

# Factors affecting the quality of life of Thalassemia $\beta$ major children

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## Research Article

# Factors affecting the quality of life of Thalassemia $\beta$ major children

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## ABSTRACT

Thalassemia is a genetically inherited blood disorder. According to the World Health Organization, 40% of the cases of thalassemia are in Asia. The main treatment for this disease is through administration of blood transfusions and iron chelation therapy. Generally, this chronic condition has an impact on the quality of life of patients due to the course of the disease and its treatment. Therefore, the purpose of this study was to determine the factors affecting the quality of life of thalassemia patients. The cross sectional design method was used in this research. The research subjects were 73  $\beta$  major thalassemia children, aged 8-18 years, undergoing treatment at the Bogor PMI Hospital, between January and March 2020. These were selected through consecutive non random sampling technique. Variables measured include serum ferritin and haemoglobin levels, as well as blood transfusion compliance and consumption of iron chelation, through questionnaires, while the quality of life was measured through  $\beta$ -dsQL generic 4.0. The data were subjected to Pearson and Spearman correlation tests. Based on the result, the mean age of the thalassemia major children was  $13 \pm 4$  years, while the value of the quality of life was  $67.10 \pm 11.27$ . There was a positive significant relationship between parental education ( $r = 0.236$ ,  $p = 0.045$ ), parental income ( $r = 0.264$ ,  $p = 0.024$ ) and the average value of quality of life. Also, there was a negative significant relationship between the average quality of life value with the age of commencing blood transfusion ( $r = -0.255$ ,  $p = 0.030$ ). Furthermore, the higher the education level and income of the parents, the higher the quality of life of thalassemia children will be. However, the higher the age of administering blood transfusion, the lower the quality of life.

**Keywords:** Thalassemia B Major, Child, Quality of Life

## INTRODUCTION

Thalassemia is a genetically inherited blood disorder, characterized by the lack or absence of hemoglobin chain synthesis, which results in decreased levels of hemoglobin in the red blood cells and anemia. Some of the abnormalities associated with it could be in the form of mutation which impairs the formation of hemoglobin. Also, the thalassemia  $\beta$  major occurs due to deficiency in the synthesis of  $\beta$  chain thereby decreasing the levels of HbA, and since there is an excess of  $\alpha$  chains, it is compensated for in the form of  $\delta$  and chains which join the  $\alpha$  chain, resulting in increased levels of HbF and HbA2 [1]. According to a report by the World Health Organization (WHO) in 2012, approximately 7% of the world's population has the thalassemia gene with the highest incidence rate of about 40% of cases in Asia [2].

In Indonesia, thalassemia  $\beta$  major is a common health problem with significant national health

cost. Currently, there are more than 10,531 thalassemia patients in the country, with an estimation of about 2,500 newborn cases each year. Based on UKK Hematology data of the Indonesian Pediatric Association in 2016, the prevalence of thalassemia major in the country was 9,121 people. According to the data released by the Indonesian Thalassemia Foundation/ Association of Parents of Sufferers (YTI/POPTI), people with the condition increased from 4,896 in 2012 to 9,028 in 2018 [3]. The Thalassemia International Federation in 2011 also included Indonesia among the countries with high risk of the disease [4].

Blood transfusion is the main means of treating anemia in thalassemia  $\beta$  major patients, which involves maintaining hemoglobin levels above 10 g/dL. There is need for lifelong regular transfusion to suppress erythropoiesis, prevent skeletal changes, extra-medullary hemopoiesis, and splenomegaly which generally affect patients' quality of life. Also, the iron resulting from both

the destruction of erythrocytes and routine transfusions usually cause hemosiderosis in various tissues or organs such as skin, liver, spleen, bone marrow, heart muscle, thyroid and other endocrine glands. Excessive accumulation of iron in various tissues and organs in the form of skin pigmentation and impaired endocrine function causes late growth and puberty, as well as physiological disorders of the heart such as cardiac decomposition, pericarditis, arrhythmias, fibrillation and enlargement of the heart. This heart disorder is the major cause of death in thalassemia  $\beta$  major. The physiology of the pancreas could as well be interfered with during this condition, thereby causing diabetes and cirrhosis of the liver. There is need of iron chelator to control those complications arising from iron overload. Moreover, the types of iron chelator used, patient compliance and knowledge, all has impact on the patients' quality of life [4]-[7].

