

# Predictors of Non-adherence to iron chelation therapy in pediatric thalassemia patients

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## Abstract

**Objective:** This study was conducted to identify predictors of non-adherence to iron chelation therapy among children suffering from  $\beta$ -thalassemia major across different treatment regimens.

**Materials and Methods:** It was a cross-sectional study carried out from 1st January 2019 to 30th June 2019. The study was conducted at the Pakistan Institute of Thalassemia, Islamabad. Children between the ages of 2 -16 years suffering from  $\beta$ -Thalassemia major and taking iron chelation therapy were included in the study. Chelation adherence for this analysis was defined as the percent of doses taken in the last 12 weeks out of those prescribed. Guardians of patients were interviewed using a questionnaire and medical records were checked. Data were analysed using SPSS 20.0. Multivariate analysis was conducted to identify the predictors for non-adherence to chelation therapy. The significant value was set at  $\leq 0.05$ .

**Results:** Mean age of the patients in our study was  $8.90 \pm 3.74$  years. There were 33 males and 64 females. Most of the patients  $n=87$  (89.7%) were taking oral iron chelation therapy. The mean score for chelation adherence was 67.12%. Among the multiple demographic, medical-related, and patient-related factors analysed, travel time from the patient's residence to treatment centre and the number of transfusions per year were found to be significant predictors ( $p$ -value  $\leq 0.05$ ) of non-adherence to iron chelation therapy.

**Conclusion:** Overall, the study provides strong evidence that healthcare-related factors play a major role in patients' adherence to treatment. A systemic approach should be taken to ensure patient adherence during the management of paediatric thalassemic patients.

**Keywords:** Adherence, chelation therapy, thalassemia.

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## 1. Introduction

Thalassemia Major is one of the most common genetic blood disorders worldwide with almost 5000-9000 children born annually with this disease in Pakistan alone. It is estimated that, in Pakistan, almost 50,000 children are suffering from this disease and another 9.8 million are carriers.<sup>1</sup> Thalassemia results from the quantitative and variable reduction of  $\beta$  globin chains. Children suffering from this condition are unable to maintain their hemoglobin because of ineffective erythropoiesis, peripheral hemolysis, and a reduction in hemoglobin synthesis.<sup>2</sup>

These patients require regular blood transfusions which eventually lead to iron overload, as one unit of blood contains 200-250 mg of iron. Besides, due to ineffective erythropoiesis, there will be increased intestinal absorption possibly due to the production of hormones GDF15 and other proteins (eg TWSGI) from erythroblasts. Both of these inhibit hepcidin

synthesis which is required to inhibit iron absorption.<sup>3,4</sup>

Increased iron may cause serious complications in thalassemic patients ultimately leading to cirrhosis of the liver, diabetes, heart disease, and hypogonadism. To prevent iron overload, iron chelation therapy (ICT) is used to enhance iron secretion from the body. Currently, three drugs are approved for use and include deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX).<sup>5,6</sup> Although these drugs are effective in removing iron, compliance with these drugs is a major concern in underdeveloped countries. Several demographic, social, and clinical factors act as barriers to adherence to ICT. This not only leads to the poor life quality of affected individuals but also increased health costs for the individuals and the government in the long run.<sup>7,8</sup>

Despite the immense burden of disease in Pakistan, no study has ever been conducted to assess the factors that predict non-adherence to iron chelation therapy. We undertook this study to identify the factors that may create hindrances to chelation therapy. Highlighting these predictors would guide

the health care professionals and government officials in the refinement of the national thalassemia program.

## 2. Materials & Methods

### Study Design, Sampling, and Setting:

It was a prospective cross-sectional study carried out from 1st January 2019 to 30th June 2019 at the Pakistan Institute of Thalassemia, Islamabad. Children between the ages of 2 -16 years suffering from  $\beta$ -Thalassemia major and taking iron chelation therapy for at least one year were included in the study. Children suffering from other chronic diseases like diabetes, tuberculosis, and asthma were excluded. The sample size was calculated using the WHO sample size calculator. Keeping population size as infinity, anticipated % frequency (p) as 95, Absolute precision required 5% of (p), Confidence level 95%, the sample size was calculated to be 81. Considering the possibility of possible non-response following formula was applied;

$N$  (Final adjusted Sample size)=  $n$  (calculated sample size)/  $1 - 20\%$ .

