INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

STRUCTURAL AND HEMODYNAMIC CHANGES ON ECHOCARDIOGRAPHY IN BETA-THALASSEMIA MAJOR PATIENTS

Original Research

Muhammad Asif Nawaz Khan[1]*, Fazlul Aziz Mian[1], Subaat Basit[1], Bilqees[2], Laiba Sarfraz[3], Shahjahan Wahid[4]

[1]Department of Cardiology, PIMS Hospital, Islamabad, Pakistan.

[2]Lady Medical Officer, Pakistan.

[3]Life Care International Hospital, Islamabad, Pakistan.

[4]Registrar Helper, Eye Hospital, Quetta, Pakistan.

Corresponding Author: Muhammad Asif Nawaz Khan, Department of Cardiology, PIMS Hospital, Islamabad, Pakistan. asifkhan4350@hotmail.com

Acknowledgement: The authors extend their gratitude to the participants, their families, and the research staff at the Department of Cardiology, PIMS Islamabad, for their invaluable support in this study.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Beta-thalassemia major is a hereditary blood disorder requiring lifelong blood transfusions, which lead to iron overload and associated complications, particularly cardiac dysfunction. Myocardial iron deposition is a significant cause of morbidity and mortality in these patients, often resulting in structural and functional cardiac abnormalities. Echocardiography is a crucial non-invasive tool for early detection of cardiac changes, allowing timely intervention. Understanding the relationship between serum ferritin levels and cardiac parameters can help optimize management strategies for affected individuals.

Objective

This study aimed to evaluate the structural and functional cardiac changes in children with beta-thalassemia major and examine the association between these changes and serum ferritin levels.

Methods: A cross-sectional study was conducted over six months at the Department of Cardiology, Pakistan Institute of Medical Sciences (PIMS), Islamabad. A total of 85 children aged 2–14 years with a confirmed diagnosis of beta-thalassemia major and a history of more than ten packed red blood cell transfusions were included. Demographic, clinical, and hematological data were collected, along with echocardiographic assessments of left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF), and the E/A ratio. Serum ferritin levels were measured, and statistical analysis was performed using SPSS version 26, with a significance threshold of $p \leq 0.05$.

Results: The mean hemoglobin level was 8.5 ± 1.2 g/dL, while serum ferritin averaged 2500 ± 850 ng/mL, indicating severe iron overload. Echocardiographic parameters showed a mean LVEDD of 42.3 ± 3.5 mm, LVESD of 28.1 ± 2.7 mm, and LVEF of 56.8 ± 6.5%. Patients with ferritin levels ≥2500 µg/L had significantly larger LVEDD (44.5 ± 3.2 mm vs. 40.1 ± 3.0 mm, $p = 0.05$), LVESD (30.2 ± 2.5 mm vs. 26.0 ± 2.4 mm, $p = 0.01$), and lower LVEF (54.0 ± 5.8% vs. 59.6 ± 5.2%, $p = 0.03$). Positive correlations were found between ferritin and LVESD ($r = +0.50$), while an inverse correlation was observed with LVEF ($r = -0.48$). No significant difference in the E/A ratio was noted ($p = 0.15$).

Conclusion: The findings indicate that children with beta-thalassemia major experience significant cardiac structural changes, with increased LVEDD, LVESD, and reduced LVEF closely linked to elevated serum ferritin levels. These results highlight the detrimental effects of iron overload on cardiac performance, emphasizing the need for more effective chelation therapy and cardiac monitoring strategies to prevent early myocardial dysfunction.

Keywords: Beta-Thalassemia Major, Cardiac Function, Echocardiography, Iron Overload, Left Ventricular Dysfunction, Serum Ferritin, Transfusion-Related Complications.

