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Original Article

Paediatrics Section

Correlation Between Serum Ferritin Levels and Echocardiographic Changes in Children with Beta-thalassaemia Major- A Cross-sectional Analytical Study

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ABSTRACT

Introduction: Heart failure secondary to iron overload is the leading cause of mortality in patients with beta-thalassaemia major. Prevention of myocardial siderosis is a key step in reducing the rate of mortality in thalassaemia children.

Aim: To study the correlation between serum ferritin levels and echocardiography parameters in children with beta-thalassaemia major.

Materials and Methods: This cross-sectional analytical study was conducted in the Department of Paediatrics, RG Kar Medical College and Hospital, Kolkata, India, from March 2020 to July 2021. A total of 85 beta-thalassaemia major children aged between 2-12 years, without any active infections or congenital heart diseases, were included in this study. Blood samples were obtained from these children for serum ferritin level assessment, and echocardiography was performed to evaluate their cardiac function. Data were statistically analysed using the Chi-square test.

Results: The mean age of patients was 7.24±2.76 years, and the age range was 1-12 years. The mean serum ferritin levels in the study were 1938.67±992.57, and more than three-fourths of our population had serum ferritin levels above 1000 ng/mL. Thirty percent of the present study population had abnormal echo findings. A significant correlation was noted between serum ferritin levels and echo parameters like Fractional Shortening (FS), Deceleration Time (DT), Early and Late Ratio (E/A), and Left Ventricular Mass (LV Mass). However, a negative correlation was found between serum ferritin levels and Ejection Fraction (EF).

Conclusion: The present study concluded that due to the significant correlation between serum ferritin levels and echocardiographic parameters, it is beneficial to conduct echocardiography in all patients with beta thalassaemia major in their first decade to gain a better understanding of cardiac function.

Keywords: Diastolic, Ejection, Fractional, Ventricular

INTRODUCTION

Thalassaemia refers to a group of inherited genetic disorders of globin chain production in which there is an imbalance between the α-globin and beta-globin chain production [1]. It is inherited in an autosomal recessive manner. Each year, 8000 children with thalassaemia are born in India, accounting for 10% of the annual worldwide incidence [2]. There are several complications of thalassaemia due to iron overloading; among them, cardiac complications are the most serious ones causing morbidity and mortality [3].

Iron overload in these children develops due to transfusional iron and increased iron absorption from the gut secondary to excessive erythropoiesis. One unit of Packed Red Blood Cell (PRBC) transfusion causes 250 mg of iron deposition in the body. This excess iron cannot be eliminated from our body physiologically. Therefore, this iron is initially deposited in the liver followed by the heart and other endocrine organs [4].

Heart failure secondary to iron overload is the most common cause of death in patients with beta thalassaemia major. Heart injuries include atrial and ventricular dilatation, arrhythmia, valvular dysfunction, pulmonary hypertension, cardiomyopathy, etc. Adaptation of the heart to the longstanding anaemia can be seen as tachycardia at rest, low blood pressure, increased end-diastolic volume, and increased cardiac output. Diastolic dysfunction generally appears before systolic dysfunction in the natural history of ventricular dysfunction [5].

Haemosiderosis-induced morbidity can be prevented by adequate chelation therapy. The most accurate method to measure iron level is liver biopsy, but it is invasive. The other way to monitor iron overload is T2 weighted MRI in the heart and liver, but this method is not easily available everywhere, while echocardiography is widely available [6,7].

Plasma ferritin can be used as an indirect marker of the body iron stores. Ferritin is increased in conditions of iron overload like thalassaemia, haemochromatosis, etc. Ferritin is falsely elevated in inflammation and infection as it is also an acute phase reactant. The normal range is 30-300 ng/mL. Serum ferritin increases after 10-12 transfusions in unchelated patients [8]. According to several studies, it is found that serum ferritin levels above 2500 ng/mL are associated with an increased risk of cardiac dysfunction [9-11]. Very few studies on cardiovascular complications of beta-thalassaemia were done in the age group of below 12 years [12,13]. In this study, all the children were below 12 years so that we can detect cardiac complications as early as possible. We could also get an idea about functional parameters of echo at this very early stage. Thus, the aim of the present study was to evaluate the relationship between serum ferritin levels and echocardiographic findings in the children of beta thalassaemia major with the hypothesis that iron overload will affect the magnitude and nature of cardiac involvement concerning various serum ferritin levels.

