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# Evaluation of echocardiographic findings in beta thalassemia major patients in a thalassemia clinic of a tertiary care hospital

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ABSTRACT

**Background:** Thalassemia is the most commonly inherited haemolytic anaemia. Cardiac involvement is the leading cause of morbidity and mortality among the children of transfusion dependant beta thalassemia major due to myocardial iron deposition leading to heart failure and arrythmia.
**Aim:** The aim was to detect early heart failure in beta thalassemia major children by evaluating the cardiac function by echocardiography.
**Materials and Methods:** An observational cross-sectional study was conducted on 85 beta thalassemia major children between the age group of 1-12 years attending Thalassemia clinic of a tertiary care medical college and hospital from March, 2020 to July, 2021. A detailed history, clinical examination and cardiac investigations were conducted among them. Echocardiography was done to evaluate the different cardiac functions like ejection fraction (EF), early and late ventricular filling velocity ratio (E/A), LV mass, etc.
**Results:** In our study 62.4% were female and 37.6% were male. Mean age of our study was 7.2±2.8 and the age range was 2-12 years. All of them were having normal systolic function but 30.6% were having abnormal diastolic function on doppler echocardiography. The mean value of EF, E/A and LV mass were 66.52±4.37, 1.49±0.33 and 68.42±27.38 respectively. A weak but significant association was found between transfusion frequency and diastolic dysfunction (p-value 0.05) in our study.
**Conclusion:** Diastolic dysfunction is the earlier cardiac complication of thalassemia children. It is beneficial to conduct echocardiography in all thalassemia patients in their first decade to gain better understanding about cardiac function.



## 1. Introduction

Thalassemia is the most commonly inherited genetic disorders causing imbalance between alpha and beta globin chain production. Alpha thalassemia is due to deletion of alpha globin gene whereas beta thalassemia is due to point mutation of beta globin gene. Unbalanced alpha and beta globin chain production leads to formation of alpha globin tetramer and appear as RBC inclusions. This makes the RBC unstable and shortens RBC survival.[1,2]

In India, it is also estimated that 8000 to 10000 children are born with beta thalassemia major every year.[3] Haemoglobin disorders are the cause for about 3.4% death in children younger than 5 years.[4] Although repeated transfusion therapy dramatically improves the quality of life but transfusion induced hemosiderosis becomes the major clinical complication of transfusion dependant thalassemia. Iron is initially deposited in liver followed by endocrine organs and heart. Iron deposition in heart causes heart failure and arrhythmias.[5] Heart failure secondary to iron

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overload is the most common cause of death in patients with beta thalassemia major. Heart injuries include atria and ventricular dilatation, arrhythmia, valvular dysfunction, pericarditis and finally heart failure due to reduced cardiac output.[6]

In India, studies regarding regular screening of cardiac complication in first decade by echocardiography are minimal. Cardiac MRI is gold standard in evaluation of cardiac iron overload, but it is not readily available in resource poor settings due to its cost. Whereas echocardiography is widely acceptable due to its cost effectivity, wide availability, less time consuming and non-requirement of anaesthesia. Therefore, it can be used as a non-invasive screening test in thalassemia patients for early diagnosis of cardiac iron overload.[7,8]

The aim of the present study is to detect early heart failure in beta thalassemia major children by observing the pertinent signs of cardiac dysfunction by echocardiography.

## 2. Materials and Methods

A observational cross-sectional study was carried out among 85 beta thalassemia major children attending Thalassemia Clinic of Paediatric department of R.G. Kar Medical College & Hospital, Kolkata from March, 2020 to July, 2021 after obtaining Institutional Ethical Committee approval and who satisfy the 'inclusion criteria'.

### *2.1. Inclusion criteria*

All children between 1 year and 12 years of age diagnosed with beta thalassemia major by haemoglobin electrophoresis attending Thalassemia Clinic of Paediatric department of R.G. Kar Medical College & Hospital, Kolkata. Informed consent was taken from the parents of the study children.

### *2.2. Exclusion criteria*

1. Children with <1year & >12years of age.
2. Children with congenital heart diseases.
3. Children with active infection or other active inflammatory conditions.
4. Children whose parents were not willing to participate and give consent were excluded from the study.

