Deferasirox; DFP, Deferiprone; SC, subcutaneous; PO, oral

## Discussion:

As of date, there are no studies that has surveyed the health state utility values (HSUV) of transfusion-dependent thalassemia (TDT) patients in Malaysia and this study aims to fill that gap. The availability of these values would aid policy makers in the decision-making process related to disease management for these group of patients, especially since TDT is a chronic and expensive disease.

The mean (SD) HSUV of 0.893 (0.167) in this study was slightly higher than the HSUVs surveyed among TDT patients using iron chelating therapy in Iran. The study, which utilized US and Iran's time trade-off value set, had a HSUV range of 0.81 to 0.86<sup>25</sup>. A similar trend was also observed on the EQ VAS scale, where our patients had a mean (SD) score of 81.22 (19.92) compared to a score of 72.9 (1.1) in Iran<sup>25</sup>. The utility value range between 0.8 to 0.9 had no reported frequencies as the plausible range on the TTO Malaysian value set had a gap between the health state 11111 (utility value = 1.00) and 11112(utility value = 0.756).

The utility values were expected to be skewed, with many patients reporting perfect health<sup>22</sup>. This violates ordinary least squares (OLS) regression assumptions. Hence, a two-part model (TPM) and the generalized linear model (GLM) was used to derive the health state utility values, controlling for age, the type of iron overload and type of iron chelator. In the two-part model, the disutility score (i.e. 1-EQ-5D-3L utility value)<sup>21,23</sup> was used to predict the HRQoL scores based on the variables. The two-part model is useful for models with mixed discrete continuous outcomes. In this study, the first part of the two-part model predicts the probability of obtaining a disutility score of 0(perfect health), followed by the second part of the model that predicts the disutility score using a regression model<sup>24</sup>. The GLM model was chosen as it allows the outcome variable to be a link function of the linear index of the covariates instead of the outcome variable simply being a linear function of the covariates. This also avoids the problem of retransformation inherent in models that transformed the outcome variable to meet OLS assumptions<sup>26</sup>.

This study found differences between the HRQoL of children and adult patients. As patients grew older, the burden of treatment may increase with higher volume of blood required, onset of complications and the need for higher dosages of iron chelating therapy, possibly contributing to the number of reported problems on the pain/discomfort and anxiety/depression domain of the EQ-5D-3L. In addition to that, the lower number of reported problems on the self-care domain of older patients may be explained by the independence and knowledge that the patient gains over the years when coping with the condition<sup>12,27</sup>.

The findings highlight that using a subcutaneous iron chelator resulted in a utility decrement of 2.8% compared to when an oral iron chelator is used. In addition to the route of administration, the number of iron chelators used can affect the HRQoL of patients. The study conducted in Iran showed a decrement of 6.9% when using a subcutaneous iron chelator or combination therapy compared to an oral chelator or a monotherapy<sup>25</sup>. Although these findings are consistent with previous studies, the utility decrement in this study and the study conducted in Iran is much smaller compared to a time trade-off study conducted in Australia<sup>28</sup> and the United Kingdom<sup>29</sup> that investigated the utility associated with the use of oral and subcutaneous iron chelating therapy. In both studies, a decrement of 28.2% and 21.4% respectively occurred when using a subcutaneous ICT compared to the oral ICT. However, it should be noted that these two studies utilized a direct elicitation valuation method with respondents from the community, while the current study and the study in Iran utilized a generic preference-based instrument with TDT patient. This highlights the effect of different valuation methods and respondents in eliciting health state utility values.

As with other chronic conditions<sup>30</sup>, this study showed that the presence of coexisting comorbidities in TDT is associated with a lower HRQoL. The decrease in HRQoL becomes statistically significant when the number of complications exceeds two. Amongst the various iron overload complications, cardiac and diabetes complications result in the highest disutility of 8.2% and 8.4% respectively. These values were higher compared to the study conducted in Iran which had a disutility of 3.6% (cardiac) and 6.0% (diabetes) when compared to patients who did not have the complication<sup>25</sup>. A cost-utility analysis conducted in the United States used the assumption that TDT patients with cardiac disease would have a 15% decrement in utility<sup>31</sup> based on TTO values for heart failure as reported in a longitudinal cohort study of health status and HRQoL<sup>32</sup>. These findings imply that the prevention of iron overload complications is crucial in preserving the HRQoL of patients.