MATERIALS AND METHODS

This cross-sectional analytical study was performed from March 2020 to July 2021, among 85 beta-thalassaemia major children between the age group of 1-12 years, who visited Thalassaemia Clinic of RG Kar Medical College and Hospital, Kolkata, West Bengal, India. The study was approved by Institutional Ethical

Committee, RG Kar Medical College (Registered with The Drugs Controller General India Registration No.ECR/322/Inst/WB/2013): RKC/178 dated 15.02.2020. Thereafter, the purpose of the study and other ethical issues were duly explained to their parents in their native language and informed consent was taken from them.

Inclusion criteria: Children between 1-12 years of age diagnosed with beta-thalassaemia major by haemoglobin electrophoresis (HPLC: High Performance Liquid Chromatography) method [14].

Exclusion criteria: Children with less than one year and more than 12 years of age, having congenital heart diseases, acute infections or other active inflammatory conditions like autoimmune and collagen diseases (systemic lupus erythematosus, juvenile idiopathic arthritis), hepatic diseases and malignancies were excluded from the study.

Sample size calculation: Study was conducted on 85 thalassaemia major children and the sample size was derived from the following formula:

$$N=\{(Z_{\alpha}+Z_{\beta})/C\}^2+3$$

Where N was the sample size, Z_{α}=probability of type I error (1.96) and Z_{β}=probability of type II error (0.84), C=0.5*ln {(1+r)/(1-r)}, where r=correlation co-efficient (0.3); from previous study by Eghbali A et al., thus the sample size came out to be N=85, considering 95% confidence level and power of test as 80%. Subjects were chosen based on convenient sampling [15].

Study Procedure

Patients of beta-thalassaemia major in the study age group attending tertiary care centre satisfying the inclusion criteria were recruited into the study. History and analysis of old records were done to assess the age at diagnosis, consanguinity history, frequency of blood transfusions, total no. of blood transfusions, chelation therapy status, and whether a patient is known case of cardiac disease or not. Ferritin level was assessed and echocardiography was done in hospital. All these were noted in a predesigned proforma sheet and a master chart was made in Microsoft Excel.

Sample for serum ferritin was collected before blood transfusion. A sandwich ELISA (SIEMENS, ADVIA Centaur, Rev.R, 2019-03, New York, USA) was performed to measure the serum ferritin level. The ADVIA Centaur Ferritin assay is a two-site sandwich immunoassay using direct chemiluminometric technology, which uses constant amounts of two anti-ferritin antibodies. The first antibody, in the Lite Reagent, is a polyclonal goat anti-ferritin antibody labelled with acridinium ester. The second antibody, in the solid phase, is a monoclonal mouse anti-ferritin antibody, which is covalently coupled to paramagnetic particles [16]. In this study, the patients were categorised into two groups depending on the serum ferritin values into those who had values more than 1000 ng/mL and the ones with less than 1000 ng/mL to evaluate the extent of iron overload. Chelation therapy is generally started in cases of serum ferritin value more than 1000 ng/mL and serum ferritin levels <1000 ng/mL are associated with lower morbidity and mortality in thalassaemia children [17,18].

Doppler echocardiography was performed on patients using an ultrasound machine Vivid S6ON having a phased array transducer of 2.0-5.0 and 2.7-8.0MHz. 2D, M-Mode and Doppler echocardiography were done as per the guidelines of the American society of Echocardiography [19]. EF and FS were assessed to evaluate the systolic function of the heart. EF is a measurement of the blood amount that the left ventricle pumps out with each contraction. FS is the fraction of any diastolic dimension that is lost in systole. Diastolic function was assessed by evaluating the E/A ratio which is measured by placing a pulsed wave doppler across the mitral valve and measuring the velocities across the valve during the initial diastole (E wave) and atrial contraction (A wave). Elevated E/A indicates increase in left ventricular end diastolic pressure. DT is the time interval from the peak of E wave to its projected baseline. It indicates the duration for equalising the pressure difference between the left atrium and left ventricle and this is a marker of diastolic left ventricular chamber stiffness. 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 by using M-mode echocardiography [19]. Echo findings were tabulated using percentile and age specific reference charts [20]. Any deviation from normal echo parameters value as per age specific charts was regarded as abnormal echo.