INTRODUCTION

Beta-thalassemia major is a hereditary hematological disorder characterized by defective beta-globin chain synthesis, resulting in severe anemia, growth retardation, expanded bone marrow activity, splenomegaly, and increased iron absorption. The condition necessitates lifelong blood transfusions, which, while essential for survival, contribute to progressive iron overload and associated complications, particularly cardiac dysfunction. Despite significant advancements in chelation therapy, cardiovascular disease remains the leading cause of morbidity and mortality in patients with beta-thalassemia major, underscoring the need for ongoing research into the cardiac manifestations of the disease (1,2,3). Globally, beta-thalassemia represents a significant health burden, with approximately 60,000–70,000 affected births annually, predominantly in the Mediterranean, Middle East, South Asia, and Southeast Asia (4). Pakistan, in particular, bears a high prevalence, with an estimated 5–7% of the population carrying the beta-thalassemia trait and over 5,000 new cases diagnosed annually (5). Given this considerable disease burden, understanding the long-term complications, particularly cardiac abnormalities, is critical to optimizing management strategies and improving patient outcomes.

Cardiac involvement in beta-thalassemia major is complex, arising from iron deposition in myocardial tissue and independent pathophysiological mechanisms. Iron overload cardiomyopathy is characterized by progressive ventricular dysfunction, arrhythmias, and heart failure, driven by toxic iron accumulation within cardiomyocytes. Structural and hemodynamic alterations can be identified using echocardiographic parameters, which have been instrumental in detecting subclinical cardiac dysfunction in thalassemia patients (6,7). Studies have reported significant deviations in left ventricular dimensions and ejection fraction in affected individuals, such as left ventricular end-diastolic diameter (LVEDD) of 38.14±4.59 mm, left ventricular end-systolic diameter (LVESD) of 25.13±3.45 mm, and left ventricular ejection fraction (LVEF) of 66.34±3.82%, highlighting early myocardial remodeling (8). Moreover, diastolic dysfunction, often presenting as a restrictive filling pattern on Doppler echocardiography, has been frequently observed, with studies indicating that over half of thalassemia major patients exhibit elevated E/A ratios, reduced atrial contraction velocities, and impaired myocardial relaxation (9,10). Despite the high prevalence of beta-thalassemia major in Pakistan, the cardiac status of affected individuals remains understudied. With transfusion-dependent children at heightened risk of iron-induced myocardial damage, there is an urgent need to assess the structural and functional cardiac changes in these patients. Echocardiography provides a non-invasive and reliable means to evaluate early cardiac abnormalities before symptomatic heart failure develops. Therefore, this study aims to assess the mean cardiac structural and hemodynamic changes in patients with documented beta-thalassemia major, providing critical insights that may guide early interventions and improve long-term patient outcomes.

METHODS

This cross-sectional study was conducted at the Department of Cardiology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, over six months following approval from the Institutional Review Board (IRB) of the Cardiology Centre, PIMS Islamabad. The study aimed to evaluate structural and hemodynamic cardiac changes in children diagnosed with beta-thalassemia major through echocardiographic assessment. The study population comprised children aged 2–14 years with a confirmed diagnosis of beta-thalassemia major who were recruited from the thalassemia clinic at PIMS. Eligibility criteria included children who had received more than ten packed cell volume (PCV) transfusions. Individuals with a history of prior cardiac surgery, congenital heart disease (CHD), rheumatic heart disease (RHD), myocarditis, or those who were HIV-positive were excluded to eliminate potential confounding factors that could independently affect cardiac function.