Compliance to iron chelation therapy is essential in the prevention of the development of iron overload complications. Apart from the increased risk of morbidity and mortality, poor compliance to iron chelating therapy has also shown to increase the cost of treating the disease<sup>33</sup>. The choice of iron chelators has been highlighted as a determinant of HRQoL in TDT patients<sup>34–36</sup> and the findings of this study further emphasizes the preference for oral iron chelation.

This study has a few limitations. First, it was not compared to a healthy general population, hence making it difficult to truly estimate the impact of the disease on the HRQoL. In addition, due to time constraints and the variation in documentation of medical records across centres, it was a challenge to obtain additional clinical parameters which could have been used to assess the severity of the disease such as the serum ferritin levels. As is common for quality of life data, the results were skewed in a way that higher scores were reported more than lower scores. A ceiling effect was also seen in our results (67.35% reported perfect health) indicating that a complete variation in health states were not fully captured.

Finally, based on a literature search, the minimum clinically importance difference (MCID) which represents the smallest amount of benefit that the patient can recognize and value has not been defined for TDT. This limits our ability to compare the actual impact of using different treatment regimens and route of administrations on the HRQoL and to assess if patients have significantly improved, declined or remained stable<sup>37</sup>. Further empirical work is required in this area.

## Conclusion:

In this study, the HRQoL of TDT patients in Malaysia were surveyed using the EQ-5D-3L instrument and converted into utility values using a Malaysian specific tariff. The mean (SD) EQ-5D-3L utility value for TDT patients were 0.893 (0.167) while the mean (SD) EQ VAS score was 81.22 (16.92). The reduction of HRQoL becomes more prominent when there are at least two coexisting complications. These findings emphasize the importance of preventing the development of iron overload complications. However, the prevention of iron overload is heavily dependent on a patient's compliance to their iron chelating therapy. The availability of these values would be useful for clinicians, researchers and policy makers in the decision-making process for disease management.

## Declarations

### Funding

No financial support was received for this study.

## Conflicts of interest

The authors declare that there is no conflict of interest.

## Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to participate

This study was registered with the Malaysian National Medical Research Registry (NMRR -17-2614-38966). This study was also approved by the Malaysian Research and Ethics Committee. Prior to each interview, written consents and assents were obtained from both caregivers & patients who were willing to

participate.

## Consent for Publication

Not Applicable

## Author contributions

AAS was involved in the revision of the paper for intellectual content and in the design, interpretation, analysis of data & proofreading the manuscript. IKC was involved in the drafting of the manuscript, analysis and interpretation of the data. JWHY was involved in the design, collection, training, validation of the study and data & proofreading the manuscript. NSM was involved in the training, validation of the study and data & proofreading the manuscript. All authors read and approved the final manuscript.