### *2.3. Study tools*

Predesigned semi-structured questionnaire, echocardiography.

### *2.4. Methodology*

Initially history, demographic details, blood transfusion history, chelation history, etc were taken and thorough clinical examination were done. Anthropometry, routine blood investigations like CBC, CRP, LFT, ferritin level were assessed and Echocardiography was done in our hospital. All these are noted in a proforma sheet and a master chart was made in Microsoft Excel.

Echocardiography was performed on patients using a Philips ultrasound machine having a transducer of 3.5/5 and 2.5/5 MHz. 2D, M-Mode and Doppler echocardiography was done as per the guidelines of American society of Echocardiography. LVIDd (left ventricular internal diameter diastole), LVIDs (left ventricular internal diameter systole), systolic and diastolic interventricular septal diameter, left ventricular posterior wall thickness – these parameters were calculated using M-Mode echocardiography. Ejection fraction (EF) and fractional shortening (FS) were also calculated using the same. EF is a measurement of blood amount that left ventricle pumps out with each contraction. FS is the fraction of any diastolic dimension that is lost in systole and calculated by this formula: (LVIDd-LVIDs/LVIDd) × 100. Transmitral flow patterns were obtained by pulsed-wave Doppler echocardiography from apical four chamber views Mitral peak early (E) and late (A) diastolic velocities, E/A ratio and E wave deceleration time (DT) were also measured to evaluate the diastolic function of left ventricle. LV mass was calculated using the formula 0.8×1.04× [(LV end diastolic diameter + posterior wall thickness + interventricular septal thickness)3– (LV end diastolic diameter)3] +0.6 and LV mass index was indexed to body surface area.

### *2.5. Statistical analysis*

Data are expressed as frequency, percentage, mean ± standard deviation and range depending on distribution. Analysis was carried out using Microsoft Excel 365 and R Studio Version 1.3.1056. Statistical significance was accepted at the level of $p < 0.05$.

## 3. Result

Table 1 shows out of 85 enrolled beta thalassemia major children 62.4% (n=53) were female and 37.6% (n=32) were male. In our study the youngest child was 2 years old whereas the oldest one was 12 years old. Among them 43.5% (n=37) were between the age group of 2-6 years and 56.5% were between the 7-12 years age group.

Table 2 shows all of them were on oral chelators and none of them were having symptoms suggestive of heart failure. According to Doppler echocardiographic findings none of them were having abnormal systolic function as evidenced by normal values of ejection fraction and fractional shortening but approximately 6% of total study population were having ejection fraction less than 60%. On doppler echo 30.6% (n=26) of total enrolled children were having abnormal diastolic function of heart which is suggestive of presence of restrictive physiology pattern in heart and rest 69.4% were having normal diastolic function

as depicted in Tables 3 and 4 shows mean and standard deviation of different echocardiographic parameters. Mean values of EF, FS, deceleration time, E/A ratio and LV mass were 66.52±4.37, 36.99±5.77, 134.80±16.12, 1.49±0.33 and 68.42±28.66 respectively. Among them the most affected parameter was the LV mass.

In our study mean haemoglobin value at admission was 6.98 ± 0.78 and 74% children were having pre-transfusion haemoglobin in the range between 5-8 g/dl. No significant association was found between pre-transfusion haemoglobin value and cardiac dysfunction (p value 0.33). Total number of transfusions ranges between 18 to 183 times, one fourth of the study population required blood transfusions more than 100 times. No significant association was found between total no of transfusions and diastolic dysfunction (p value 0.16). Table 5 shows among 85 children, 6 of them were on twice monthly blood transfusions, 74 children were receiving monthly blood transfusions and only 5 children required transfusions once in 2 months. A very weak but significant association was also found between transfusion frequency and diastolic dysfunction (p value 0.05).