The sample size was calculated using the WHO sample size calculator, ensuring a 95% confidence level and a 5% margin of error. Given that the estimated prevalence of beta-thalassemia carriers in Pakistan ranges between 5% and 7% (5), a population proportion of 5% was used, resulting in a required sample size of 73 participants. To account for potential non-responses or incomplete data, the final sample size was increased to 85 patients. Demographic and clinical data were collected through a structured data collection tool designed specifically for this study. This tool recorded relevant patient details, including age, gender, family history, socioeconomic status, duration since diagnosis, number of blood transfusions, and hematological parameters such as hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Each participant underwent a comprehensive echocardiographic assessment to evaluate cardiac structural and hemodynamic changes. Two-dimensional echocardiography was performed to measure left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF), and E/A ratio. LVEDD and LVESD were measured using M-mode echocardiography in the parasternal long-axis view, ensuring perpendicular alignment of the M-mode cursor through the interventricular septum, left ventricular cavity, and posterior wall to prevent measurement errors. LVEF was assessed using both visual estimation and Simpson's method, the latter of which involved tracing the endocardial borders in apical four-chamber (A4C) and two-chamber (A2C) views to ensure accuracy. Diastolic function was evaluated using pulsed-wave Doppler to measure the E/A ratio, which represents early diastolic (E wave) and atrial contraction (A wave) velocities across the mitral valve. Ethical considerations were strictly adhered to, following the principles outlined in the Helsinki Declaration (1975, revised 1997). The study received approval from the Institutional Review Board (IRB) of the Cardiology Centre, PIMS Islamabad. Written informed consent was obtained from the parents or guardians of all participants before enrollment. Statistical analyses were conducted using SPSS version 26. Descriptive statistics were computed, with qualitative variables such as gender, blood group, family history, and socioeconomic status reported as frequencies and percentages, while quantitative variables, including age, duration of disease, hematological parameters, and echocardiographic measurements, were expressed as mean ± standard deviation. Effect modifiers such as age, gender, family history, socioeconomic status, and duration of blood transfusions were stratified, and post-stratification independent sample t-tests were applied to assess statistical significance. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

The study included 85 children diagnosed with beta-thalassemia major. The age distribution showed that 29.4% were aged 2–5 years, 41.2% were 6–10 years, and 29.4% were 11–14 years. The cohort comprised 52.9% males and 47.1% females. A positive family history of thalassemia was reported in 76.5% of participants. Socioeconomic classification indicated that 58.8% of the patients belonged to the low-income group, 35.3% to the middle-income group, and 5.9% to the high-income group. The duration since diagnosis varied, with 47.1% of patients diagnosed within the past five years, 41.2% between six and ten years, and 11.8% for more than ten years. Blood transfusion frequency was every two weeks for 58.8% of patients, every three weeks for 29.4%, and every four weeks or more for 11.8%.

Table I: Baseline characteristics of the study sample (n=85)

Variable	Category	n (%)
Age Group (years)	2–5	25 (29.4)
	6–10	35 (41.2)
	11–14	25 (29.4)
Gender	Male	45 (52.9)
	Female	40 (47.1)
Family History of Thalassemia	Yes	65 (76.5)
	No	20 (23.5)
Socioeconomic Status	Low	50 (58.8)
	Middle	30 (35.3)
	High	5 (5.9)
Duration Since Diagnosis (years)	≤ 5	40 (47.1)
	6–10	35 (41.2)

Variable	Category	n (%)
	>10	10 (11.8)
Transfusions Intervals	After2 weeks	50 (58.8)
	3 weeks	25 (29.4)
	4 and above weeks	10 (11.8)

The mean hemoglobin (Hb) level was 8.5 ± 1.2 g/dL, ranging from 6.0 to 11.0 g/dL, indicating persistent anemia despite regular transfusions. The mean serum uric acid (UA) level was 5.8 ± 1.4 mg/dL, ranging from 3.5 to 8.5 mg/dL, remaining within the pediatric reference range. Serum ferritin levels averaged 2,500 ± 850 ng/mL, with values ranging from 1,200 to 4,500 ng/mL, significantly exceeding the normal pediatric reference range and indicating severe iron overload due to frequent transfusions. The mean cholesterol level was 165 ± 35 mg/dL, within the standard acceptable limits for children.

Table II: Biochemical investigations of study sample (n=85)

Parameter	Mean ± SD	Range
Hemoglobin (Hb) (g/dL)	8.5 ± 1.2	6.0 – 11.0
Uric Acid (UA) (mg/dL)	5.8 ± 1.4	3.5 – 8.5
Ferritin (ng/mL)	2500 ± 850	1200 – 4500
Cholesterol (mg/dL)	165 ± 35	110 – 240

