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Frequency of Cardiac Complications in Thalassemia Major Patients

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ABSTRACT

Background: Thalassemia major (TM) is a genetic hemoglobinopathy characterized by chronic anemia and iron overload due to frequent blood transfusions. Cardiac complications are a significant cause of morbidity and mortality in these patients, primarily due to iron accumulation in the heart. Early identification and management of these complications are essential to improve outcomes. **Objectives:** To assess the frequency and types of cardiac complications in children with beta-thalassemia major and to identify their association with age, gender, duration of transfusion, and serum ferritin levels. **Study Settings:** Department of Pediatrics, Allied Hospital Faisalabad. **Duration of Study:** 10th May 2024 to 9th November 2024. **Data Collection:** This cross-sectional study included 110 children aged 5–15 years with confirmed beta-thalassemia major, who had received at least five blood transfusions. Data collection involved clinical history, examination, serum ferritin levels, electrocardiography, and echocardiography to evaluate cardiac complications. Cardiac complications were categorized into cardiomegaly, congestive cardiac failure, cardiomyopathy, and pulmonary hypertension. **Results:** The frequency of cardiac complications was 60.45%, with cardiomegaly being the most common (51.85%), followed by congestive heart failure (24.69%), cardiomyopathy (14.81%), and pulmonary hypertension (8.64%). Cardiac complications were more frequent in patients with transfusion duration >5 years (64.49%, p=0.057) and serum ferritin ≤15 µg/ml (70.59%, p=0.162). However, age, gender, and serum ferritin levels were not significantly associated with cardiac complications. **Conclusion:** Cardiac complications are common in beta-thalassemia major patients, with cardiomegaly being the most frequent. Early screening and management of these complications are crucial to reduce morbidity and mortality in this high-risk population.

INTRODUCTION

Thalassemia is a prevalent genetic disorder with an autosomal recessive inheritance pattern, characterized by anemia and small, dysfunctional red blood cells.[1] Globally, it affects 60,000 births annually, with β-thalassemia being the most severe type.[1] Defective hemoglobin synthesis in β-thalassemia leads to hemolysis, ineffective erythropoiesis, and chronic anemia.[2-3] Based on clinical presentation, it is classified as β-thalassemia major (BTM), requiring transfusion before 2 years of age; β-thalassemia intermedia (BTI), requiring transfusion after age 2; and β-thalassemia minor, which is typically asymptomatic.[4]

Regular transfusions, while lifesaving, pose risks such as iron overload, transfusion-transmitted infections, and alloimmunization.[6] In Pakistan, 5%-8% of the population carries the β-thalassemia gene, with rates as high as 62.2% in affected families.[3] Cardiac complications, including arrhythmias, heart failure, and pulmonary hypertension, are common in β-TM, with iron overload being a major contributing factor.[5] Heart disease accounts for over half of all deaths in these patients, emphasizing the need for routine cardiac monitoring via echocardiography and Holter ECG.[6]

Khalid S et al. reported that 60.6% of 155 patients with β-TM had cardiac complications, including cardiomegaly (57.4%) and congestive heart failure (21.9%).[8] Given limited local data, this study aims to quantify cardiac complications in β-TM patients, enabling early detection and targeted treatment strategies to reduce mortality.

Cardiac dysfunction is the main clinical problem in thalassemia major patients that may lead to early death. Very limited local data is available on this topic. So, this study is planned to assess the frequency of cardiac complications in beta thalassemia major patients. It will help to formulate guidelines for early detection and treatment of complications that will help to reduce morbidity and mortality in this high risk population.

METHODOLOGY

This descriptive, cross-sectional study was conducted at the Department of Pediatrics, Allied Hospital Faisalabad, from 10th May 2024 to 9th November 2024. The sample size was calculated using the WHO sample size calculator for two proportions, with a confidence level of 95%, a frequency of cardiac complications of 60.6%, and a margin of error of 8.5%. The calculated sample size was 134 patients; however, 110 patients meeting the inclusion criteria were enrolled using non-probability consecutive sampling.

The study included children of both genders, aged 5–15 years, with a confirmed diagnosis of beta thalassemia major. Beta thalassemia major was defined as previously diagnosed cases with microcytic hypochromic anemia (Hb <10.5, MCV <70, MCH <26) and hemoglobin electrophoresis showing fetal hemoglobin levels between 10–98%, absent hemoglobin A1, and >3% hemoglobin A2. Patients were required to have received ≥5 blood transfusions and were on follow-up at the Center for Thalassemia Care. Exclusion criteria included patients with acute illnesses, inflammatory kidney or liver conditions, known congenital or acquired cardiac diseases, diabetes mellitus, thyroid diseases, or those taking medications that could affect the QT interval (e.g., antibiotics, antifungals, antimalarials, and antiarrhythmics). Patients with other hemoglobinopathies, such as thalassemia intermedia or sickle cell disease, were also excluded.