STATISTICAL ANALYSIS

Test for independence were carried out using Chi-square test and unpaired t-test. Pearson correlation coefficient with 95% confidence interval was used to conduct the correlation test. Analysis was carried out using Microsoft Excel 365 and R-Studio Version 1.3.1056 and p-value <0.05 was taken as statistically significant.

RESULTS

In present study, 85 major beta-thalassaemia children were enrolled fulfilling the inclusion and exclusion criteria between the age group of 1-12 years. The mean age was 7.24±2.76 years. Out of 85 children, 53 (62.35%) were female and 32 (37.65%) were male. History revealed that 15 (17.65%) out of 85 children were having parents with a consanguineous type of marriage. Seventeen (20%) had a ferritin level less than 1000 ng/mL. Mean serum ferritin value was 1938.67±992.57 ng/mL. Total number of transfusions ranged between 18 to 183 times, 24.70% (n=21) of the study population required blood transfusions more than 100 times. All the children in study population were receiving chelation therapy regularly [Table/Fig-1].

Characteristics	n=85 (%)
Age in years	
1-6	37 (43.53%)
7-12	48 (56.47%)
Gender	
Male	32 (37.65%)
Female	53 (62.35%)
Weight	
<3rd percentile	20 (23.53%)
≥3rd percentile	65 (76.47%)
Height	
<3rd percentile	31 (36.47%)
≥3rd percentile	54 (63.53%)
Types of marriage	
Consanguinity	15 (17.65%)
Non-consanguinity	70 (82.35%)
Age at diagnosis (Limit 3 month-36 month)	
≤6 months	39 (45.88%)
7-12 months	30 (35.30%)
>1 year	16 (18.82%)
Transfusion frequency	
Every 2 weeks	6 (7.06%)
Every 4 weeks	74 (87.06%)
Every 6 weeks	5 (5.88%)
Serum ferritin	
<1000 ng/mL	17 (20.00%)
≥1000 ng/mL	68 (80.00%)
Total no. of transfusions (Limit 18-183)	
≤100	64 (75.30%)
>100	21 (24.70%)
On chelation therapy	85 (100%)

[Table/Fig-1]: Baseline characteristics of study subjects.

In present study, it was found that mean weight and height of study population were 18.15±4.64 kg and 110.60±12.44 cm, respectively.

[Table/Fig-2] shows out of 15 children having parents with history of consanguineous marriage, 1 (6.67%) had a ferritin level less than 1000. Out of 70 children having parents with history of no consanguinity, 16 (22.86%) had a ferritin level less than 1000. Types of marriage did not show significant association with ferritin level (p-value 0.4254). Out of 74 children who went for transfusion every four week, 14 (18.92%) had a ferritin level less than 1000 and 60 (81.08%) had greater than and equal to 1000. Ferritin levels did not show significant association with transfusion frequency (p-value 0.07385).

Variables	Serum ferritin value		Total	p-value*
	<1000	≥1000		
Type of marriage				
Consanguinity	1 (6.67%)	14 (93.33%)	15 (100%)	0.4254
Non-consanguinity	16 (22.86%)	54 (77.14%)	70 (100%)	
Transfusion frequency				
Every 2 week	0 (0%)	6 (100%)	6 (100%)	0.0738
Every 4 week	14 (18.92%)	60 (81.08%)	74 (100%)	
Every 6 week	3 (60%)	2 (40%)	5 (100%)	

[Table/Fig-2]: Association of serum ferritin values with different study variables.
*Chi-square, Statistically significant at p<0.05

Mean ferritin value of children with abnormal echocardiographic findings (n=26) and children with normal echocardiographic findings (n=59) were 2683.04±1111.07 and 1610.6±732.72, respectively which showed statistical significance (p-value 0.0001) as depicted in [Table/Fig-3]. All 26 (30%) children with abnormal echo findings were having increased LV mass also and rest 59 (70%) children had normal LV mass.