## 4. Discussion

β thalassemia is an autosomal recessive inherited haemoglobin disorder resulting in decrease synthesis of β globin chains causing severe anaemia which needs frequent blood transfusions. Although transfusion and chelation therapy has drastically improved the life expectancy of thalassaemia children, repeated transfusions lead to iron overload in different organs resulting in different complications like cardiomyopathy, hepatic fibrosis & cirrhosis, hypogonadism, short stature, hypothyroidism and other endocrine problems. Heart failure secondary to iron overload is the leading cause of mortality in patients with β thalassemia major.[9,10] Prevention of myocardial siderosis is a key step to reduce rate of mortality in thalassaemia children. Two factors mainly contribute the changes in cardiac structure and function – a) Iron overload and b) Increase in cardiac output (CO); iron overload due to repeated blood transfusions causes structural changes in heart resulting in decrease of left ventricular function and chronic anaemia along with marrow expansion causes volume overload and increase in cardiac output resulting in increased contractility of the heart which further aggravates the cardiac stress. Cardiac manifestations of thalassemia children are heart failure, arrythmia and ultimately premature death.[11,12] In recent years, many methods have been taken into consideration to study anatomical changes of the heart. However functional changes can be easily observed by echocardiography.

The study was conducted upon 85 transfusion dependant β thalassemia major children to evaluate the cardiac status by echocardiographic findings. Very few studies on cardiovascular complications of β thalassemia were done in the age group of below 12 years. In our study all the patients were less than 12 years of age. Mean age in our study was 7.24±2.76 as comparable to the Shivanna NH et al study whereas studies by Samira Z Sayed et al and Noor Mohammad Noori et al patients were more than 10 years of age.[13–15]

As per study, the average age of onset of heart failure in thalassemia children is 16 years if the child is not on regular transfusion and chelation therapy, however the age of onset increases with initiation of transfusion and chelation therapy.[9] In our study all the children are asymptomatic and no one was having the clinical signs and symptoms of heart failure which is comparable to the study of Hala Agha et al where out of 32 children none of them had clinical evidence of cardiac failure.[16] Studies by Leon et al and Athanasios et al showed that 7 out of 24 patients and 6 out of 197 patients had features of cardiac failure respectively.[17,18]

In our study all the 85 children had normal left ventricular ejection fraction suggestive of normal systolic function of heart. In contrary to that diastolic dysfunction was present in 26 (30.6%) children and rest were having normal diastolic function as on doppler echocardiography. Similarly, Chate SC in his study showed that out of 32 thalassemia children diastolic dysfunction was present in 19 (59.37%) patients and rest were having normal cardiac functions on echo whereas none of them were having systolic dysfunction as evidenced by normal ejection fraction.[19] Similar kind of findings were also noted in studies by Spirito et al and Hankins et al.[20,21]

LV mass was increased in one third of the study population i.e., these children had LV mass more than 95th percentile for the corresponding age and sex in normal children. 69% had less than 95th percentile for the corresponding age and sex when plotted on the age specific reference intervals for indexed left ventricular mass in children. Mean LV mass was 68.42 and LV mass index was 91.08. Similar findings were observed in studies done by Samira Z Sayed et al, Ameen Mosa et al and Assad Abdullah Abbas et al.[14,22,23] Both LV mass and LV mass index were seen increased in these studies. LV mass and LV mass index are increased in thalassemia due to multiple factors like chronic anaemia, tissue hypoxia and iron overload. The following dimensions left ventricular internal diameter in end diastole and end systole, interventricular septal thickness and posterior wall thickness of ventricular wall which were used to calculate the LV mass, also observed to be increased in these patients above the average normal levels. Similar findings were also seen in studies by Samira Z Sayed et al and Ameen Mosa et al.[14,22]

Our study reveals that pre-transfusion haemoglobin was between 5-8 g/dl in 74% of the children. This may be due to limited availability of blood transfusions, patients were from remote areas, financial issues and moreover non-

**Table 1:** Age and gender wise distribution of beta thalassemia major children (n=85).

| Age in years | Female | Male | Total |
|---|---|---|---|
| 2-6 | 21 (24.7%) | 16 (18.8%) | 37 (43.5%) |
| 7-12 | 32 (37.7%) | 16 (18.8%) | 48 (56.5%) |
| Total | 53 (62.4%) | 32 (37.6%) | 85 (100%) |

