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ORIGINAL ARTICLE

Frequency of cardiac complications in Beta-thalassemia patients at National Institute of Child Health, Karachi, Pakistan

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ABSTRACT… Objective: To determine the frequency of cardiac complications in beta-thalassemia children. **Study Design:** Cross-sectional study. **Setting:** Department of Pediatric Medicine, National Institute of Child Health (NICH), Karachi, Pakistan. **Period:** March 2024 to August 2024. **Methods:** Children of either gender, aged 5 to 15 years and diagnosed cases of beta-thalassemia major were analyzed. At the time of enrollment, the demographic details of each child, such as gender and age were documented. Information related to the child's disease duration, transfusion frequency, and type of therapy, were recorded. Chest X-rays (CXR), electrocardiograms (ECG), and echocardiograms, were performed at NICVD and evaluated by an experienced cardiologist to determine the frequency of cardiac complications. **Results:** In a total of 188 children, 102 (54.3%) were male. The mean age was 9.5±2.9 years. The mean disease duration, and blood transfusions over lifetime were 68.5±24.6 months, and 150.4±42.7, respectively. There were 152 (80.9%) patients who were undergoing both transfusion and chelation therapy. Cardiac complications were prevalent in 103 (54.8%) children. Cardiomegaly was the most common cardiac abnormality, found in 96 (51.1%), while congestive heart failure was identified in 33 (17.6%) children. Older age group (p=0.028), and increasing disease duration (p0.004) were noted to have significant association with cardiac complications. **Conclusion:** The prevalence of cardiac complications, particularly cardiomegaly and heart failure, were very high in children with beta-thalassemia major. Prolonged disease duration and older age are significant risk factors, highlighting the importance of early diagnosis and aggressive management of iron overload.

Key words: Beta-thalassemia, Cardiomegaly, Congestive Heart Failure, Hemoglobin, Serum Ferritin.

INTRODUCTION

Thalassemia represents a group of genetically inherited disorders characterized by the reduced or absent production of alpha or beta globin chains in hemoglobin, resulting in two primary classifications: alpha-thalassemia and beta-thalassemia.[1] Alpha-thalassemia is predominantly seen in Asian and African populations, while beta-thalassemia (β-thalassemia) is more commonly observed in Mediterranean regions, although it is also prevalent in Southeast Asia and Africa.[1,2]

Beta-thalassemia (β-thalassemia) is an autosomal recessive disorder marked by decreased production of the β-globin chains in hemoglobin.[3] There are three primary forms; thalassemia major, thalassemia intermedia, and thalassemia minor.[4] Thalassemia Major usually manifests within the first two years of life, causing severe anemia, poor growth, and skeletal deformities, necessitating lifelong blood transfusions. Thalassemia Intermedia requires periodic transfusions, while Thalassemia Minor typically does not necessitate transfusions or specific treatments.[5]

Thalassemia is among the most prevalent hemoglobinopathies globally, with the World Health Organization (WHO) estimating that around 270 million people are carriers of the condition, including 70 million carriers of β-thalassemia.[6] Annually, around 68,000 children are born with beta-thalassemia, with the global carrier prevalence estimated at 1.5%, or 80-90 million people.[7] In Pakistan, the prevalence of β-thalassemia is particularly high, with approximately 6% of the population being

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affected, and the gene carrier rate is estimated at 5-7%. Over 50,000 thalassemia patients receive treatment from dedicated centers.[8,9]