Parameter	Children with abnormal echo findings, n=26 (30%) (mainly increased LV mass)	Children with normal echo findings, n=59 (70%) (normal LV mass)	p-value*
Ferritin levels (Mean±SD)	2683.04±1111.07	1610.6±732.72	0.0001

[Table/Fig-3]: Association between echocardiographic findings and mean serum ferritin value.
*Chi-square, Statistically significant at p<0.05

Cardiac functions were examined by Doppler echocardiography and results are given in [Table/Fig-4]. Mean values of EF, E/A and LV mass were 66.52±4.37, 1.49±0.33 and 68.42±27.38, respectively. [Table/Fig-5] shows a negative significant correlation between serum ferritin level and FS and a positive significant correlation between ferritin and DT with p-value of 0.0018 and 0.022, respectively.

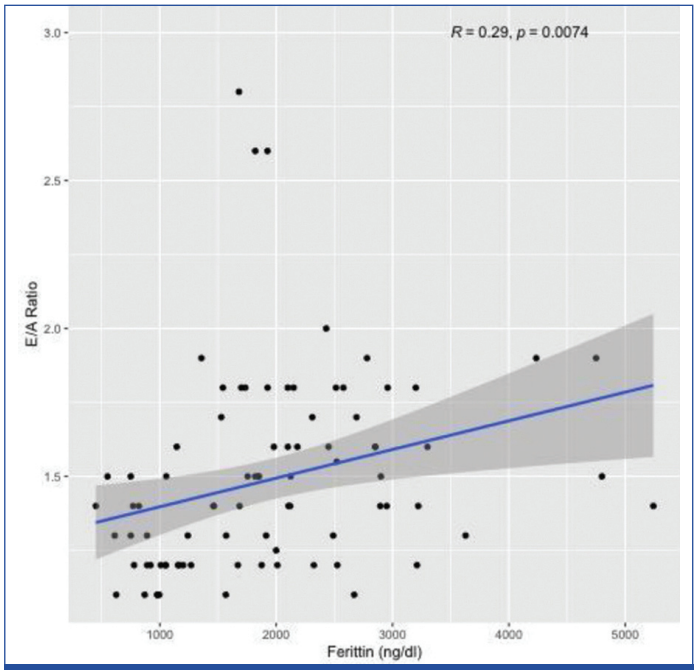
Echo parameters	Min	Max	Mean	SD
EF%	58	78	66.52	4.37
FS%	21	58	36.99	5.77
DT	90	211	134.80	16.12
E/A Ratio	1.1	2.8	1.49	0.33
LV Mass	31	210	68.42	27.38

[Table/Fig-4]: Cardiac function of children with major beta thalassaemia.
EF: Ejection fraction; FS: Fractional shortening; DT: Deceleration time; E/A: Early and late ratio; LV Mass: Left ventricular mass

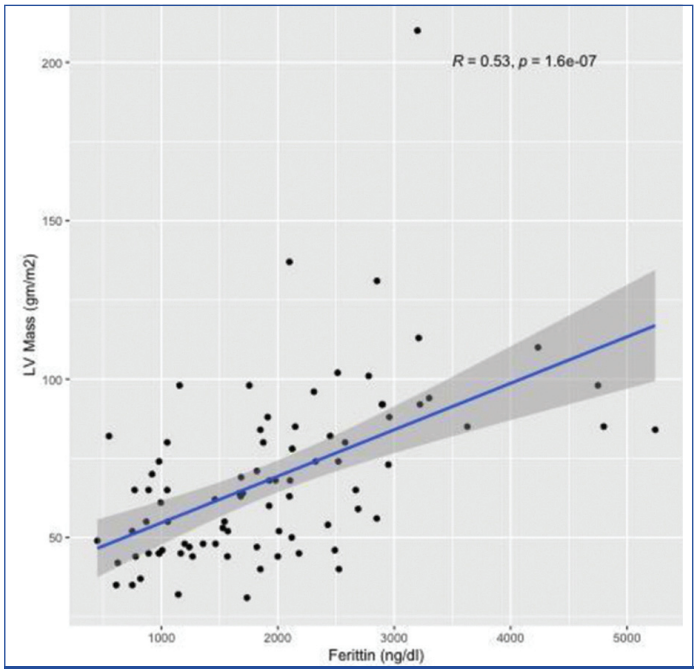
[Table/Fig-6] shows a significant weak but positive correlation between ferritin and echo parameter E/A (r=0.29, p-value 0.0074) with the help of a scatter plot. A correlation coefficient of r=0.53 between ferritin and echo parameter LV mass suggested a moderate and positive significant correlation with p-value of 0.0001 and is represented graphically with the help of a scatter plot in [Table/Fig-7].