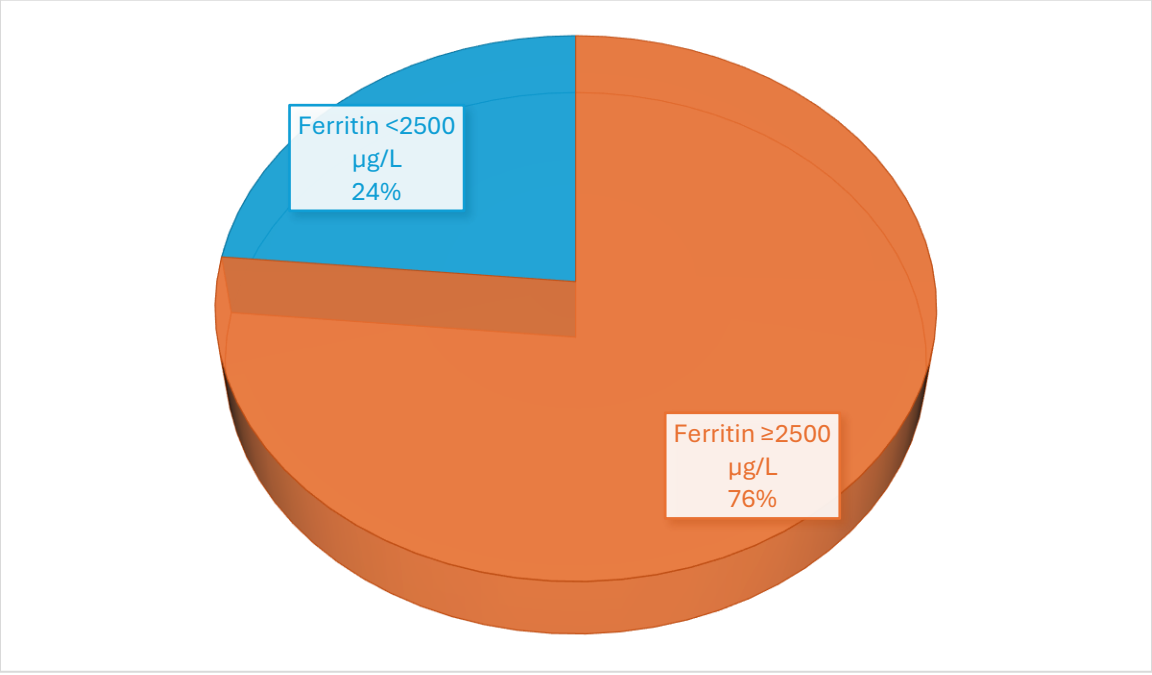


Figure 1 Distribution of serum ferritin among study sample (n=85)

Serum ferritin levels were markedly elevated in the majority of patients, with 76% having ferritin levels ≥2500 µg/L, whereas 24% had levels below this threshold. The hematological indices demonstrated a mean corpuscular volume (MCV) of 65.4 ± 4.8 fL (range: 58.0–

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

75.0), below the normal range and consistent with microcytosis. The mean corpuscular hemoglobin (MCH) was 22.3 ± 1.5 pg (range: 20.0–25.0), also below the reference range, indicating hypochromia. The mean corpuscular hemoglobin concentration (MCHC) was 32.8 ± 1.1 g/dL (range: 30.0–35.0), within the normal reference range.

Table III: Primary outcomes of the study sample (n=85)