The management of beta-thalassemia patients requires lifelong regular blood transfusions and iron chelation therapy (ICT) to mitigate iron overload.[10] Frequent transfusions, however, lead to a number of complications, including cardiac disease, hypogonadism, parathyroid dysfunction, thyroid abnormalities, diabetes, and renal disease.[11] Of all complications, cardiac issues are the leading cause of mortality in beta-thalassemia patients, particularly heart failure induced by myocardial iron overload.[12] In a study by Yaghobi M et al., 76.4% of transfusion-dependent beta-thalassemia patients experienced cardiac complications.[11] Similarly, a Pakistani study by Khalid S et al. found that 60.6% of beta-thalassemia major patients had cardiac complications, with cardiomegaly being the most common at 57.4%, followed by congestive cardiac failure (21.9%), cardiomyopathy (10.3%), pulmonary hypertension (6.5%), and rare cases of pericarditis (0.6%) and arrhythmia (0.6%).[13]

Despite advancements in the management of thalassemia major, cardiac complications remain the most significant cause of mortality and a major source of morbidity, especially in developing countries like Pakistan. Limited data is available on the frequency and type of cardiac complications in Pakistani beta-thalassemia patients. This study, conducted at a tertiary care hospital in Karachi, aimed to determine the frequency of cardiac complications in beta-thalassemia children.

METHODS

This cross-sectional study was conducted among inpatients admitted to the Pediatric Medicine Units 1, 2, and 3 at the National Institute of Child Health (NICH), Karachi, Pakistan from March 2024 to August 2024. The sample size has been calculated using the OpenEpi software, referencing the study by Khalid S et al., which reported 60.6% of beta-thalassemia patients having cardiac complications.[13] By setting a confidence interval of 95% and a margin of error at 7%, the sample size was determined to be 188 patients. Non-probability, consecutive sampling technique was adopted. Approval from Institutional Ethical Committee was acquired (letter number: IERB-01/2023, dated: 13-03-2023). Informed and written consents were taken from parents/guardians. Inclusion criteria were children of either gender, aged 5 to 15 years and diagnosed cases of beta-thalassemia major. Exclusion criteria were children with co-morbid conditions unrelated to β-thalassemia or its complications were excluded.

At the time of enrollment, the demographic details of each child, such as gender and age were documented. Information related to the child's β-thalassemia diagnosis, including disease duration, transfusion frequency, and type of therapy, were recorded. Blood samples were collected under aseptic conditions to measure hemoglobin and serum ferritin levels. Assessments, including chest X-rays (CXR), electrocardiograms (ECG), and echocardiograms, were performed at NICVD and evaluated by an experienced cardiologist. All data were meticulously recorded in a proforma by the researchers.

Data were analyzed using the IBM-SPSS Statistics, version 26.0. For quantitative variables such as age, disease duration, number of blood transfusions, temperature, blood pressure, respiratory rate, hemoglobin, and ferritin levels, mean and standard deviation were calculated. Frequency and percentages were calculated for qualitative variables such as gender, age groups, type of therapy, presenting symptoms, cardiac dysfunction, and types of cardiac complications. To control for effect modifiers such as gender, age, disease duration, and type of therapy, stratification was performed applying chi-square test taking $p<0.05$ as statistically significant.

RESULTS

In a total of 188 children, 102 (54.3%) were male, and 86 (45.7%) female. The mean age was 9.5±2.9 years. The mean disease duration, and blood transfusions over lifetime were 68.5±24.6 months, and 150.4±42.7, respectively. The mean hemoglobin and serum ferritin levels were 7.8±0.8 g/dl, and 2809.8±964.1 ng/mL, respectively.

Table-I is showing distribution of demographics and clinical characteristics of children.

Characteristics		Frequency (%)
Gender	Male	102 (54.3%)
	Female	86 (45.7%)
Age groups (years)	5-9	112 (59.6%)
	10-15	76 (40.4%)
Disease duration (years)	<3	42 (22.3%)
	3-5	71 (37.8%)
	>5	75 (39.9%)

Table-I. Demographic and clinical characteristics (n=188)

There were 152 (80.9%) patients who were undergoing both transfusion and chelation therapy. The most common symptoms were fatigue, dyspnea, swelling, tachypnea, and weight loss, noted in 113 (60.1%), 85 (45.2%), 66 (35.1%), 57 (30.3%), and 47 (25.0%), respectively. Figure-1 is showing details about the frequency of presenting symptoms in children.

