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Study of Significance of Echocardiography and Estimation of Serum Ferritin Levels in Beta-thalassemia Major Patients

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Abstract: *Objectives:* Mean prevalence of thalassemia is nearly 3.5%. Approximately 4% of world's population is carrier of alpha and beta thalassemia. Cardiac complications are the most common cause of death in β-Thalassemia major. In India, studies regarding screening of cardiac complications in first decade by echocardiography are minimal. This study was done to assess the significance of Echocardiography in early detection of cardiac complications in Beta-thalassemia major patients. *Methods:* This study was conducted from March-2021 to October-2022 on 60 Beta-Thalassemia major patients aged between 2 to 18 years coming to Al-Ameen Medical College Hospital, Vijayapura. Patients with congenital heart disease or terminal illness were excluded. After detailed history and clinical examination, investigations were done; which included complete blood count, serum ferritin estimation, Chest X-ray, Electrocardiography and Echocardiography. Patients were categorized into two age groups, 2-9 years and 10-18 years respectively and the results were compared. *Results:* 71.67% (n=43) patients had increased Left Ventricular Mass of which 40% (n=24) belonged to 10-18 years and 31.67% (n=19) belonged to 2-9 years age group. Among 16.67% (n=10) patients who had pulmonary hypertension, 10% (n=6) belonged to 10-18 years and 6.67% (n=4) belonged to 2-9 years age group. Correlation of Serum ferritin levels with Cardiac abnormalities was statistically insignificant. *Conclusion:* Cardiac complications can occur in first decade also secondary to chronic anaemia and iron overload. Whereas Serum Ferritin levels are not representative of cardiac abnormalities, Echocardiography should be used as screening tool in asymptomatic Beta-Thalassemia major patients even in first decade of life.
Keywords: β-Thalassemia major, Echocardiography, Serum Ferritin.

Abbreviations: β-TM, β-Thalassemia major; TDT, Transfusion-dependent thalassemia; CIO, Cardiac iron overload; PH, Pulmonary hypertension; TR, Tricuspid regurgitation; MRI, Magnetic resonance

Introduction

Thalassemia is the most common of all inherited hemoglobinopathies. Among 270 million carriers of different hemoglobinopathies, 30% are carriers of β thalassemia in the world population [1]. Beta Thalassemia major is a severe form in which patients require early transfusion therapy [2]. These patients require regular blood transfusion throughout their lives, so iron overload should be looked for in such patients and further complications should be avoided. Beta thalassemia has higher prevalence of cardiac iron overload than other subtypes of thalassemia [3].

One method for evaluating iron overload in thalassemia patients is measuring serum ferritin which is simple and feasible method. Several studies have demonstrated the link between serum ferritin level and prognosis of patients [4]. It is most available means for follow up and altering the dose of chelation therapy. Effects of iron overload can be decreased and possibly reversed by chelation therapy [5-6].

Cardiac complications are reported to be the cause of deaths in 71% of the patients with beta thalassemia major [7-8]. Echocardiography is useful non-invasive tool for early detection of silent cardiac dysfunction which is the early pathophysiology in transfusion dependent Beta Thalassemia major patients. Though cardiac MRI is the gold standard in evaluating cardiac iron load (CIO), Echocardiography is

widely used because of its advantages such as its cost effectiveness, widely availability, less time consumption when compared to MRI [8-9]. In India, studies regarding regular screening of cardiac complications in first decade by echocardiography are minimal.

Apart from detection of pertinent cardiac changes it is also necessary to find whether the levels of ferritin in serum correlate with cardiac changes evaluated by Echocardiography. This study was done to assess the significance of serum ferritin levels which will help in titration of chelation therapy. Early detection of silent myocardial insult or cardiac complications by echocardiography is very important and crucial to optimize and administer ideal chelation of myocardial iron deposition and improve outcome. Hence, by improving the quality of life and life span of beta thalassemia major patients.

Hence, with the following Objectives we proceeded with this study;

(1) To study the clinical profile and evaluate β-Thalassemia major patients aged between 2 to 18 years of age using Echocardiography and serum ferritin levels who are receiving regularly 1 or more transfusions per month visiting tertiary care.
(2) To establish the significance of Echocardiography in these patients.
(3) To study the co relation between Serum Ferritin levels and Cardiac function through echocardiography in these patients.