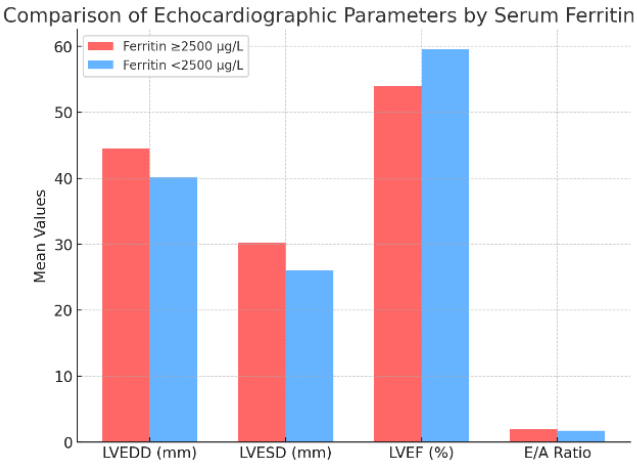
Parameter	Study Mean ± SD	Study Range	Reference Range	Reference Source
MCV (fL)	65.4 ± 4.8	58.0 – 75.0	70 – 98	Children's FBC Reference Ranges (11)
MCH (pg)	22.3 ± 1.5	20.0 – 25.0	24.0 – 31.0	
MCHC (g/dL)	32.8 ± 1.1	30.0 – 35.0	32 – 36	
LVEDD (mm)	42.3 ± 3.5	36.0 – 48.0	36 – 54	Echocardiographic Reference Ranges (12)
LVESD (mm)	28.1 ± 2.7	24.0 – 34.0	23 – 40	
LVEF (%)	56.8 ± 6.5	45.0 – 70.0	56 – 78	
E/A Ratio	1.8 ± 0.3	1.2 – 2.4		

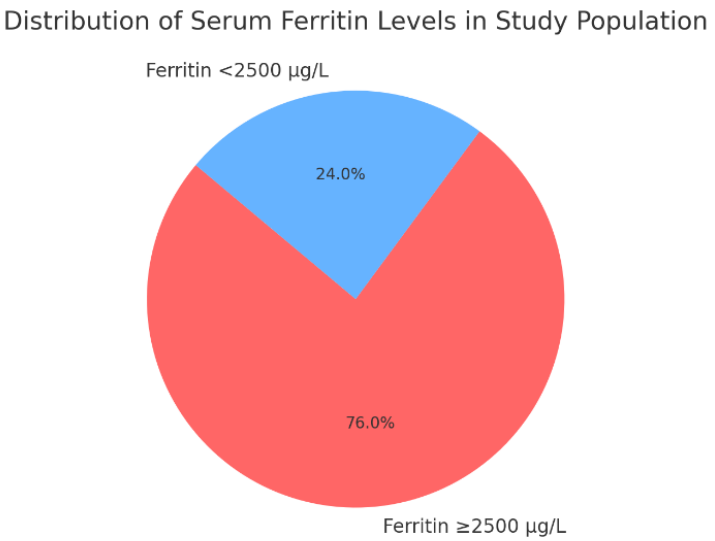
Echocardiographic parameters revealed a mean left ventricular end-diastolic diameter (LVEDD) of 42.3 ± 3.5 mm (range: 36.0–48.0) and a mean left ventricular end-systolic diameter (LVESD) of 28.1 ± 2.7 mm (range: 24.0–34.0), both within the standard reference values. The mean left ventricular ejection fraction (LVEF) was 56.8 ± 6.5% (range: 45.0–70.0), positioned at the lower limit of the normal range, suggesting potential early cardiac dysfunction. The mean E/A ratio was 1.8 ± 0.3 (range: 1.2–2.4), indicating preserved diastolic function in the majority of patients.

Table IV: Correlation of serum Ferritin and Echocardiographic parameters of study sample (Ferritin ≥2500 µg/L versus Ferritin <2500 µg/L)

Parameter	Ferritin ≥2500 µg/L (Mean ± SD)	Ferritin <2500 µg/L (Mean ± SD)	p-value	Correlation Coefficient (r)
LVEDD (mm)	44.5 ± 3.2	40.1 ± 3.0	0.05	+0.45
LVESD (mm)	30.2 ± 2.5	26.0 ± 2.4	0.01*	+0.50
LVEF (%)	54.0 ± 5.8	59.6 ± 5.2	0.03*	-0.48
E/A Ratio	1.9 ± 0.4	1.7 ± 0.3	0.15	+0.20

Correlational analysis demonstrated a significant association between serum ferritin levels and echocardiographic parameters. Patients with ferritin levels ≥2500 µg/L had a larger mean LVEDD (44.5 ± 3.2 mm vs. 40.1 ± 3.0 mm, p = 0.05) and LVESD (30.2 ± 2.5 mm vs. 26.0 ± 2.4 mm, p = 0.01) compared to those with ferritin <2500 µg/L. LVEF was significantly lower in the high-ferritin group (54.0 ± 5.8% vs. 59.6 ± 5.2%, p = 0.03), indicating reduced systolic function. A positive correlation was observed between serum ferritin and LVESD (r = +0.50), while an inverse correlation was found between serum ferritin and LVEF (r = -0.48). No significant difference in the E/A ratio was observed between the two groups (1.9 ± 0.4 vs. 1.7 ± 0.3, p = 0.15), suggesting that diastolic function was largely preserved despite iron overload.