The final adjusted sample size was thus found to be 101. An estimated non-probability consecutive sampling technique was used.

### Data Collection Procedure:

Initially, 101 patients were recruited into the study, however complete data information could be collected from only 97 children, others with incomplete or no responses were excluded from the study. Demographic and clinical data were collected by interviewing the guardians of children and by reviewing record files. Parental knowledge about the disease was assessed by a pre-validated structured questionnaire comprised of 16 items and three response options (Yes, No, Don't Know). Items were scored using 0 (for incorrect answers or do not know) and 1 (for correct answers). The total score was a summation for the 16 items. A score of 0-5 was considered as low, 6-10 as acceptable, and 11-16 as high.

The socioeconomic class was categorized as low, middle, and high based on the income, education, and occupational status of the family. Adherence to chelation therapy was calculated over three months. It was taken as a percentage of doses taken in the 12 weeks out of those prescribed. An adherence to chelation therapy of at least 80% was taken as optimal.

### Ethical Considerations:

An institutional review board approval was obtained prior to data collection. The aims of the study were explained to all potential participants and their guardians and written informed consent was obtained from those who were willing to participate.

### Statistical Analysis:

Data were analyzed using SPSS version 20.0. Descriptive statistics were used to describe the characteristics of participants.

A univariate regression analysis was conducted to identify factors associated with non-adherence to chelation therapy. Significant factors in univariate regression analyses ( $p < 0.20$ ) were entered into a multivariate logistic regression analysis to assess the effect of several factors as predictors of treatment non-adherence. For this analysis, the backward selection was used and non-significant variables were removed singularly in order of least significance. Independent predictors of the outcome variable were identified by keeping the  $p\text{-value} \leq 0.05$  as significant.

## 3. Results

The results of our study showed an age range of 3 -15 years, with an average age of  $8.90 \pm 3.74$  years. The female to male ratio was 1.93:1. Most of the participants belonged to a poor socioeconomic class with a generally low level of education. The sociodemographic and clinical characteristics of our study population are shown in Table 1.

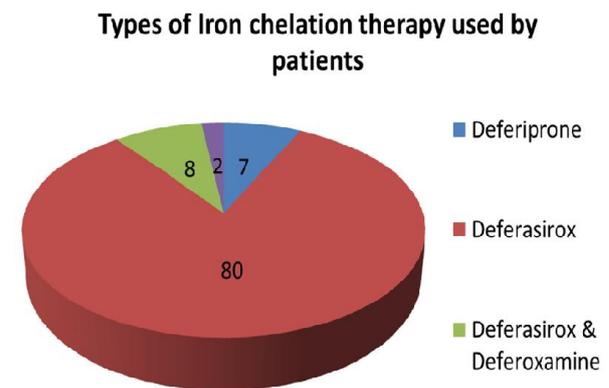
**Table 1: Sociodemographic and clinical characteristics of the study population**

<i>Variables</i>		<i>N (%)</i>	<i>Range</i>	<i>Mean</i>	<i>SD</i>
<b>Age (years)</b>	<i>Age &lt; 10 yrs</i>	53 (54.6)	3-15 yrs	8.90	3.74
	<i>Age <math>\geq</math> 10 yrs</i>	44 (45.4)			
<b>Gender</b>	<i>Boys</i>	33 (34)			
	<i>Girls</i>	64 (66)			

<b>Age at 1st chelation</b>		2-10	2.89	1.23
<b>No of transfusions (yrs)</b>		12-24	15.11	3.25
	Poor	68 (70)		
	Middle	29 (30)		
	High	0 (0)		
<b>Other siblings with thalassemia</b>		29 (30)		

The participants were taking different types of ICT, however, the majority (79%) were taking oral iron chelator Deferasirox Figure 1. The average rate of adherence to ICT was  $67.12 \pm 22.66$  with a range of 11.11-100. A significant number of children, that is 62 (63.9%) showed non-adherence to chelation (defined as avg adherence:  $< 80\%$ ). In the univariate analysis, 16 factors were evaluated for being possible predictors of non-adherence. The results are shown in Table 2. 30% of the children already had a previously affected sibling with thalassemia major and these children were more likely to be non-adherent to ICT. The p-value was significant. Patients belonging to the poor socio-economic class and those who were not receiving any free medications from either NGO or government programs were more likely to be non-adherent. About 21 (21.64%) participants mentioned that they forget to take a dose at least sometimes and another 18 (18.55%) accepted that they had intentionally decreased the dose.