Material and Methods

This hospital based cross sectional study was conducted on patients in the age group of 2-18 years whose diagnosis was confirmed and documented as β Thalassemia Major and who were on regular blood transfusion, visiting Department of Pediatrics, Al-Ameen Medical College Hospital, Vijayapura. The patients were selected based on inclusion and exclusion criteria. Study was conducted from March 2021 to October 2022.

Inclusion Criteria: Patientsin the age group of 2 to18 years with Diagnosis confirmed as β Thalassemia Major by electrophoresis and who were on regular blood transfusion requiring one or more blood transfusion per month for more than one year; were considered and enrolled for the study.

Exclusion criteria: Patients / Parents not giving consent to participate in the study and Patients with congenital heart disease or terminal illness were excluded from the study.

Methodology: The study was approved by Institutional Ethical Committee. Informed parental consent was obtained from all the parents of patients enrolled in the study after explaining to them in detail about the study in their own language.Clinical history taking and analysis of old records was done which included the following: preliminary data, history regarding parents' consanguinity, family history, hemoglobin electrophoresis report confirming the diagnosis of Beta thalassemia major, age at diagnosis, frequency of blood transfusions, number of transfusions and chelation therapy; the duration and dose of chelation therapy.

Apart from examination for Vitals including Heart rate, Respiratory rate, Blood pressure and Temperature, Anthropometry was done which included measurement of height, weight and body surface area of the patients. General Physical Examination was performed followed by Systemic examination which included: Cardiovascular system examination for murmurs and rhythm abnormalities, Respiratory system examination to rule out lung infections, and Per Abdomen examination was done to assess for Hepatosplenomegaly.

Investigations which were done included: Complete Hemogram, Estimation of Serum ferritin level was done 2 times one month apart. The separated serum was used for the estimation of serum ferritin levels using ELISA based serum ferritin assay kit by chemiluminescence immunoassay method. Chest X-ray was done to look for the evidence of cardiomegaly using cardiothoracic ratio for age.

Electrocardiography (ECG): Standard 12 lead ECG was performed. Based on R/S ratio RVH and LVH were determined when R/S ratio is decreased in the respective leads. QTc interval

was calculated using Bazzet's formula. ECG was also used to know rhythm disturbances.

Echocardiography: It was performed by the same observer on all patients using a Siemens ultrasound machine, 2D Echo, M mode, and Doppler echocardiography was done as per the guidelines of American Society of Echocardiography [10]. Both electrocardiographic and echocardiographic examination were performed minimum 48 hours after the last transfusion. Left Ventricular end systolic and diastolic diameter, systolic and diastolic interventricular septum thickness, posterior wall thickness of Left Ventricle in systole and diastole was calculated using M–mode echocardiography. Following parameters were assessed and recorded to arrive at the estimation of Left Ventricle (LV) mass: LVEDD (LV end diastolic diameter), IV Sd (end diastolic interventricular septum diameter), PWd (LV posterior wall thickness in diastole). Left ventricular mass was calculated using the prescribed formulae utilizing aforementioned values [11].

Ejection fraction and fractional shortening were also determined. Tricuspid Regurgitant (TR) velocity and pulmonary pressure gradient were measured for estimation of pulmonary hypertension by continuous wave Doppler. Pulmonary hypertension was diagnosed when the mean pulmonary artery pressure was more than 25 mm of Hg.

Statistical analysis: Parameters pertaining to important aspects of history, anthropometry and physical examination were noted. Laboratory finding, Electrocardiography and Echocardiography related findings were also recorded. All characteristics were summarized descriptively. For continuous variables, the summary statistics of sample number, mean, standard deviation were employed. For categorical data, the number and percentages were used in the data summaries and data analyzed by Chi square test for association, comparison of means using 't' test, sensitivity, specificity and diagrammatic presentation. Data were analyzed to determine association between variables. The association between age, sex, frequency of blood transfusion and serum ferritin level were established. Chi-square test was used to compare the groups. A two-tailed p value of <0.05 was considered to be statistically significant. Other suitable methods of analysis used as per need. Statistical analysis was done using IBM SPSS version 23software.