Echo parameters	Ferritin	
	Pearson correlation coefficient, r	p-value*
EF%	-0.21	0.059
FS%	-0.33	0.0018
DT	0.25	0.022
E/A ratio	0.29	0.0074
LV mass	0.53	0.0001

[Table/Fig-5]: Correlation between serum ferritin levels and echocardiography profile.
*Pearson Correlation test, Statistical significant at p<0.05



[Table/Fig-6]: A correlation of r=0.29 between ferritin and echo parameter E/A ratio suggested a weak and positive significant association since p-value is 0.0074 and is represented graphically with the help of a scatter plot.



[Table/Fig-7]: A correlation of r=0.53 between ferritin and echo parameter LV mass suggested a moderate and positive significant association since p-value is less than 0.0001 and is represented graphically with the help of a scatter plot.

From [Table/Fig-8] we observe that 48.24% accuracy could be obtained if ferritin levels are used to classify the outcome remarks of echo. The sensitivity was found to be 96.15%, the specificity was found to be 27.12%. Overall, it was concluded that ferritin has poor accuracy rate in detecting cardiac involvement of thalassaemia patient and that is why it is not reliable for the study.

Parameter=Ferritin	Value	95% CI
Sensitivity	96.15%	80.36%-99.90%
Specificity	27.12%	16.36%-40.27%
PPV	36.77%	32.83%-40.89%
NPV	94.12%	69.12%-99.13%
Accuracy	48.24%	37.26%-59.34%

[Table/Fig-8]: Sensitivity analysis of ferritin.

DISCUSSION

The study was conducted on 85 transfusion dependant beta-thalassaemia major patients between age group of 1-12 years to study the association between serum ferritin levels and echocardiographic parameters of cardiac function.

In the present study, children between 1-12 years of age were included. Study by Eghbali A et al., was done between 3-46 years age group whereas studies by Sayed SZ et al., and Noori N et al., included patients more than 10 years of age [15,21,22].

In the present study, 17.65% children had history of consanguinity. A similar study by Sayed SZ et al., showed around 32% of thalassaemia patients were from consanguineous marriage where the prevalence is high [21]. Therefore, it is important to screen the relatives of the carriers for genetic counselling and premarital testing to prevent these births. In present study, the minimum age at initial diagnosis of thalassaemia was three months in comparison to six months in Sayed SZ et al., and Mohammad AM's studies [21,23]. Thalassaemia children mostly present in infancy at around six months of age, but some are screened for thalassaemia earlier due to their past history of sibling death.

In present study, 23.53% of thalassaemia patients were underweight and 36.47% had short stature. In Usha BK et al., study approximately one third of their patients were underweight and had short stature [12]. Nutritional deficiencies in thalassaemia patients are mainly due to haemolytic anaemia, increased nutritional requirements, several organ dysfunctions due to iron overload causing growth hormone deficiency, hypothyroidism, diabetes, etc., [24]. Despite being on oral chelation therapy, only 20% (n=17) had a ferritin level of less than 1000 ng/mL and rest of the study population had a serum ferritin level more than 1000 ng/mL. This similar kind of findings had been seen in the study of Usha BK et al., [12]. But in Sayed SZ et al., study, it was shown that all the study population had serum ferritin value more than 1000 ng/mL [21].

Although this study showed that 93.33% of children born of consanguineous marriage had serum ferritin level more than 1000 ng/mL but the types of marriage did not show significant association with ferritin level. In this study, it was noticed that all of the children who received blood transfusion every two week interval had serum ferritin level more than 1000 ng/mL. But ferritin level did not show significant association with frequency of transfusion.

The study showed that out of 85 thalassaemia children 30% (n=26) had abnormal echo findings, whereas remaining 70% (n=59) had normal echo report. 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 [20]. Mean LV mass was 68.42. Similar findings were observed in studies done by Sayed SZ et al., and Abdullah Abbas A et al., [21,25]. LV mass is increased in thalassaemia due to multiple factors like chronic anaemia, tissue hypoxia and iron overload.