However, these factors related to patient negligence failed to reach significant value.



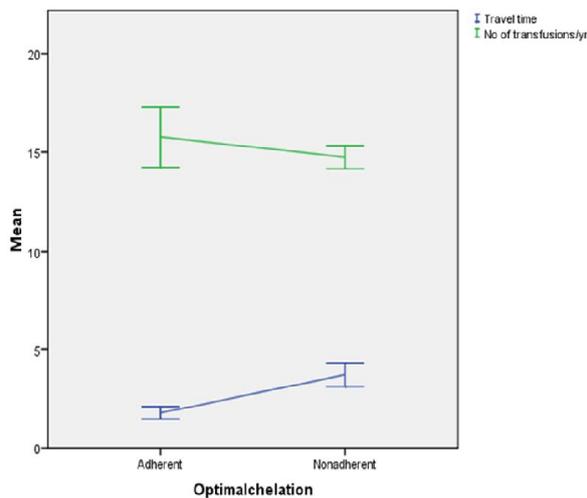
**Figure 1: Pie chart showing pervarious types of iron chelation therapies used by children**

**Table 2: Univariate analysis of predictors associated with non-adherence to chelation therapy**

Variables	Optimal Chelation		OR (Confidence interval)	p-value
	Yes	No		
<b>Age group &lt;10 yrs</b>	21/35 (60%)	32/62 (52%)	0.71 (0.31-1.65)	0.42
<b>Gender (Male)</b>	11/35 (31%)	22/62 (35%)	1.20 (0.49-2.90)	0.68
<b>Age at diagnosis (After 9 mths)</b>	07/35 (20%)	12 /62 (19%)	0.96 (0.33-2.71)	0.93
<b>Treatment duration</b>	5.60±3.58	6.09±3.20	1.04 (0.92-1.18)	0.48
<b>Treatment type (Deferisirox)</b>	26/35 (74%)	54/62 (87%)	2.33 (0.80-6.75)	0.11
<b>Siblings with thalassemia (No)</b>	29/35 (82%)	39 /62 (62%)	0.35(0.12-0.97)	0.04
<b>Financial status (Low)</b>	21/35 (60%)	47/62 (76%)	2.08 (0.85-5.09)	0.10
<b>Free Medications (No)</b>	04/35 (11%)	22/62 (35%)	4.26 (1.33-13.65)	0.01
<b>Side effects (yes)</b>	12/35 (34%)	16 /62 (26%)	0.37(0.27-1.64)	0.66
<b>Easy availability of medications. (Always)</b>	07/35 (20%)	02/62 (3.2%)	0.17 (0.03-0.89)	0.03
<b>No of doses /week</b>	21.89±12.05	19.97±9.58	0.98 (0.94-1.02)	0.32
<b>Travel time</b>	1.80±0.95	3.72±2.36	2.31 (1.44-3.69)	0.00
<b>No of transfusions/year</b>	15.77±4.44	14.74±2.30	8.88(1.76-44.67)	0.00
<b>Knowledge about Thalassemia (Low)</b>	06/35 (17%)	25/62 (40%)	3.35 (1.21-9.27)	0.02
<b>Forget intake of medicine (Never)</b>	22/35 (62%)	37/62 (59%)	0.84 (0.29-2.40)	0.74
<b>Decrease dose intentionally (Rarely)</b>	03/35 (8%)	02/62 (3.2%)	0.42 (0.56-3.21)	0.40

Reference categories: Age;  $\geq 10$  years, Gender; Female, Age at diagnosis; Before 9 months, Treatment type; others, siblings with thalassemia; yes, financial status; middle class, free medications; yes, side effects; No, Easy availability of medications; Sometimes, knowledge about thalassemia; acceptable, forget medication intake; sometimes, decrease dose; sometimes.