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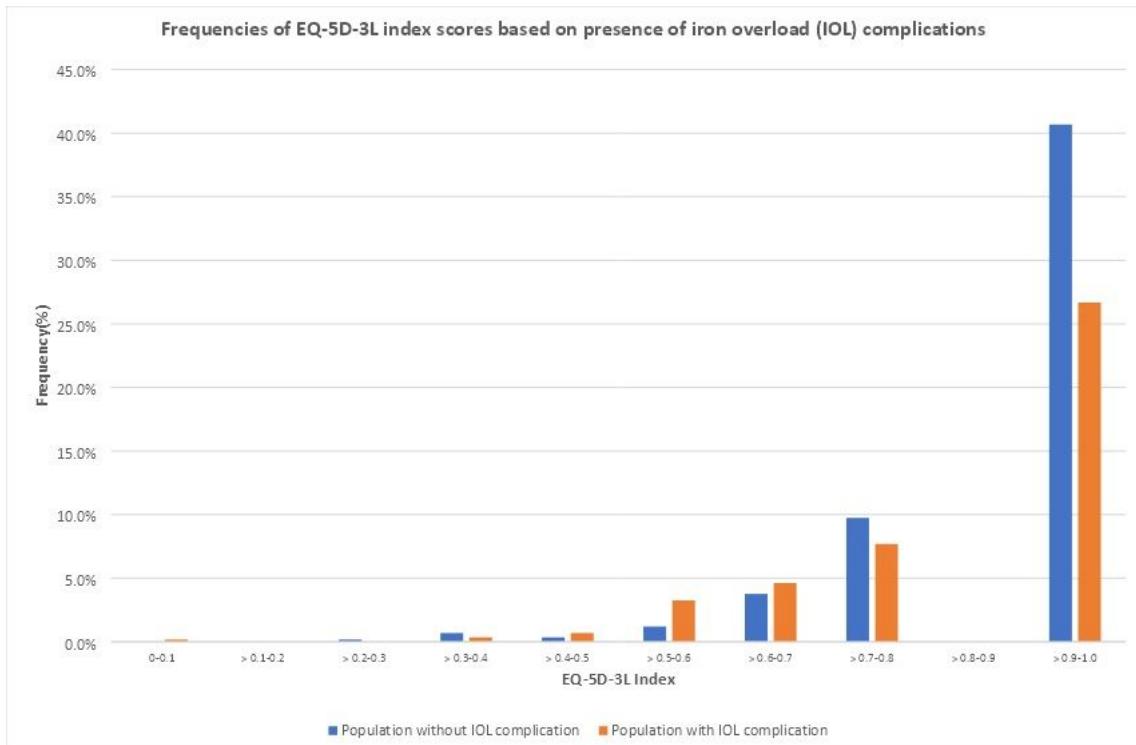
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## References

1. Rund D, Rachmilewitz E. β-Thalassemia. *N Engl J Med.* 2005;353:1135–46.
2. Weatherall D, Clegg J. Historical perspectives: in *The Thalassemia syndromes* 4th edition. Blackwell Scientific, Oxford UK, 2001.
3. Elizabeth G, Ann TM. Genotype-phenotype diversity of beta-thalassemia in Malaysia: treatment options and emerging therapies. *Medical Journal of Malaysia.* 2010; 65.
4. George E. Beta-thalassemia major in Malaysia, an ongoing public health problem. 2001.
5. Ibrahim MH. Malaysian Thalassaemia Registry Report. 1st ed. Medical Development Division, Ministry of Health Malaysia.2019.
6. Ibrahim HM, Hassan A, George E, Goh AI, et al. Management of Transfusion Dependent Thalassaemia. In: Health Technology Assessment Section MDD. (ed.). Putrajaya: CPG Secretariat; 2009. pp. 1–21.
7. Cappellini M-D, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the management of transfusion dependent thalassaemia (TDT). Cyprus: Thalassaemia International Federation Nicosia; 2014.
8. Telfer P, Constantinidou G, Andreou P, Christou S, Modell B, Angastinotis M. Quality of life in thalassemia. *Ann N Y Acad Sci.* 2005;1054:273–82.
9. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med.* 1993;118:622–9.
10. Ismail A, Campbell MJ, Ibrahim HM, Jones GL. Health related quality of life in Malaysian children with thalassaemia. *Health Quality of life Outcomes.* 2006;4:39.
11. Suzanah A, Zulaiha M, Fazrul AA, Kamaruzaman W. Thalassaemia: a study on the perception of patients and family members. *Med J Malaysia.* 2011;66:327.
12. Sazlina S, Asauji Y, Juni MH. Predictors of health related quality of life among children and adolescents with beta thalassemia in three hospitals in Malaysia: a cross sectional study. *International Journal of Public Health Clinical Sciences.* 2015;2:1–12.
13. Dahlui M, Hishamshah MI, Rahman A, Aljunid SM. Quality of life in transfusion-dependent thalassaemia patients on desferrioxamine treatment. *Singapore medical journal.* 2009;50:794.
14. Ismail M, Chun CY, Shahar S, et al. Quality of life among thalassaemia children, adolescent and their caregivers. *Sains Malaysiana.* 2013;42:373–80.
15. Karimi M, Brazier J. Health, health-related quality of life, and quality of life: what is the difference? *Pharmacoeconomics.* 2016;34:645–9.
16. Shafie AA, Thakumar AV. Multiplicative modelling of EQ-5D-3L TTO and VAS values. 2019.
17. Naing L, Winn T, Rusli B. Practical issues in calculating the sample size for prevalence studies. *Archives of orofacial Sciences.* 2006;1:9–14.
18. Shafie AA, Hassali MA, Liau SY. A cross-sectional validation study of EQ-5D among the Malaysian adult population. *Qual Life Res.* 2011;20:593–600.
19. Surapolchai PSW, Sinlapamongkolkul P, Udomsubpayakul U. Biopsychosocial Predictors of Health-Related Quality of Life in Children with Thalassemia in Thammasat University Hospital. *J Med Assoc THai.* 2010;93:65–75.
20. StataCorp. *Stata Statistical Software: Release 14.* College Station. TX: StataCorp LP; 2015.
21. Li L, Fu AZ. Some methodological issues with the analysis of preference-based EQ-5D index score. *Health Serv Outcomes Res Method.* 2009;9:162–76.