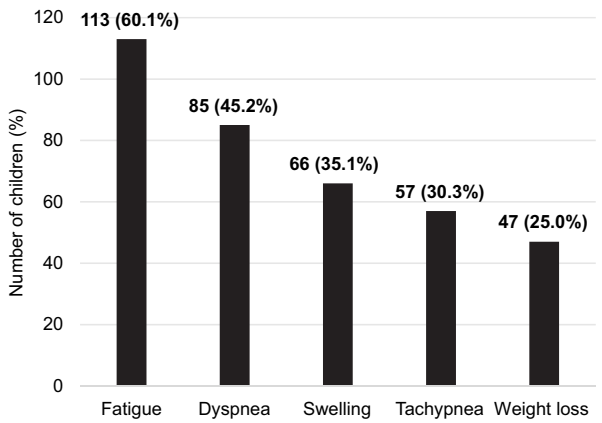

Figure-1. Presenting symptoms (n=188)

Cardiac complications were prevalent in 103 (54.8%) children. Cardiomegaly was the most common cardiac abnormality, found in 96 (51.1%), while congestive heart failure was identified in 33 (17.6%) children. Figure-2 is showing details about the frequency of various cardiac complications identified in children in this study.

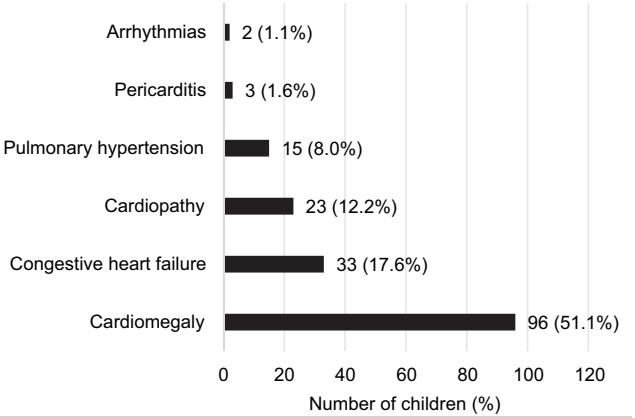

Figure-2. Frequency of cardiac complications

Gender was not found to have any significant association with the presence of cardiac complications (p=0.533). Older age group (p=0.028), and increasing disease duration (p0.004) were noted to have significant association with cardiac complications, and the details are shown in Table-II.

DISCUSSION

The frequency of cardiac complications observed in this was 54.8%. It was noted that cardiomegaly (51.1%), and congestive heart failure (17.6%) were the most frequent cardiac complications observed among children with beta-thalssaemia. These findings align closely with the findings of Khalid et al.,[13] who also reported a high prevalence of cardiomegaly (57.4%) and heart failure (21.9%) in their cohort.

Characteristics		Cardiac Complications (n=103)	No Cardiac Complications (n=85)	P-Value
Gender	Male	58 (56.3%)	44 (51.8%)	0.533
	Female	45 (47.3%)	41 (48.2%)	
Age groups (years)	5-9	54 (52.4%)	58 (68.2%)	0.028
	10-15	49 (47.6%)	27 (31.8%)	
Disease duration (years)	<3	18 (17.5%)	24 (28.2%)	0.004
	3-5	33 (32.0%)	38 (44.7%)	
	>5	52 (50.5%)	23 (27.1%)	

Table-II. Association of cardiac complications with gender, age, and disease duration (N=188)