DISCUSSION

Cardiac complications remain a major concern for patients with beta-thalassemia major, particularly those undergoing frequent transfusions. Myocardial iron deposition is a critical factor contributing to cardiac dysfunction, and its early detection through echocardiographic assessment is essential for preventing long-term complications. This study examined the clinical, biochemical, and echocardiographic parameters of children with beta-thalassemia major, with a specific focus on the association between serum ferritin levels and cardiac function. The findings revealed that a substantial proportion of patients (76%) had serum ferritin levels ≥2500 µg/L, highlighting significant iron overload. This aligns with studies conducted in developing countries, where access to timely and adequate chelation therapy is often challenging due to financial and healthcare constraints (13,14,15). Elevated ferritin levels were associated with structural and functional cardiac alterations, as evidenced by significant differences in LVEDD, LVESD, and LVEF between patients with ferritin levels above and below 2500 µg/L. These findings are consistent with studies from other regions where chronic iron overload contributes to progressive ventricular dilation and reduced systolic function (16,17). However, in contrast to findings from high-income countries where effective chelation therapy has mitigated cardiac complications, this study underscores the persistent challenge of managing iron burden in resource-limited settings (19).

The echocardiographic assessment in this study suggested borderline cardiac dysfunction in patients with excessive iron deposition. The significant correlation between serum ferritin levels and LVEDD (+0.45), LVESD (+0.50), and LVEF (-0.48) reinforces the impact of iron toxicity on myocardial performance. These results support previous research that established iron-induced myocardial remodeling as a precursor to both systolic and diastolic dysfunction (18). While global research highlights the effectiveness of intensive chelation in reducing cardiac complications, the current findings suggest that the strategies implemented in this region may be insufficient to prevent subclinical myocardial changes (19). The observed reduction in LVEF in patients with severe iron overload further emphasizes the necessity for early intervention through optimized chelation protocols. The mean hemoglobin level of 8.5 ± 1.2 g/dL in this cohort reflects persistent anemia despite regular transfusions, a trend commonly observed in patients with transfusion-dependent beta-thalassemia major. This aligns with previous studies in Pakistan, which have attributed suboptimal hemoglobin maintenance to inconsistent blood transfusion practices and limited donor availability (5). The hematological indices, including MCV (65.4 ± 4.8 fL) and MCH (22.3 ± 1.5 pg), were consistent with the characteristic microcytic, hypochromic anemia of beta-thalassemia major, corroborating findings from both local and international studies (19,20).

Biochemical parameters revealed that uric acid and cholesterol levels were within normal reference ranges, suggesting that beta-thalassemia major and iron overload may not have a significant impact on these parameters in this population. This contrasts with reports from other studies that have observed hyperuricemia and dyslipidemia in thalassemia patients, potentially due to differences in patient demographics, genetic predispositions, nutritional status, or chelation regimens (21). The absence of significant lipid alterations in this study may indicate that factors such as dietary habits and metabolic adaptations play a role in maintaining lipid homeostasis in these patients. While this study provides valuable insights into the cardiac status of children with beta-thalassemia major, certain limitations should be considered. The cross-sectional nature of the study precludes the assessment of longitudinal changes in cardiac function and

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

iron burden. The sample size, although adequate for statistical analysis, remains relatively small and may not fully capture the variability in disease progression across different patient subgroups. Additionally, cardiac MRI, which is the gold standard for myocardial iron quantification, was not included due to resource limitations, and echocardiographic findings may not fully reflect the extent of myocardial iron overload. Future studies incorporating serial echocardiographic assessments alongside T2* MRI would provide a more comprehensive understanding of disease progression and the effectiveness of chelation therapy. The findings highlight the urgent need for improved iron monitoring and chelation strategies to mitigate cardiac complications in patients with beta-thalassemia major. Strengthening healthcare infrastructure to ensure early detection and aggressive management of iron overload is essential for reducing the burden of cardiac morbidity. Further research focusing on the long-term impact of iron chelation, the role of newer therapeutic agents, and the identification of additional risk factors influencing cardiac health in this population is warranted.