In present study, mean value of ferritin, EF, FS and E/A were 1938.67±992.57, 66.52±4.37%, 36.99±5.77% and 1.49±0.33, respectively. Similar findings were also observed in the study by Eghbali A et al., [15]. Significant correlation was also found between serum ferritin level and echocardiographic parameters. In Eghbali A et al., study, they found weak but significant association between serum ferritin level and EF and also between serum ferritin level and FS [15]. Papadopoulou-Legbelo K et al., and Dewanti CN et al., in their study showed that ferritin was associated with echo findings like E/A, EF and FS [26,27]. Another study by Shivanna NH et al., proved that patients who had higher serum ferritin level presented with higher LVD dt and lower EF [13]. In line with these studies, present study showed that increase in serum ferritin level was significantly correlated with decrease in FS and increase in DT, E/A ratio and LV mass. There are also some studies like Usha BK et al., Khalilian MR et al., who did not find any statistically significant correlation between serum ferritin level and echocardiographic parameters [12,28].

Right ventricle is more susceptible to the ill effects of iron overload due to its thin wall [29]. It is noted that E/A ratio is increased in beta thalassaemia major children representing diastolic dysfunction. The preload phase is increased due to chronic anaemia and elevating the E/A ratio. Initially, iron deposition in the myocardium does not affect the left ventricular contractility rather it causes the restrictive diastolic dysfunction of left ventricle [30].

Therefore, echocardiography can be used as a screening modality in thalassaemia children to detect early cardiac complications. Though mortality due to cardiac complication occur mostly in second decade, the pathologic changes mostly occur in first decade [31]. So, this should be diagnosed early by easily available and non-invasive technique like echocardiography. Similar studies have been tabulated in [Table/Fig-9] [12,13,15,26-28].

S. No.	Author's name and year	Place of study	Sample size	Parameters compared	Conclusion
1	Eghbali A et al., 2015 [15]	Iran	66	Serum ferritin with diastolic cardiac function (EF, FS, E/A, DT)	Significant correlations found between serum ferritin and EF and also between serum ferritin and FS
2	Shivanna NH et al., 2015 [13]	Karnataka, India	30	Serum ferritin level and number of blood transfusions with echocardiographic parameters (PWT-d, PWT-s, LViedd, LViesd, septal thickness, E/A and EF)	PWT-d, PWT-s, LViedd, LViesd and septal thickness were positively related and EF was negatively correlated with both increase in serum ferritin and number of blood transfusions and all the parameters were statistically significant.
3	Khalilian MR et al., 2016 [28]	Iran	107	Serum ferritin with echocardiographic parametres like EF, FS, E/A, Tricuspid Annular Plain Systolic Excursion (TAPSE) and pulmonary arterial pressure	No significant relationship between serum ferritin level and echocardiographic findings.
4	Usha BK et al., 2018 [12]	Tamil Nadu, India	54	Serum ferritin with ECG findings of RVH and LVH. Serum ferritin with echo parameters like LV mass, Pulmonary Hypertension (PH)	No significant association between serum ferritin and ECG findings. Serum ferritin had a poor positive correlation with LV mass and PH.
5	Papadopoulou-Legbelo K et al., 2009 [26]	Greece	93	Serum ferritin with EF, FS, E/A and DT.	As the ferritin levels increased, all the M-mode echocardiographic indices increased too, while the EF and FS were lower among the patients compared to controls.
6	Dewanti CN et al., 2021 [27]	Indonesia	45	Serum ferritin with impaired heart functions like EF, E/A and TAPSE	Serum ferritin was negatively correlated with EF and TAPSE but positively correlated with E/A ratio.
7	Present study	West Bengal, India	85	Serum ferritin with echo parameters like EF, FS, E/A, DT and LV mass	A significant correlation was noted between serum ferritin level and echo parameters like FS, DT, E/A and LV mass. But no correlation was found between serum ferritin level and EF.

[Table/Fig-9]: Similar previously published studies [12,13,15,26-28].

Limitation(s)

Present study findings cannot be projected at a community level as this is an institutional based study. There was no baseline data available on the initial heart function parameter. All the echocardiographic parameters should have to be compared with cardiac MRI and normal controls.

CONCLUSION(S)

In thalassaemia patients, cardiac complications that arise in their first decade are mostly asymptomatic. The present study concluded that 30% of the study population had an increase in LV mass, but none of them were showing clinical features of heart failure. Moreover, serum ferritin values significantly correlated with several echocardiographic parameters like FS, LV mass, E/A ratio and DT.

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