Salama et al.,[14] documented a range of cardiac issues, including arrhythmias and pulmonary hypertension, in beta-thalassemia patients. In our study, we also observed cases of pulmonary hypertension (8.0%) and arrhythmias (1.1%), though at slightly lower rates. Among adult thalassemia population, a recent study by Mameq et al.,[15] revealed that dilated cardiomyopathy (18.6%), and pulmonary hypertension (30.0%) were the most common cardiac complications. Fazal-ur-Rehman et al.,[16] analyzing patients of beta-thalassemia major showed that heart failure and cardiomegaly were observed in 41.1% patients. These differences could be due to differences in patient management practices, including the frequency of echocardiographic monitoring and the use of newer imaging techniques. As pointed out by Pepe et al.,[17] the use of cardiovascular magnetic resonance (CMR) has significantly improved the identification of cardiac abnormalities in thalassemia patients, guiding changes in chelation therapy and reducing the burden of cardiac complications. In ternational data has shown that as many as 70% of the moralities among β-thalassemia children could be attributed to cardiac complications.[18] Given the high prevalence of cardiac complications, routine cardiac assessment should become standard care in managing beta-thalassemia major. Conventional echocardiography, while widely used, may not detect subtle myocardial dysfunction. Incorporating advanced methods like "Tissue Doppler Imaging (TDI)" for iron overload assessment could provide early signs of cardiac dysfunction, even in asymptomatic patients. This approach could guide early interventions, potentially preventing progression to severe cardiac disease.

When assessing the age distribution, older children (aged 10-15 years) were more likely to have cardiac complications compared to younger children (5-9 years) ($p=0.002$). This is consistent with findings from Ibrahim et al.,[19] where myocardial dysfunction, as detected by advanced echocardiographic techniques like TDI, was found to be more prevalent in older beta-thalassemia patients. The progressive iron overload with age, exacerbated by years of transfusion therapy, is likely responsible for the increasing incidence of cardiac dysfunction in older children.[20] This age-related trend emphasizes the need for early and continuous monitoring of cardiac function in older patients to prevent the progression of silent myocardial damage into overt heart failure or cardiomyopathy. Disease duration also showed a significant association with the presence of cardiac complications ($p<0.001$). This is consistent with the findings of Esfahani et al.,[21] who reported that prolonged disease duration, coupled with high ferritin levels, was a key predictor of myocardial involvement in beta-thalassemia patients. Our study's observation further corroborates that iron overload—accumulated over prolonged transfusion therapy—plays a pivotal role in the development of cardiac complications. This reinforces the critical importance of timely and effective iron chelation therapy to mitigate the toxic effects of iron deposition in myocardial tissues.[22] While transfusions are essential for survival, these contribute to iron overload, necessitating chelation therapy, which, if inadequate, allows iron to accumulate in vital organs like the heart. Pepe et al.,[17] highlighted how CMR-guided changes in chelation therapy have significantly lowered the risk of heart failure and arrhythmias, suggesting that improved chelation protocols may reduce the burden of cardiac complications in future studies.

Our findings further suggest that not all children with beta-thalassemia are at the same level of risk for cardiac complications. Factors such as age, disease duration, and transfusion history should inform individualized risk assessments. Clinicians may need to adopt a stratified approach to monitoring, where high-risk patients (older, longer disease duration, higher ferritin levels) are prioritized for more frequent cardiac evaluations and more aggressive chelation therapy.

The present study had some limitations. Being a single center study, our study requires verification in large multicenteric trials involve large set of children with beta-thallasemia. Further prospective and longitudinal studies are required to correlate age related changes with the cardiac diseases and outcomes among children with

beta-thalassemia.

CONCLUSION

This study concluded that the prevalence of cardiac complications, particularly cardiomegaly and heart failure, were very high in children with beta-thalassemia major. Prolonged disease duration and older age are significant risk factors, highlighting the importance of early diagnosis and aggressive management of iron overload. Future studies should focus on integrating advanced imaging techniques, like CMR and tissue Doppler, to detect early cardiac dysfunction and optimize therapeutic strategies for thalassemia patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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2	Muhammad Ashfaq	Study concept, Methodology.	
3	Bader u Nisa	Proof reading,	
4	Khatidja Ally	Critical review.	