CONCLUSION

This study highlights the substantial impact of iron overload on cardiac function in patients with beta-thalassemia major, emphasizing the need for vigilant monitoring and timely intervention. The findings reinforce the critical role of effective chelation therapy in preventing cardiac complications, particularly in resource-limited settings where management challenges persist. The association between iron burden and early cardiac dysfunction underscores the necessity for improved treatment strategies and more comprehensive screening protocols to detect subclinical myocardial changes. Strengthening healthcare infrastructure, optimizing transfusion and chelation regimens, and addressing barriers to care are essential steps toward improving long-term outcomes in this vulnerable population.

Author Contribution

Author	Contribution
Muhammad Asif Nawaz Khan*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Fazlul Aziz Mian	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Subaat Basit	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Bilqees	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Laiba Sarfraz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Shahjahan Wahid	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

REFERENCES

1. Galadanci NA, Johnson W, Carson A, Hellemann G, Howard V, Kanter J. Factors associated with left ventricular hypertrophy in children with sickle cell disease: results from the DISPLACE study. Haematologica. 2022 Oct 10;107(10):2466. https://doi.org/10.3324/haematol.2021.280480

2. Susanah S, Rakhmilla LE, Ghozali M, Trisaputra JO, Moestopo O, Sribudiani Y, Idjradinata PS, Maskoen AM. Iron Status in Newly Diagnosed β-Thalassemia Major: High Rate of Iron Status due to Erythropoiesis Drive. BioMed Research International. 2021;2021(1):5560319. https://doi.org/10.1155/2021/5560319

3. Lee WJ, Mohd Tahir NA, Chun GY, Li SC. The impact of chelation compliance in health outcome and health related quality of life in thalassaemia patients: a systematic review. Health and Quality of Life Outcomes. 2024 Feb 2;22(1):14. https://doi.org/10.1186/s12955-023-02221-y

4. Kattamis A, Forni GL, Aydinok Y, Viprakasit V. Changing patterns in the epidemiology of β-thalassemia. European Journal of Haematology. 2020 Dec;105(6):692-703. https://doi.org/10.1111/ejh.13512

5. Khaliq S. Thalassemia in Pakistan. Hemoglobin. 2022 Jan 2;46(1):12-4. https://doi.org/10.1080/03630269.2022.2059670

6. Faranoush M, Faranoush P, Heydari I, Foroughi-Gilvaee MR, Azarkeivan A, Parsai Kia A, Sadighnia N, Elahinia A, Zandi A, Rezvany MR, Hashemi-Madani N. Complications in patients with transfusion dependent thalassemia: A descriptive cross-sectional study. Health Science Reports. 2023 Oct;6(10):e1624. https://doi.org/10.1002/hsr2.1624

7. Kontoghiorghes GJ. Iron load toxicity in medicine: from molecular and cellular aspects to clinical implications. International Journal of Molecular Sciences. 2023 Aug 18;24(16):12928. https://doi.org/10.3390/ijms241612928

8. Elhawary EE, Tolba OA, Elkaffas AA, Shabana AH. Right ventricular function in β-thalassemia children: comparing three-dimensional echocardiography with other functional parameters. Pediatric Research. 2022 Jun;91(7):1709-14. https://doi.org/10.1038/s41390-021-01900-0

9. Deraz SE, Abd El Naby SA, Mahmoud AA. Assessment of ventricular dysfunction in Egyptian children with Beta-thalassemia major. Hematology/Oncology and Stem Cell Therapy. 2021 Sep 1;14(3):206-13. https://doi.org/10.1016/j.hemonc.2020.07.003