**Table 2:** Age wise distribution of Systolic Function by measuring Ejection Fraction (EF) on Doppler Echo (n=85).

| Age in Years | Systolic Function (EF<60%) | Systolic Function (EF>60%) | Total |
|---|---|---|---|
| 2-6 | 2 (2.4%) | 35 (41.2%) | 37 (43.5%) |
| 7-12 | 3 (3.5%) | 45 (52.9%) | 48 (56.5%) |
| Total | 5 (5.9%) | 80 (94.1%) | 85 (100%) |

**Table 3:** Age wise distribution of diastolic function of beta thalassemia major children on Doppler Echo (n=85).

| Age in Years | Abnormal Diastolic Function | Normal Diastolic Function | Total |
|---|---|---|---|
| 2-6 | 10 (11.8%) | 27 (31.7%) | 37 (43.5%) |
| 7-12 | 16 (18.8%) | 32 (37.7%) | 48 (56.5%) |
| Total | 26 (30.6%) | 59 (69.4%) | 85 (100%) |

**Table 4:** Echocardiographic measurements in beta thalassemia major patients.

| Echo Parameters | Min | Max | Mean | SD |
|---|---|---|---|---|
| EF% | 58 | 78 | 66.52 | 4.37 |
| FS% | 21 | 58 | 36.99 | 5.77 |
| DT | 90 | 211 | 134.80 | 16.12 |
| E/A Ratio | 1.1 | 2.8 | 1.49 | 0.33 |
| LV Mass | 31 | 210 | 68.42 | 27.38 |
| LV Mass Index | 45 | 212 | 91.08 | 28.66 |

EF – Ejection Fraction, FS – Fractional Shortening, DT – Deceleration Time, E/A – Early & Late Ratio, LV Mass – Left ventricular mass.

**Table 5:** Correlation between diastolic function and transfusion frequency in beta thalassemia major children (n=85). (p-value 0.05)

| Transfusion Frequency | Abnormal Diastolic Function | Normal Diastolic Function | Total |
|---|---|---|---|
| Twice Monthly | 4 (4.71%) | 2 (2.35%) | 6 (7.06%) |
| Monthly | 22 (25.88%) | 52 (61.18%) | 74 (87.06%) |
| Once in 2 months | 0 (0%) | 5 (5.88%) | 5 (5.88%) |
| Total | 26 (30.59%) | 59 (69.41%) | 85 (100%) |

availability of transports in lockdown period as the study was conducted during corona pandemic. No Significant association was found between total number of transfusions and cardiac abnormality unlike the study by Nathan et al where significant was correlation noted between number of units transfused and echocardiographic abnormalities when they receive more than 100 transfusions.[24] In contrary we found significant associations between frequency of blood transfusions and echocardiographic abnormalities as p value was 0.05.

Cardiomyopathy is mainly seen as the cardiac complication of thalassemia patients which progress to heart failure and death. It may be of two types- i) Dilated type where dilatation of left ventricle with decreased cardiac contractility is seen, ii) Restrictive type which is mainly a left ventricular filling defect-here heart failure is preceded by pulmonary hypertension. According to literature, iron can affect all cardiac structures including papillary muscles, conduction system and pericardium. The epicardial region of the left ventricular free wall is the most affected. Diastolic dysfunction generally appears before systolic dysfunction in the natural history of ventricular dysfunction.[12,25] Therefore, echocardiography can be the best screening method to diagnose the diastolic dysfunction early in transfusion dependant thalassemia children even before the clinical symptoms of cardiac failure develop. Moreover, provision should be made to provide early screening echocardiography for those children whose requirement of blood transfusion frequency is more as they are prone to suffer from cardiac dysfunction at an earlier age.

## 5. Conclusion

Cardiac complication may arise in the first decade also which are mostly asymptomatic, therefore serial screening echocardiography is necessary for early diagnosis and in order to adjust cardio protective therapy. Left ventricular diastolic function is affected earlier than the systolic function in patients with transfusion dependant beta thalassemia major. Transfusion frequency is the poor sensitive marker for the detection of cardiac dysfunction in thalassemia major patients.

## 6. Conflict of Interest

The authors declare that there is no conflict of interest.

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