After obtaining ethical approval from the Ethical Review Committee and CPSC, eligible patients were enrolled. Informed consent was obtained from parents for investigations and the use of data for research purposes. Data collection included detailed history, clinical examination, and risk factors such as age, gender, duration of transfusion, and serum ferritin levels (obtained from the Pathology Department). Electrocardiography and echocardiography were conducted in the Cardiology Department to evaluate cardiac complications.

Cardiac complications were categorized into four types: cardiomegaly, diagnosed based on symptoms such as shortness of breath and swelling (edema) in the belly or legs, confirmed by an enlarged heart on a chest X-ray; congestive cardiac failure, diagnosed via a chest X-ray showing an enlarged heart and fluid or extra blood flow in the lungs; cardiomyopathy, identified by cardiomegaly on a chest X-ray accompanied by tachycardia, bradycardia, or dysrhythmias; and pulmonary hypertension, defined as a mean pulmonary arterial pressure (mPAP) >25 mmHg due to pulmonary vasculature remodeling. Overall, cardiac complications were labeled “Yes” if any of these individual complications were present.

Data were recorded on a pre-designed proforma and analyzed using SPSS version 25. Quantitative variables, such as age, duration of transfusion, and serum ferritin levels, were expressed as mean ± standard deviation. Qualitative variables, such as gender and cardiac complications (cardiomegaly, congestive cardiac failure, cardiomyopathy, and pulmonary hypertension), were presented as frequencies and percentages. To control for effect modifiers, data were stratified by age, gender, duration of transfusion, and serum ferritin levels. Post-stratification, the Chi-square test was applied to determine the effect of these variables on the outcome. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 provides an overview of the demographic and clinical characteristics of 134 patients. The age distribution shows that the majority (57.46%) of the patients were between 5 and 10 years old, with a mean age of 9.52 ± 1.91 years. The remaining 42.54% were between 11 and 15 years old, with the same mean age and standard deviation. Regarding the duration of transfusion, 20.15% of patients had a transfusion duration of ≤5 years, while the majority (79.85%) had a transfusion duration of >5 years, with a mean duration of 7.20 ± 2.11 years. Serum ferritin levels were ≤15 µg/ml in 25.37% of the patients and >15 µg/ml in 74.63%, with an overall mean ferritin level of 21.37 ± 6.78 µg/ml. Cardiac complications were present in 60.45% of the patients, while 39.55% were free of complications. Among the patients with cardiac complications, cardiomegaly was the most common type (51.85%), followed by congestive heart failure (24.69%), cardiomyopathy (14.81%), and pulmonary hypertension (8.64%).

Table 2 examines cardiac complications in relation to age, gender, duration of transfusion, and serum ferritin levels among the 134 patients. Among patients aged 5–10 years, 61.04% had cardiac complications, compared to 59.65% in the 11–15-year age group (p = 0.871). Regarding gender, 59.26% of males and 62.26% of females had cardiac complications, with no statistically

significant difference (p = 0.728). Duration of transfusion showed a trend toward significance, with 44.44% of patients with ≤5 years of transfusion and 64.49% with >5 years of transfusion developing cardiac complications (p = 0.057). Serum ferritin levels did not show a significant association with cardiac complications; 70.59% of patients with ferritin ≤15 µg/ml and 57.0% with ferritin >15 µg/ml had cardiac complications (p = 0.162). Overall, while age, gender, and serum ferritin levels were not significantly associated with cardiac complications, a longer duration of transfusion showed a potential trend toward higher complication rates.

Table 1

Demographic and Clinical Data of the Patients (n=134)

Variable	Group	No. of Patients	%	Mean ± SD
Age Distribution (years)	5-10	77	57.46	9.52 ± 1.91
	11-15	57	42.54	9.52 ± 1.91
Duration (years)	≤5	27	20.15	7.20 ± 2.11
	>5	107	79.85	7.20 ± 2.11
Serum Ferritin (µg/ml)	≤15	34	25.37	21.37 ± 6.78
	>15	100	74.63	21.37 ± 6.78
Cardiac Complications	Yes	81	60.45	-
	No	53	39.55	-
Types of Cardiac Complications	Cardiomegaly	42	51.85	-
	Congestive heart failure	20	24.69	-
	Cardiomyopathy	12	14.81	-
	Pulmonary hypertension	7	8.64	-

Table 2

Cardiac Complications with Respect to Age, Gender, Duration of Transfusion and Serum Ferritin Level

Variable		Yes (n=81)	No (n=53)	P-value
Age (years)	5-10	47 (61.04%)	30 (38.96%)	0.871
	11-15	34 (59.65%)	23 (40.35%)	
Gender	Male	48 (59.26%)	33 (40.74%)	0.728
	Female	33 (62.26%)	20 (37.74%)	
Duration (years)	≤5	12 (44.44%)	15 (55.56%)	0.057
	>5	69 (64.49%)	38 (35.51%)	
Serum ferritin (µg/ml)	≤15	24 (70.59%)	10 (29.41%)	0.162
	>15	57 (57.0%)	43 (43.0%)	