Results

This study was conducted from March-2021 to October-2022 on 60 Beta-Thalassemia major patients aged between 2 to 18 years coming to Al-Ameen Medical College Hospital, Vijayapura. Patients were divided into two age groups. One group consisted of patients aged 2-9 years and the other group 10-18 years; and the results were compared. There were 32(53.33%) patients in 2-9 years age group and 28(46.67%) patients in 10-18 years age group (Table 1).The mean age was 9.45 ± 4.9 years with a range of 2–18 years.

Table-1: Demographical, Clinico-Diagnostic and other Radiological Parameters

A: Demographic	
Age	2-9 years age group - 53.33% (n=32) 10-18 years age group - 46.67% (n=28)
Gender	Male– 58.34%(35) Female– 41.67% (25)
Residence	Rural – 46.67% (28) Urban – 53.33% (32)
Consanguinity	Consanguineous Parents– 56.67% (n=34) Non-consanguineous parents–43.33% (n=26)
Socioeconomic Status	Low Socioeconomic Status of all the families
B: Clinical	
Heartrate	Tachycardia–35% (n=21) Normal – 65% (n=39)
Hepatomegaly	Present in all patients
Splenomegaly	Present in all patients
C: Laboratory Parameters	
MeanHemoglobin	(6.70 ± 1.51) gm/dl
Serumferritin level	>1000 ng/ml – 70% (n=42) <1000 ng/ml – 30% (n=18) Mean 1498.62 ± 590.02 ng/ml

D: Chest X-Ray	Cardiomegaly in 58.34% Normal in 41.67%
E: ECG Findings	Normal ECG - 63.33% (n=38) Abnormal ECG - 36.67% (n=22)
F: Echocardiography Findings	Abnormal -71.67% (n=43) Normal – 28.33% (n=17)

The minimum age at the time of diagnosis of thalassemia in our study was 4 months. The median age at the first transfusion was six months (range 4-16 months).Patients comprised of 35 males and 25 females. 53.33% of them were from urban areas. 56.67% (n=34) patients were born to parents with consanguineous marriage (Table 1).In our study, 95% (n=57) of patients of thalassemia major were on regular monthly blood transfusions whereas only 5% (n=3) of patients whose age was <=3 years were on blood transfusions once in two months. All of them were on chelation therapy.

Clinicopathological Parameters: 35% (n=21) of our patients had tachycardia and 65% (n=39) had normal heart rate for the age. Splenomegaly is important clinical feature and it was evident in all of our patients (Table 1). In our study, platelet counts had negative correlation with increase in spleen size with Negative significant correlation (Pearson correlation coefficient r = -0.361) (Figure 1).Mean haemoglobin at admission was 6.70gm/dl with minimum being 3gm/dl.There was presence of higher level of serum ferritin (more than 1000ng/ml) in 70% (n=42) of patients in spite of being on oral chelators. The mean serum ferritin concentration in patients aged between 2-9 years was 1334.06 ± 612.12 ng/ml, while in patients aged between 10-18 years; mean serum ferritin was 1686.68 ± 511.62 ng/ml (Table 2).

Fig-1: Correlation of Spleen size & Platelet Count (r=-0.36131, p Value= 0.0045)