According to a study, there are negative impacts of blood transfusion and iron chelation on the physical, emotional and functioning aspects of  $\beta$ -major thalassemia patients [8]. A research on the quality of life of thalassemia patients concluded that the quality of life depends on ferritin levels, complications of iron overload and family income [9]. Another study however, concluded that there was no significant difference in the quality of life of children with thalassemia compared with the healthy ones, but a significant difference was found in gender [10].

Based on a study conducted in India, 74% of thalassemia patients had a poor quality of life, and about 44% had psychological problems such as anxiety symptoms, depression and behavioral disorders. In general, the disease has a negative effect on physical function, emotions, social skills and other abilities needed in schools [10]. This low quality of life is related to several factors such as improper diagnosis and management, chronic disease course, changes in physical appearance, delay in physical growth, delay in sexual development, psychiatric disorders etc. Therefore, the purpose of this study was to determine the factors affecting the quality of life of thalassemia patients.

#### METHODOLOGY

This was an observational analytic study with a cross sectional design. It was conducted at PMI Hospital, Bogor between January and March 2020. The consecutive non-random sampling technique was used to select the research subjects. Also, the data was collected through

interview using a transfusion compliance questionnaire recommended by the Minister of Health, Indonesia, in 2018 consisting of 4 questions and the Morisky Medication Adherence Scales (MMAS-8) questionnaire made up of 8 question items. Each item with correct answer was given a score of 1 and 0 for a wrong answer. The compliance variable was divided into 3 categories, namely, high compliance with a score of 8, moderate compliance for scores between 6 and 7 while low compliance was used for scores less than 6.

The growth disorders were assessed using the CDC 2000 stature age percentile curve, and patients with percentile less than 5 were with growth disturbance. The height was measured using a microtoise with a measuring capacity of 2 meters with an accuracy of 0.1 cm. Also, the hemoglobin levels were measured through the electrophoresis method, while the serum ferritin levels were measured through the immunochemiluminescent method.

Then, the inclusion criteria include  $\beta$ -major thalassemia patients aged 8-18 years, receiving blood transfusions and iron chelation therapy at PMI Hospital, and the parents or guardians of patients willing to sign the informed consent forms. The sample size was determined using the infinite-finite population formula with a significance level of 95% of 1.96. A prevalence of 74% was used for sample calculation with a measurement accuracy of 0.05, and based on these, 73 thalassemia  $\beta$  major patients aged 8-18 years were needed as the study subjects. Also, the data collected were processed using SPSS 25, with Pearson or Spearman correlation test at a significance level  $\leq 0.05$ . Furthermore, the permission for the research was granted by the Research Ethics Commission of the Faculty of Medicine Trisakti University, with number 162/KER-FK / V/ 2020.

#### RESULTS AND DISCUSSION

The study was conducted at the PMI Hospital, Bogor, West Java, involving children with  $\beta$  major thalassemia, receiving treatment, blood transfusion and routine control at the hospital between January and March 2020. A total of 82 subjects went through the anthropometric examinations involving the body weight and height, as well as laboratory examinations such as routine blood tests and serum ferritin levels. However, only 73 patients met the inclusion and exclusion criteria of the study.

**Table 1: Demographic Characteristics of Research Subjects (n=73)**

Characteristic	Mean $\pm$ SD	N	%
Age (year)			
8-12	13 $\pm$ 4		38
13-18			35
Height (cm)	137 $\pm$ 28		
Body weight (kg)	39 $\pm$ 11		
Parent education			
Low		10	13.70
Middle		29	39.73
High		34	46.58
Parent income			
< UMR		36	49.32
$\geq$ UMR		37	50.68
Siblings (+TM)			
Yes		13	17.81
No		60	82.19
Family (+TM)			
Yes		5	6.85
No		68	91.15

+TM: thalassemia  $\beta$  Mayor Patient, UMR: minimum regional wage

According to Table 1, the average age of the patients is 13  $\pm$  4 years. A total of 38 subjects were aged 8-12 years and 35 aged 13-18 years. The mean height and weight of the subjects were 137 cm and 39 kg respectively. Also, majority of the parents, 34 (46.5%), had high level of education, with 37 (50.68%) on income equal to or above the regional minimum wage. In addition, 13 (17.81%) subjects had siblings with  $\beta$  major thalassemia, while 5 (6.85%) had

families with thalassemia  $\beta$  major. Based on Table 2, majority of the subjects, 49 (67.12%), started receiving blood transfusion between ages 1-5 years, while for ages <1 year and > 5 years were 12.33% and 20.55% respectively. Also, the majority of the subjects, 39 (53.24%), had their Hb levels between 6-8 g / dL while 51 of 73 subjects (69.86%) had ferritin level > 1000-2500, while 43 (58.9%) complied with the blood transfusions regimen.