10. Frans EH, Rahman MA, Ontoseno T, Ugrasena ID. Correlation between Serum Ferritin and Heart Function in Children with Major Thalassemia at Dr. Soetomo Hospital. Indonesian Journal of Clinical Pathology and Medical Laboratory. 2019;26(1):96-101. http://dx.doi.org/10.24293/ijcpml.v26i1.1401

11. Abbam G, Mensah K, Appiah SK, Nkansah C, Daud S, Aikins CN, Osei-Afoakwa AN, Osei-Boakye F, Derigubah CA, Mohammed S, Tandoh S. Complete Blood Count Reference Intervals for Children Aged Less Than 1 to 12 Years in the Northern Region of Ghana. BioMed Research International. 2024;2024(1):6607281. https://doi.org/10.1155/2024/6607281

12. Landon G, Denjoy I, Clero E, Silenok A, Kurnosova I, Butsenin A, Gourmelon P, Jourdain JR. Reference values of electrographic and cardiac ultrasound parameters in Russian healthy children and adolescents. Scientific Reports. 2021 Feb 3;11(1):2916. https://doi.org/10.1038/s41598-021-82314-0

13. Sayed NM, Mashahit MA, El-Husseiny NM, Ali RA, Ahmed GA, Ibrahim MK. Cardiac Structural and Functional Changes Evaluated by Echocardiography and Two-Dimensional Strain in Patients with Beta Thalassemia.

14. Patsourakos D, Aggeli C, Dimitroglou Y, Delicou S, Xydaki K, Koukos M, Tsartsalis D, Gialeli F, Gatzoulis KA, Tousoulis D, Tsioufis K. Speckle tracking echocardiography and β-thalassemia major. A systematic review. Annals of hematology. 2024 Sep;103(9):3335-56.

15. Alkindi S, Panjwani V, Al-Rahbi S, Al-Saidi K, Pathare AV. Iron overload in patients with heavily transfused sickle cell disease—correlation of serum ferritin with Cardiac T2* Mri (Cmrtools), Liver T2* Mri, and R2-Mri (Ferriscan®). Frontiers in medicine. 2021 Oct 25;8:731102. http://dx.doi.org/10.3389/fmed.2021.731102

16. Sari RE. Iron Overload Cardiomyopathy. Sumatera Medical Journal. 2024 Sep 5;7(3):159-67. https://doi.org/10.32734/sumej.v7i3.17796

17. Liu S, Chen M, Tang L, Li X, Zhou S. Association between serum ferritin and prognosis in patients with ischemic heart disease in intensive care units. Journal of Clinical Medicine. 2023 Oct 16;12(20):6547. https://doi.org/10.3390/jcm12206547

18. Solmaz H, Cabuk AK, Altin Z, Albudak Ozcan E, Ozdogan O. Left ventricular systolic dyssynchrony index and endothelial dysfunction parameters as subclinical predictors of cardiovascular involvement in patients with beta-thalassemia major. Echocardiography. 2021 Jun;38(6):825-33.

19. Elhawary EE, Tolba OA, Elkaffas AA, Shabana AH. Right ventricular function in β-thalassemia children: comparing three-dimensional echocardiography with other functional parameters. Pediatric Research. 2022 Jun;91(7):1709-14.

20. Shiang Yui WE, Said SS, Sabudin RZ, Alauddin H, Ithnin A. Microcytic to hypochromic ratio as a discriminant index of thalassaemia trait in subjects with hypochromic anaemia. Malays J Pathol. 2020 Aug;42(2):195-201. https://www.mjpath.org.my/2020/v42n2/hypochromic-anaemia.pdf

21. Chaloemwong J, Tantiworawit A, Rattanathammethee T, Chai-Adisaksopha C, Rattarittamrong E, Norasetthada L, Charoenkwan P, Louthrenoo W. Hyperuricemia, urine uric excretion, and associated complications in thalassemia patients. Annals of Hematology. 2019 May 1;98:1101-10. https://doi.org/10.1007/s00277-019-03630-0