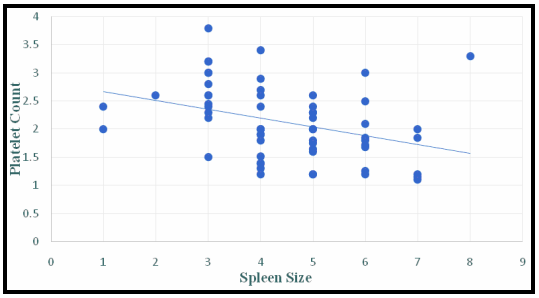


Table-2:Comparison of Findings Between 2 Age Groups

Parameters	2-9 years age group	10-18 years age group
Patients	53.33% (n=32)	46.67% (n=28)
Mean Hemoglobin	(6.98 ± 1.31) gm/dl	(6.39 ± 1.68) gm/dl
Serum Ferritin Level	>1000 ng/ml – 53.12% (n=17) <1000 ng/ml – 46.88% (n=15) Mean 1334.06 ± 612.12 ng/ml	>1000 ng/ml - 89.29% (n=25) <1000 ng/ml -10.71% (n=3) Mean 1686.68 ± 511.62 ng/ml
Echocardiography	Abnormal – 59.38% (n=19)	Abnormal – 85.71% (n=24)
LV mass- Echo	Increased – 59.38% (n=19) Normal – 40.62% (n=13)	Increased – 85.71% (n=24) Normal – 14.29% (n=4)
LVMI	104.50 ± 63.77	135.15 ± 32.40
LVEF (EF%)	69.27% ± 6.39	65.14% ± 5.20
LVFS (FS%)	38.67% ± 5.83	34.60 ± 3.51
TRV	2.41 ± 0.21	2.47± 0.22
PHT	Present - 12.5% (n=4)	Present -21.43% (n=6)

*Electrocardiography (ECG):*63.33% (n=38) patients had normal ECG findings and in 36.67% (n=22) of patients ECG was abnormal (Table 1). 19 out of the 42 patients with higher serum ferritin values had LVH findings on ECG where it was not seen in 23 of them. Whereas statistically no association was found between serum ferritin and RVH findings on ECG. Overall ECG was abnormal in 36.67% of patients. Qtc interval was in the normal range

in all patients. Electrocardiography did not show arrhythmias.

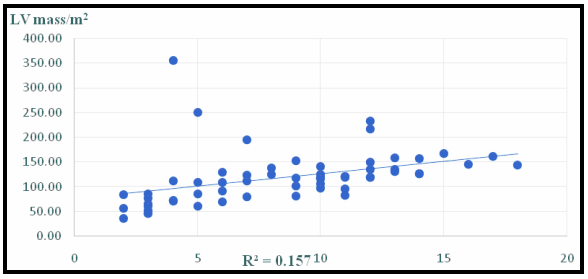
Echocardiography (Echo): Echocardiography findings were abnormal in majority of patients i.e., 43 patients (71.67%) had abnormal Echo findings (Table 1). Abnormal Echofindings were present in both the age groups (2-9 years and 10-18 years). Even though majority of patients in 10-18 years age group had abnormal Echo finding, significant proportion. i.e., 19 out of 32 patients (59.38 %) in 2-9 years also had abnormal echocardiographic findings. Which is statistically significant with p value being 0.0239 (Table2). Echocardiographic parameters which were considered in our study were summarized in Table 3.

Table-3:EchocardiographyParameterin all the Thalassemia Major patients

Echocardiography Parameter	Mean	Median	SD
LV Mass	102.30	100.5	53.32
LV Mass/m^2	118.81	118.18	53.43
LV Ejection Fraction (EF%)	65.5	67	6.18
LV Fractional Shortening (FS%)	32.9	37	5.26
TRV	2.4	2.5	0.22

LV Mass was increased in 71.67% patients (n=43) i.e., these patients had LV mass more than 95th centile for the corresponding age and gender in normal children. And LV Mass was normal in 28.33% patients (n=17). With respect to LV Mass in different age groups, we found that in 10-18 years age group, 85.71% (24 out of 28) patients had LV Mass increased. Whereas LV Mass was also increased in 59.38% (19 out of 32) patients belonging to 2-9 years age group; though comparatively less in number, yet it was statistically significant (Table 2).

Fig-2: Correlation of Age with LV Mass/m^2 (LVMI) (r=0.39, p value 0.0016)



There is Positive correlation (Pearson Correlation r=0.39) which exists between LVMI and age with statistical significance (p value 0.0016) (Figure 2). When we compared the results of same correlation in the two aforementioned age groups we arrived at similar result of positive correlation with statistical significance (Table 2). Whereas in this study, we found that there is weak positive correlation of LV mass/m^2 with the serum ferritin level.

In this study it was found that there is weak positive correlation of LVMI with the serum ferritin level (Figure-3). Also, there was statistically non-significant negative correlation between Serum Ferritin level and Ejection Fraction (Figure 4). 78.57% (33 out of 42) patients had increased LV mass and 21.43% (9 out of 42) had normal LV mass despite their serum ferritin level being more than 1000 ng/ml. 10 patients, even with serum ferritin <1000 ng/dl had increased LV mass and 8 had normal LV Mass.6 patients (6 out of 28, 21.43%) in the 10-18 years age group had pulmonary hypertension; whereas 4 patients in 2-9 years age group also had pulmonary hypertension (4 out of 32, 12.5%) (Table 2).