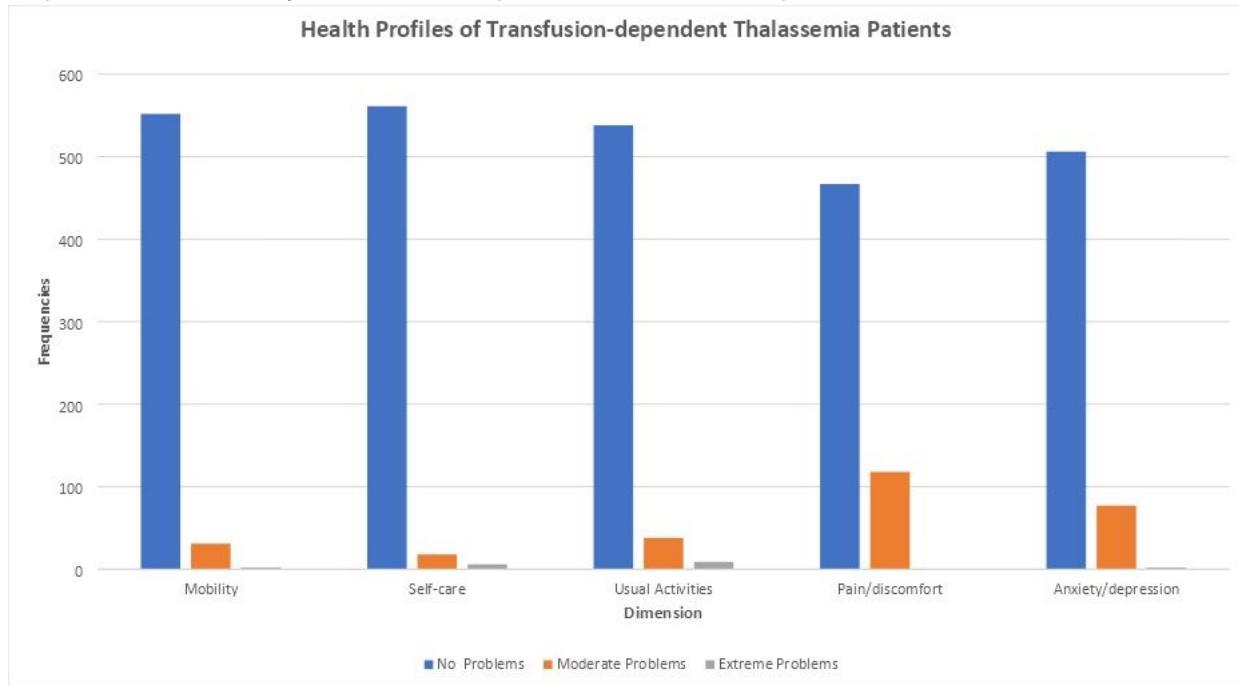
22. Huang IC, Frangakis C, Atkinson MJ, et al. Addressing ceiling effects in health status measures: a comparison of techniques applied to measures for people with HIV disease. *Health services research*. 2008;43:327–39.
23. Jalkanen K, Aarnio E, Lavikainen P, Jauhonen H-M, Enlund H, Martikainen J. Impact of type 2 diabetes treated with non-insulin medication and number of diabetes-coexisting diseases on EQ-5D-5 L index scores in the Finnish population. *Health Qual Life Outcomes*. 2019;17:117.
24. Belotti F, Deb P, Manning WG, Norton EC. twopm: Two-part models. *The Stata Journal*. 2015;15:3–20.
25. Seyedifar M, Dorkoosh FA, Hamidieh AA, et al. Health-Related Quality of Life and Health Utility Values in Beta Thalassemia Major Patients Receiving Different Types of Iron Chelators in Iran. *International journal of hematology-oncology stem cell research*. 2016;10:224–31.
26. Deb P, Norton EC, Manning WG. *Health Econometrics Using Stata*. Stata Press, 2017.
27. Thavorncharoensap M, Torcharus K, Nuchprayoon I, Riewpaiboon A, Indaratna K, Ubol. B-o. Factors affecting health-related quality of life in Thai children with thalassemia. *BMC Hematology*. 2010;10:1.
28. Osborne RH, Lourenço RDA, Dalton A, et al. Quality of life related to oral versus subcutaneous iron chelation: a time trade-off study. *Value in health*. 2007;10:451–6.
29. Karnon J, Tolley K, Oyee J, Jewitt K, Ossa D, Akehurst R. Cost-utility analysis of deferasirox compared to standard therapy with desferrioxamine for patients requiring iron chelation therapy in the United Kingdom. *Curr Med Res Opin*. 2008;24:1609–21.