In the multivariate analysis by backward logistic regression only travel time and number of transfusions in a year were found to be statistically significant independent predictors of non-adherence to ICT. Figure 2



Error Bars: 95% CI

**Figure 2: Graph showing the relationship between the number of transfusions/year and travel time to adherence to chelation therapy**

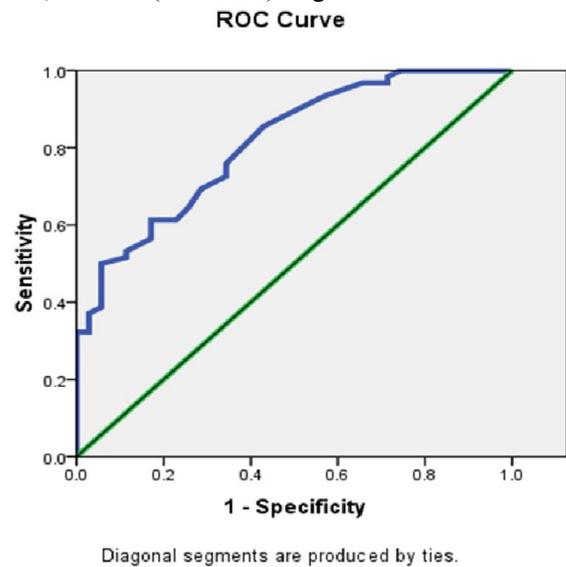
With every unit increase in travel time from home to the treatment center patients were more likely to become non-adherent to ICT. Whereas, increasing the no of transfusions in a year had a negative correlation with non-adherence to ICT. The difference was found to be significant at 0.03. Table 3

**Table 3: Multivariate analysis of predictors associated with non-adherence to chelation therapy**

<i>Variables</i>	<i>OR(Confidence Interval)</i>	<i>p-value</i>
<i>Travel time</i>	2.63 (1.56-4.43)	0.00
<i>Number of transfusions</i>	0.81 (0.67-0.98)	0.03

To evaluate the ability of the final model, generated by multivariate analysis, in predicting non-adherence a

ROC curve was drawn. It was found to be a good and reliable predictor of non-adherence with an AUC of 0.812, 95% CI (0.72-0.89). Figure 3



**Figure 3: Receiver operating characteristics for predictors of non-adherence to chelation therapy through multivariate logistic regression analysis**

#### 4. Discussion

Although South Asia is considered an area with a high incidence and prevalence of thalassemia major, this is the first study that looks into factors that may act as barriers to ICT which constitutes a major treatment modality for these patients. The results of our study indicate that a large majority of children (64%), in our study population were non-adherent to ICT. A study carried out in India demonstrated that 63% of children showed average and 4% showed poor compliance to ICT whereas the rest 33% had a good compliance score.<sup>13</sup> The results of a Jordanian study showed adherence rates ranging from 47 % to 73%.<sup>14</sup> Our study utilized a pill count method for measuring adherence which does not rely on mere patient recall and by definition considered 80% adherence as optimal. The Indian study utilized a compliance score based on pre and post-transfusion hb,<sup>11</sup> whereas both self-report and serum Ferritin measurement levels were used for

measuring adherence among Jordanian children.<sup>14</sup> In our opinion, objective methods of measuring adherence are more reliable and should be utilized in clinical and research settings. Although, the method and scoring criteria were different in our study and those quoted above, making it difficult to compare the results but still we deduce that the rate of adherence in our population was less when compared with other studies.

Adherence to ICT is the main factor affecting the quality of life in thalassemia patients. Gaps in ICT lead to raised levels of labile plasma iron which is toxic to tissues.<sup>15</sup> Several demographic, medical, and social factors may act as barriers to ICT. In our study, we evaluated 16 such factors. Kloub et al<sup>14</sup> in their study found age to be a significant predictor of treatment adherence, as adolescents, less than 16 yrs of age showed significantly greater adherence to ICT when compared to those over the age of 16. Whereas gender did not affect treatment adherence. This was most likely because younger children are more amenable to the parental directive and are directly under their supervision. Our study was carried out in children less than 16 years and although children under 10 yrs of age were more compliant with ICT. The difference was found to be non-significant. Similarly, no gender-based prejudices were identified with regard to treatment adherence.