Fig-3: Correlation of Serum Ferritin with LV Mass/m^2(r=0.176, p Value=0. 177)

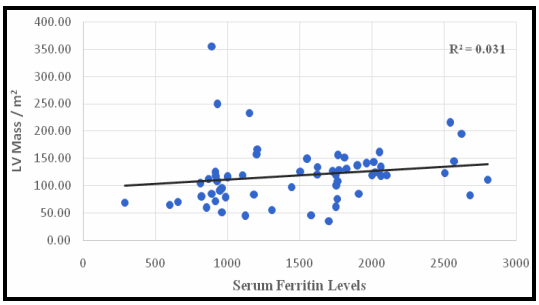
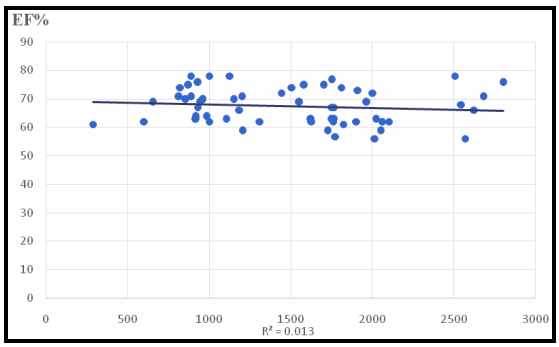


Fig-4: Relationship between Serum Ferritin Level and Ejection Fraction (r=-0.11486, p Value=0.382)



Discussion

An International Survey conducted by Carpenter et al. reported Thalassemia prevalence as follows: 47% disease prevalence in Europe, 30% prevalence in North America, 32% prevalence in South America, 43.5% prevalence in Middle East, 25% in North Africa,53% prevalence in Southeast Asia which was the highest and 44% prevalence in West Asia [12]. Mutations of β globin genes are seen prominently in South East Asia [13]. In Indian Scenario, prevalence is high in Punjab and Sindhis according to some studies [14-15]. Easy and early access to the facilities highlights the importance of geographical distribution.

In the present study 53.33% (n=32) of the patients were from urban set up and 46.67% (n=28) patients were from rural area. Urban population has easy access to regular transfusion and regular chelation therapy hence better outcome. The mean age of 60 patients which were part of our study was 9.45 ± 4.9 years with a range of 2-18 years which was lower than the studies conducted by Ghafour AS et al and Iarussi D et al [16-17]. Majority of the studies on cardiovascular complications done in the Mediterranean region and the South East Asian counties, involved patients who were more than ten years [18-19]. Cardiac complications can occur early in spite of regular blood transfusions and well administered chelation therapy.

In the present study males were more than females, similar to the result obtained by Torres et al [20]. Though the probability of the child inheriting the disease does not show sex predilection, it is seen more commonly in boys in few of the studies.In our study, 56.67% (n=34) were born to consanguineous parents and 43.33% (n=26) of them to non-consanguineous parents. It implies that the parents of the proband are heterozygous and obligate carriers reflecting the high frequency of carriers in the population. It can be due to de novo mutations also. It is important as the relatives of carriers should also be screened and genetic counseling and premarital testing can prevent these births. A positive family history of thalassemia major was recorded in 67.5% of the patients, and 55.5% of them gave a history of consanguineous marriage of parents in the study conducted by Koreti et al [21].

Because of limited availability of blood transfusion and healthcare facility patients coming from peripheral areas with poor financial and socioeconomic status, present with severe anemiaas found out in the study by Chanpura et al [22]. However, this was not the case in our study as both the groups from urban and rural population were on regular transfusions and still presented with severe anemia. Mean hemoglobin at the time of admission in all of our patients was 6.70 ± 1.51 g/dl. There was minor difference between 2 age group in this regard as 2-9 years age group patients had mean hemoglobin to be 6.98 ± 1.31 gm/dl, whereas it was 6.39 ± 1.68 gm/dl in 10-18 years age group. All patients were on regular chelation therapy.