**Table 2: Clinical Characteristics (n=73)**

Characteristic	N	%
Pre transfusion Hb(g/dL)		
<6	10	13.70
6-8	39	53.42
$\geq$ 8	24	32.88
Ferritin level (ng/mL)		
$\leq$ 1000	4	5.48
>1000-<2500	51	69.86
$\geq$ 2500	18	24.66
Transfusion compliance	34	46.58
Yes	43	58.90
No	30	41.10
Compliance with iron chelation therapy		
Low	34	46.58
Middle	23	31.51
High	16	21.92
Growth Disturbance		
Yes	56	76.71
No	17	23.29
Age of starting transfusion(year)		
<1	9	12.33
1-5	49	67.12

> 5	15	20.55
Iron chelation type		
Oral	52	71.23
Parenteral	5	6.85
Combination	16	21.92
Self-perception of health status		
Ugly	0	0
Enough	10	13.70
Good	44	60.27
Very good	19	26.05
Perfect	0	0

According to the CDC TB / U curve, a total of 56 subjects (76.71%) experienced growth disturbance. Based on the compliance criteria in the consumption of iron chelator, 46.58% had low compliance and 52 (71.23%) of the subjects took the oral type, 5 (6.85%) administered the iron chelator parenterally, while 16 (21.92%) received the combination. Then, the majority 60.27%, of the subjects had good health status based on self-perception. Table 3 shows the

value of quality of life of the research subjects based on different domains. In relation to the physical domain, the mean value was  $65.33 \pm 14.66$  with the lowest score of 22 and the highest being 100. The average score for emotional domain was 67.47, social was 76.51, while the one related to school was 57.32. Then, the lowest average quality of life value obtained was 27, while the highest was 87 with an average value of  $67.10 \pm 11.27$ .

**Table 3: Quality of Life (QOL) Value Based on Each Domain**

Domain QOL	Value of QOL		
	Mean $\pm$ SD	Lowest	Highest
Physical	$65.33 \pm 14.66$	22	100
Emotional	$67.47 \pm 15.30$	25	95
Social	$76.51 \pm 13.45$	20	95
School	$57.32 \pm 13.80$	20	100
The mean QOL score	$67.10 \pm 11.27$	27	87

According to Table 4, 54 (73.97%) of the 73 subjects had a poor quality of life from the physical domain. Also, most of the subjects had poor quality of life in the domains of emotional function and school, put at 54.47% and 80.82% respectively. For the social function, 54 subjects

(73.97%) were categorized under good quality of life. In addition, the psychosocial domain and function in total had 67.12% and 71.12%, respectively, included in the poor quality of life category.

**Table 4: Domains and QOL Patient**

Domain	QOL			
	Good		Not Good	
	n	%	n	%
Physical function	19	26.03	54	73.97
Emotional function	33	45.21	40	54.79
Social function	54	73.97	19	26.03
School function	14	19.18	59	80.82
Psychosocial function	24	32.88	49	67.12
Function in total	21	28.77	52	71.23

Based on Table 5, there is a significant positive correlation between the degree of weakness between the average quality of life of a child with thalassemia  $\beta$  major and education with  $p = 0.045$ . There was also a significant positive

relationship ( $p$  value = 0.024) between parents' income and the average quality of life value. However, there was no significant relationship between the average quality of life of thalassemia  $\beta$  major children with Hb, ferritin



levels, transfusion adherence, compliance with consumption of iron chelator, growth disturbance and type of iron chelator. Furthermore, a significant negative correlation was found

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between the mean quality of life of thalassemia  $\beta$  major children and the age at which blood transfusion began, at  $p = 0.030$ .