Kloub et al found that study subjects belonging to poor socioeconomic class and those who already had another affected sibling were prone to non-adherence.<sup>14</sup> Our univariate analysis results revealed a similar trend with patients with lower income (p-value 0.10) and those having an affected sibling more likely to be non-adherent (p-value 0.04) Health care in Pakistan and other low-income countries are not free,<sup>17</sup> therefore, patients can't purchase medications at all times. Similarly, when these patients are already overburdened financially because of healthcare-related costs of one diseased offspring, the next affected sibling is more likely to be neglected. This emphasizes the importance of universal health coverage that is practiced in the modern world, where health is equal and free for all.<sup>18</sup> Health care is primarily the responsibility of the state. Policymakers in conjunction with non-governmental organisations (NGOs) should design and implement steps to promote the availability of free medications to thalassaemic patients as our study shows patients who were not getting free medications had more odds of being non-adherent than those who

were getting such medications through NGO or govt program, the p-value was found to be significant in univariate analysis denoting an association. Awareness about thalassemia also had some role in determining patient compliance, with those more knowledgeable about the disease showing improved adherence during univariate analysis (p-value 0.02). Previous studies have supported this finding at some levels.<sup>19</sup> However, in regression analysis when other factors were taken into consideration and interdependence between all factors was considered, these individual variables were not found to be significant predictors of treatment adherence. Other studies by Manal et al and Sidhu et al also fail to denote an association between knowledge about thalassemia and treatment adherence.<sup>20,21</sup>

The central finding of our study was that travel time from home to the treatment center and no transfusions in the past year were found to be the most powerful predictors of non-adherence after multivariate analysis. We found that increased travel time and decreased frequency of transfusions directly corresponded to reduced adherence. This is most likely since increased travel time would lead to increased fuel consumption and resultant increased cost for the affected child's family, hence in a developing country, it is not unusual for the already poverty-stricken population to skip the treatment altogether to avoid such expenses. Although this factor has not been explored in the context of thalassemia, a study by Varela et al<sup>22</sup> in Malawi reported that an estimated 40 to 50% of the population lacked either proper mode of transport or did not have the money to access transport even to a local hospital. Therefore depicts the importance of proper transport to avail basic health care. Increased frequency of transfusion in our study leads to increased adherence, which signifies the fact that increased iron load and resultant increased side effects combined with the strain of repeated hospital visits due to transfusions make the patient realize the gravity of the situation leading to improved ICT adherence. The results of a study by Kloub et al<sup>14</sup> were contrary to our findings and did not report any significance associated with the number of transfusions.

Standard management of thalassemia needs a multidisciplinary approach involving pediatric hematology, transfusion medicine, endocrinology, cardiology, and psychology along with a well-structured blood bank system. Unfortunately, developing countries like Pakistan lack such facilities,

due to which patients avoid proper treatment. This leads to a vicious cycle and it affects the overall health and life expectancy of patients.<sup>23</sup>

## 5. Conclusion

To conclude, travel time and the number of transfusions given per year are powerful predictors of non-adherence to ICT. These barriers lead to grave systemic side effects for the patient later on in life and also add to the economic burden for the government due to increased health-related costs.

Our results imply that at a state level, the availability of treatment to thalassemic children should be ensured to all children free of cost to improve ICT adherence. To combat, transportation barriers particular attention should be given to far-flung areas with difficult access to thalassemia centers, and small centers for thalassemia should be made in all government hospitals so that regular treatment of the majority of the thalassemic population could be ascertained.

Health care personnel should educate parents of thalassemic children, at the initial stages regarding the side effects due to treatment non-adherence. Moreover, Clinicians need to regularly assess, monitor and promote adherence behavior. Where adherence is a problem, a systemic approach should be taken and considerations of patient and family-specific factors should be made and included in formulations and management.

**CONFLICTS OF INTEREST-** None

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**Potential competing interests:** None to report

**Contributions:**

M.K, N.T, G.R- Conception of study

M.K, RSA, N.T, G.R- Experimentation/Study conduction

M.K, RSA, N.T, G.R- Analysis/Interpretation/Discussion

M.K, RSA, N.T- Manuscript Writing

M.K, RSA, N.T- Critical Review

M.K- Facilitation and Material analysis

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