Chronic anaemia causes increase in volume overload and heart rate. Cardiomegaly and myocardial dysfunction can be attributed to long standing hypoxia due to chronic anaemia. 35 patients out of 60 had Cardiomegaly on chest x ray, but only 28 out of 42 patients with serum ferritin levels more than 1000 ng/ml had Cardiomegaly as chest X-Ray finding. Cardiac iron overload cannot be attributed to raised iron and corresponding serum ferritin level alone. Splenomegaly is important clinical feature and it was evident in all the patients.

In our study, 85.71% patients (24 out of 28) in 10-18 years age group had LV Mass increased. Whereas LV Mass was also increased in 59.38% (19 out of 32) patients belonging to 2-9 years age group which was

statistically significant. In a study by Meloni et al it was seen that low risk of pulmonary hypertension was found in well transfused thalassemia major patients than thalassemia intermedia [23]. In our study, Pulmonary hypertension was seen in 10Thalassemia major patients.6 patients in 10-18 years age group had pulmonary hypertension whereas 2-9 years age group also had4 pulmonary hypertension patients (4 out of 32, 12.5%).

There is poor negative correlation between TRV and EF but weak positive correlation exists between TRV and LVMI suggesting that right and left ventricular dysfunction can occur independently (Table 4). Mean Ejection fraction was found to be 65.5%. Overall, it was found to be normal for age. No significant correlation was found between Ejection fraction and serum ferritin in our study (p=0.38). Studies by Yaprak et al and Ashena et al had the same finding [24, 4]. However, study by Bosi et al. revealed weak but significant correlation between left ventricular ejection fraction and serum ferritin level [25]. Some studies revealed negative correlation between serum ferritin and ejection fraction [26].

Table-4:TR Velocity and its correlation

Parameters	TRV and EF	TRV and LVM/m^2
Pearson correlation coefficient (r)	-0.2515	0.298690608
p Value	0.05257	0.020440006
Interpretation	Weak Negative Correlation	Poor Positive Correlation

Serum ferritin is commonly used for monitoring iron overload and it correlates with cardiac impairment and survival as suggested by one of the studies [27]. But serum Ferritin can be elevated as an acute phase reactant in infections and inflammation. It can also be raised in hepatic damage. In present study, most of the patients with Serum ferritin levels with values more than 1000 ng/dl were from 10-18 years age group compared to 2-9 years age group, which was statistically significant (p value P=0.002); suggesting that total number of transfusions determines the level of serum ferritin being higher than 1000 ng/dl. We found that mean serum ferritin level among all patients to be 1498.62 ± 590.02 ng/dl which was lower in contrast to studies by Aessopos et al. and our results in this regard were similar to Mohammad Reza Khalilian et al [27-28]. Higher mean serum ferritin levels in other studies can be attributed to less frequent and incorrect use of iron chelation.

Hemosiderosis, Cardiac Iron Overload can be prevented by chelation therapy directed towards iron chelation. Once patients cross specific number of transfusions, better compliance should be achieved with the current chelation therapy or appropriate modification of chelation therapy should be done as required. Subcutaneous deferoxamine can be made in early age so that early cardiac changes of dysfunction can be prevented. Study by Brittenham GM et.al has revealed better effect of subcutaneous chelation therapy by deferoxamine when compared to oral chelation in preventing cardiac Iron deposition [29].

In this study, Echocardiography findings were not compared with MRI; arriving at the efficacy of this procedure in exactly estimating Cardiac Iron Load (CIO) is not possible. Also, Serum ferritin is not an indicator of cardiac iron overload as discussed earlier. Even though mortality secondary to cardiac complications is seen in second decade, the pathologic changes start occurring in first decade itself. This should be diagnosed early by easily available, affordable, non-invasive technique like echocardiography. Echocardiography should be used for regular periodic monitoring. Thalassemia major patients should have regular echocardiography screening for any cardiac complications starting in the first decade itself.

Conclusion

Serum Ferritin level should be estimated regularly for every transfusion dependent thalassemia patient and accordingly regular chelation therapy should be administered. Cardiac changes and complications are known

to occur early in life. Whereas Serum Ferritin levels are not representative of cardiac abnormalities and complications, Echocardiography should be used as screening tool in asymptomatic Beta-Thalassemia major patients even in first decade of life making Echocardiography as part of Thalassemia care.

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