30. Lubetkin EI, Jia H, Franks P, Gold MR. Relationship among sociodemographic factors, clinical conditions, and health-related quality of life: examining the EQ-5D in the US general population. *Qual Life Res*. 2005;14:2187–96.
31. Delea TE, Sofrygin O, Thomas SK, Baladi J-F, Phatak PD, Coates TD. Cost effectiveness of once-daily oral chelation therapy with Deferasirox versus infusional Deferoxamine in Transfusion-dependent Thalassaemia patients. *Pharmacoeconomics*. 2007;25:329–42.
32. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making*. 1993;13:89–102.
33. Delea TE, Edelsberg J, Sofrygin O, et al. Consequences and costs of noncompliance with iron chelation therapy in patients with transfusion-dependent thalassemia: a literature review. *Transfusion*. 2007;47:1919–29.
34. Abetz L, Baladi J-F, Jones P, Rofail D. The impact of iron overload and its treatment on quality of life: results from a literature review. *Health Quality of Life Outcomes*. 2006;4:73.
35. Porter J, Bowden DK, Economou M, et al. Health-related quality of life, treatment satisfaction, adherence and persistence in β-thalassemia and myelodysplastic syndrome patients with iron overload receiving deferasirox: results from the EPIC clinical trial. *Anemia*. 2012; 2012.
36. Scalzone L, Mantovani LG, Krol M, et al. Costs, quality of life, treatment satisfaction and compliance in patients with β-thalassemia major undergoing iron chelation therapy: the ITHACA study. *Curr Med Res Opin*. 2008;24:1905–17.
37. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. *Controlled clinical trials*. 1989;10:407–15.

## Figures



**Figure 1**

Frequencies of EQ-5D-3L utility values based on the presence of iron overload complications



**Figure 2**

Health profiles of transfusion-dependent Thalassemia patients