**Table 5: Bivariate Relationship between Independent Variables and QOL (n=73)**

Variables	QOL	
	Correlation Coefficient	p
Hb	0.045	0.706
Ferritin level	0.107	0.366
Transfusion compliance	-0.039	0.745
Compliance of iron chelator therapy	0.121	0.308
Growth disturbance	0.118	0.947
Parent education	0.236	0.045*
Parent income	0.264	0.024*
Type of iron chelator	0.057	0.631
Age of starting transfusion	-0.255	0.030*

\* $p < 0.05$

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The quality of life of  $\beta$  major thalassemia (TM) children is influenced by factors such as global, external, interpersonal, and personal conditions. Global conditions include government policies related to health services for TM patients in terms of facilities, infrastructure, blood supply for transfusion, as well as the provision of iron chelator. The external conditions include the presence or absence of infection or other comorbidities, degree of activity, environment, weather or seasons, number of siblings, education and economic status of parents. Interpersonal conditions which play important roles in the quality of life of TM patients include social relationships in the family, involving parents and siblings, as well as relationships with friends. Personal conditions include race, sex, age, disease onset and status, nutritional status, 4 well as genetic makeup [1]-[2], [11].

In general, the assessment of quality of life is 4 objective. Self-assessment is the gold standard for assessing quality of life. However, for children, cognitive development is the major consideration for assessing the quality of life, which is done accompanied by the parents. PedsQL is an instrument used in assessing the quality of life of both the affected children and the parents.

Based on the demographic characteristics of the subjects, the ages are almost the same, both the 8-12 years and 13-18 years. This shows that the government policies related to TM patients such as medical expenses provided by the government, improvement of health facilities and the development of iron chelation drugs, all increase the life expectancy of TM patients.

The results of this study showed that 76.71% of the subjects with thalassemia major  $\beta$

experienced growth disorders. This prevalence is higher than in a previous study conducted in India, in which 54% of thalassemia major children had growth disorders.<sup>12</sup> Also, impaired growth due to endocrinopathy is most commonly found in patients with transfusion-dependent  $\beta$  major thalassemia. According to a study, the rate of longitudinal growth was lower in thalassemia patients after 4 years old compared with normal children and bone development was delayed after 6-7 years old. Lower and reduced puberty growth rates are the main cause of retardation in growth experienced by thalassemia sufferers, thereby leading to short statures. This affects the patients' quality of life, especially from the physical domain. Also, decreased insulin like growth hormone factor-I (IGF-1) secretion occurs in most thalassemia patients due to chronic anemia, hypoxia, and liver diseases, as well as iron overload and endocrinopathy [13]-[15].

Based on the compliance with blood transfusion, 58.9% of the subjects routinely undergo transfusion. The level of adherence is influenced by psychosocial factors, economic conditions, and fear on the risk of contracting hepatitis infection and HIV through the transfusion [14]. Then, physical changes such as in the face, darkened skin or enlarged abdomen of children usually make parents to cover up the condition of the children through shame, which leave high number of patients who do not routinely perform transfusions [12]-[13], [15].

Pre-transfusion Hb levels were  $7.28 \pm 1.1$  g / dL, with the lowest Hb levels at 4.5 and the highest at 8.9 g / dL. There was no significant relationship between the mean quality of life of TM children with Hb levels in this study. This might be due to other factors which could

influence Hb levels such as the transfusion interval usually determined by the economic status of TM patients. Other researchers reported that through regular blood transfusion and maintenance of Hb levels at  $\geq 9$  g / dL, children with thalassemia would experience normal growth and development until the age of 10-12 years, thereby improving the children's quality of life. Low levels of hemoglobin and hematocrit usually result in changes in facial shape and spleen enlargement which would eventually affect physical appearances of TM patients [12]-[13], [16]. In this study, a positive weak relationship was established between the average quality of life of TM patients and the age of starting blood transfusion ( $r = -0.255$ ,  $p = 0.030$ ). Blood transfusion conducted at higher ages usually has a negative impact on the quality of life of these TM patients.

The iron which comes from the destruction of erythrocytes and through blood transfusions on a regular basis, usually result in iron overload. The iron is then deposited in various organs such as the liver, pancreas, heart, endocrine and gonad glands. Various complications could occur due to iron overload and these include endocrinopathy, diabetes mellitus, hypothyroidism, hypoparathyroid and adrenal insufficiency fibrosis or cirrhosis of the heart, as well as heart disorders such as cardiomyopathy which could lead to heart failure, a major cause of death in thalassemia patients [17]-[19].