DISCUSSION

Cardiac complications are a significant concern in thalassemia major, contributing to increased morbidity and mortality. The underlying mechanisms include chronic anemia from infrequent transfusions and iron overload in the heart due to frequent transfusions. Transfusion-dependent patients receive up to 20 times the normal iron intake, leading to its accumulation and subsequent damage to the liver, heart, and endocrine organs. While iron chelation therapy has greatly improved patient outcomes, cardiac failure remains a major cause of death in thalassemia patients.[9]

In this study, total cardiac complications among thalassemia major patients were 60.45%, comparable with other studies, according to Borgne Pignatti C et al, heart dieses is responsible for more than half of the death in TM.[10] In this study, patients in the age range of 5 – 10 years had cardiac complications in 61.04% cases as compared to patients in the age range of 11-15 years had cardiac complications in 59.65% cases. Patients who received transfusion for < 5 years, had cardiac complications in 44.44% cases, who received transfusion for >5 years had cardiac complications in 64.49% cases. Patients who had serum ferritin level in the range of ≤15ng/ml and >15 ng/ml had cardiac complications in 70.59% and 57.0% cases respectively. So frequency of cardiac complications (CC) increases with age, duration of transfusion and serum ferritin level with significant P- Value. In a study[8], patients who received transfusion for < 5 years, had cardiac complications in 46.2% cases, who received transfusion for 5-10 years had cardiac complications in 71.4% cases while those who received transfusion for > 10 year had cardiac complications in 85.7% cases. Patients who had serum ferritin level in the range of 3001-4000ng/l and >4000ng/l had cardiac complications in 76.9% and 76.6% cases respectively, as compared to those with serum ferritin level in the range of 2001-3000ng/l had complications in 56.3% cases, indicating that cardiac complications were mainly due to iron over load.[8]

Most of the patients had cardiomegaly on CXR without clinical feature of congestive cardiac failure. Out of 94 patients. 89 (94.68%) had cardiomegaly, while 34 (66.1%) had congestive cardiac failure.[11] In my study, type of cardiac complication was cardiomegaly in 42 (51.85%), congestive cardiac failure in 20 (24.69%), Cardiomyopathy in 12 (14.81%) and pulmonary hypertension in 07 (8.64%) patients. According to study conducted at Gomal Medical College, Dera Ismail Khan 25.5% patient of thalassemia major have Cardiomegaly on CXR, but they were not having other clinical feature of CCF. Frequency of cardiomegaly increases with age, duration of transfusion and serum ferritin level.[11]

Cardiomyopathy represents one of the most frequently found cardiac complications in thalassemia major patients. According to one international study CMP is a leading cause of morbidity and mortality (63.6-71%).[12] Frequency of cardiomyopathy increases with age, duration of transfusion and serum ferritin level. Patients in the age range of 11-16 years had cardiomyopathy in 3

(12.5%) out of 24. Patients who had received transfusion for 5-10 years, 40 (71%) had CC versus patients who had duration of transfusion >10 years had 18 (85%) patients having CC with P-value 0.001. Patients who had serum ferritin level > 4000 ng/l, CC was found in 36 (76%) patients out of 47 with significant P-Value.[8]

Pulmonary hypertension is a part of cardiopulmonary complication of beta-thalassemia. With improvements in the treatment of thalassemia major (TM) (regular transfusion and chelation therapy), frequency of pulmonary hypertension has been decreased in TM and considered to be primary cardiomyopathy in thalassemia intermedia (TI), but still important component of cardiac dysfunction in TM. In one international study of 110 patients, aged 32.5 ± 11.4 year, age related pulmonary hypertension was encountered in nearly 60% of cases, having caused right heart failure in 6 of them, all patients had reserved left ventricular systolic function.[13] In a study, pulmonary hypertension was found in 10 (10%) patients of thalassemia major out of 155. The association of age, duration of transfusion and serum ferritin level with frequency of pulmonary hypertension was not significant.[8]

Cardiac dysfunction in β-thalassemia patients, particularly in transfusion-dependent thalassemia (TDT), is primarily driven by iron overload. Secondary contributors include deficiencies in essential nutrients such as carnitine, thiamine, vitamin D, and selenium, autoimmune diseases (e.g., hypothyroidism, hypoparathyroidism, hypogonadism), and hepatitis C infection.[14] Iron overload arises mainly from repetitive blood transfusions, alongside contributing factors such as ineffective erythropoiesis, peripheral hemolysis, and increased iron absorption from the intestine.[15] Prior to the introduction of iron chelation therapy, β-thalassemia patients commonly suffered from heart-related complications, including pericarditis, myocarditis, high-output heart failure, and arrhythmias. The implementation of iron chelators has dramatically decreased cardiac mortality, resulting in improved patient survival.[16] Although iron chelation therapy has advanced, cardiac iron deposition and its toxic effects persist as the leading cause of mortality in patients with thalassemia.[17]

CONCLUSION

This study concluded that that frequency of cardiac complications in thalassemia major patients is quite high with cardiomegaly as the most common cardiac complication. So, we recommend that early detection and treatment of complications should be done in order to reduce morbidity and mortality in this high risk population.

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