Various factors are responsible for the growth disturbance experienced by thalassemia patients. These could be ethnic, genetic and hormonal factors of each patient. Nutritional, vitamins C and D deficiencies, lack of physical activity and psychological disorders all contribute to growth disorders in TM patients [12]-[13]. Also, hypogonadotropic-hypogonadism results from damage to the hypothalamus and anterior pituitary due to iron overload. Moreover, gonadotropins produced by the anterior pituitary are very sensitive to oxidative damage caused by iron overload. Therefore, the overload in the anterior pituitary gland could damage this gland thereby resulting in the disruption of the GH pathway. In addition, damage to the anterior pituitary causes impaired GH secretion, which hinders the production of IGF-I and IGFBP3 by the liver. This eventually affects the rate of bone growth thereby causing short statures [19]. The condition of hypothyroidism usually plays a role in growth disorders in TM children. Additionally, thyroid hormone plays an important role in bone maturation, affects GH secretion and chondrocytes directly by increasing IGF-I

secretion, and stimulates chondrocyte maturation [18]-[20].

Generally, iron chelation therapy is very necessary for all patients with repeated transfusions to remove excess iron. This excess iron normally pills up in organs such as liver, heart and endocrine glands. Currently in Indonesia, there are 3 types of iron chelation drugs, namely; deferoxamine, deferiprone and deferasirox. This therapy is usually given when the serum ferritin levels  $> 1000$  ng / mL or transferrin saturation  $> 70\%$ . It could also be administered when the laboratory data are not available or when the patient is estimated to have received 3-5 liters or 10-20 times pack red blood (PRC) transfusion. This type of investigation is the gold standard for detecting excess iron in the heart and liver using magnetic resonance imaging (MRI) with the T2\* program. Normally, the deposits in the heart and liver do not correlate precisely with serum ferritin levels, therefore, patients with serum ferritin levels below 2500ng / mL, often have a large amount of iron deposits in the heart with MRI T2\*  $< 20$  millisecond (ms) values, or MRI T2 \* values liver  $< 6.3$  ms [21]-[24]. This iron chelation therapy requires high commitment and adherence from the patients, as well as the family and community supports. The choice of iron chelator for each individual could be different considering its effectiveness, side effects, availability, price, quality of life and patients comfort, considering the fact that it has to be used continuously. Although it is given free of charge by the government, patient's compliance in the consumption of iron chelator is low. This low level of compliance is influenced by psychological factors (the patient feels bored), low knowledge of the benefits of administering iron chelation therapy, side effects of the drug such as nausea and vomiting, as well as its availability. Based on a previous study, irregular consumption of iron chelation drug usually affects the growth of thalassemia children [8]. The therapy aims to detoxify excess iron binding to plasma which is not bound by transferrin / binding iron non transferrin (NTBI) plasma and removes it from the body [17].

The average quality of life value of the subjects was  $< 70$ , meaning poor quality of life, in the physical, emotional, and school domains. The same results were obtained in a previous study which concluded that thalassemia is a chronic disease with a negative influence on quality of life and muscle strength in children [25]. Splenectomy, short stature, malnutrition and length of hospital stay are significantly associated with poor quality of life [26]. In the school

domain, the problem of absenteeism during transfusion usually hampers the academic involvement of the patients due to routine hospital visits [27].

Also, parental education is an important factor at the level of family social status. The pattern of care given to a child determines the psychosocial development of such child. Proper education about the disease, modes of treatment, and possible complications due to irregular treatment could affect the compliance level with blood transfusion and iron chelation therapy which directly impact on the life expectancy of TM children [28]. This study showed that higher levels of parental education and family economic status improved the quality of life of sufferers. Similarly, the knowledge and understanding of the disease, its treatment and the importance of undergoing regular treatment determine the compliance to the therapies capable of improving the patients' quality of life. The participation level of medical personnel and nurses is also an important key for compliance in undergoing treatment.

The limitation of this study is the fact that many other factors that ought to be considered as variables, were not investigated. These include the clinical picture of the patient, hormone levels, vitamin D status, zinc levels, infection conditions and other comorbidities in TM patients which could affect patients' quality of life.

## CONCLUSION

The results showed that 71.23% of respondents had poor quality of life. also, the prevalence of transfusion adherence, compliance with the consumption of iron chelator and growth disturbance experienced in TM patients were 41.1%, 21.92% and 76.71% respectively. In addition, the higher the level of education and income of parents, the higher the quality of life of TM children. Furthermore, the higher the age of commencing the transfusion, the lower the quality of life of TM children.

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