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Research Article

Frequency of Heart Failure in Thalassemia Patients on Chelation Therapy

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ABSTRACT

Background: Beta-thalassemia major is a transfusion-dependent hemoglobin disorder in which repeated blood transfusions can lead to progressive iron overload and cardiac injury. Although chelation therapy reduces iron-related complications, heart failure may still occur because of poor chelation adherence, persistent anemia, high serum ferritin levels, and delayed cardiac surveillance.

Objective: To determine the frequency of heart failure among beta-thalassemia major patients receiving chelation therapy and to assess its association with demographic, laboratory, transfusion-related, and clinical factors.

Methods: This cross-sectional study was conducted in the Department of Pediatric Medicine, DHQ Hospital, Dera Ghazi Khan, over six months. A total of 100 children aged 5–15 years with confirmed beta-thalassemia major receiving oral deferasirox chelation therapy for at least one year were enrolled through non-probability consecutive sampling. Demographic characteristics, disease duration, transfusion pattern, chelation regularity, hemoglobin level, serum ferritin, chest X-ray findings, and echocardiographic parameters were recorded. Heart failure was diagnosed on the basis of predefined clinical findings and echocardiographic evidence of reduced ejection fraction. Data were analyzed using SPSS version 20.0, and associations were assessed using the chi-square test, with $p \leq 0.05$ considered statistically significant.

Results: The mean age of the patients was 9.8 ± 2.9 years, and 56.0% were male. The mean disease duration was 6.7 ± 2.7 years. Heart failure was identified in 20 patients, giving an overall frequency of 20.0%. The mean serum ferritin level was 3778 ± 1675 ng/mL, while the mean pre-transfusion hemoglobin level was 8.6 ± 1.1 g/dL. Among patients with heart failure, hepatomegaly was the most common clinical finding, observed in 90.0%, followed by respiratory distress in 75.0%, basal crepitations in 65.0%, pitting edema in 55.0%, and raised jugular venous pressure in 40.0%. The mean ejection fraction was lower in patients with heart failure than in those without heart failure. Heart failure was significantly associated with shorter transfusion interval, lower hemoglobin category, higher serum ferritin category, poor chelation regularity, and cardiomegaly on chest X-ray.

Conclusion: Heart failure was present in one-fifth of beta-thalassemia major children receiving deferasirox chelation therapy. High serum ferritin, low pre-transfusion hemoglobin, frequent transfusion requirement, poor chelation regularity, and cardiomegaly were significantly associated with heart failure, highlighting the need for optimized transfusion support, strict chelation adherence, regular ferritin monitoring, and routine cardiac evaluation in thalassemia care.

Keywords: Beta-Thalassemia, Heart Failure, Iron Chelating Agents, Deferasirox, Blood Transfusion.

INTRODUCTION

Beta-thalassemia major is a severe inherited hemoglobin disorder characterized by defective or absent beta-globin chain synthesis, ineffective erythropoiesis, chronic hemolytic anemia, and lifelong dependence on red-cell transfusion therapy [1]. Current international guidelines emphasize that transfusion-dependent thalassemia requires regular transfusion, structured iron monitoring, and continuous chelation therapy to prevent progressive organ injury [2]. Despite improvements in survival, beta-thalassemia remains a major public health challenge in regions with high carrier frequency, particularly the Mediterranean region, Middle East, South Asia, and Southeast Asia [3]. Recent global reviews show substantial variation in prevalence and birth incidence across countries, reflecting differences in screening

programs, consanguinity patterns, migration, and access to specialized care [4]. The Global Burden of Disease 2021 analysis further confirmed that thalassemia continues to contribute to considerable morbidity, mortality, and disability-adjusted life years across many low- and middle-income countries [5]. Therefore, early recognition of complications remains central to improving long-term outcomes in affected children.

Repeated transfusion is essential for survival in beta-thalassemia major; however, it inevitably causes progressive iron accumulation because the human body has no active mechanism for excreting excess iron. Contemporary international experience shows that the prognosis of transfusion-dependent thalassemia is strongly influenced by the adequacy of transfusion support, monitoring infrastructure, chelation access, and adherence to long-term treatment [6]. Transfusional iron overload may involve the liver, endocrine organs, and myocardium, but cardiac involvement is particularly important because it can remain silent until clinically significant systolic dysfunction, arrhythmia, pulmonary hypertension, or overt heart failure develops [7].

Iron chelation therapy is the cornerstone of preventing iron-mediated organ injury. Oral deferasirox has improved the feasibility of long-term chelation, especially in pediatric patients, but its effectiveness depends on dose optimization, tolerability, affordability, monitoring, and regular intake [8]. Poor adherence, missed doses, high serum ferritin levels, and suboptimal transfusion control may allow ongoing iron accumulation even among children who are formally prescribed chelation. Cardiac complications in thalassemia are multifactorial, involving chronic anemia, high-output circulation, myocardial iron deposition, oxidative injury, inflammation, fibrosis, and cardiomyopathy [9]. Echocardiography remains a practical tool for identifying reduced ejection fraction and structural abnormalities, while cardiac magnetic resonance T2* is preferred for direct assessment of myocardial iron where available.

In Pakistan, beta-thalassemia major remains a major inherited disorder because of high carrier frequency, consanguineous marriages, limited premarital screening, delayed diagnosis, and uneven access to comprehensive thalassemia services [10]. Many children receive transfusions and chelation through public hospitals or charitable centers where serum ferritin monitoring, adherence counseling, echocardiography, and advanced cardiac imaging may not be consistently available. Evaluating the frequency of heart failure among children already receiving chelation therapy is therefore clinically important, as it may identify preventable gaps in transfusion adequacy, iron control, chelation adherence, and cardiac surveillance. The present study was conducted to determine the frequency of heart failure in beta-thalassemia major patients on chelation therapy and to assess its association with demographic, laboratory, transfusion-related, and clinical factors in the Pakistani pediatric context.

METHODOLOGY

This cross-sectional study was conducted in the Department of Pediatric Medicine, DHQ Hospital, Dera Ghazi Khan, over a period of six months. The study was designed to determine the frequency of heart failure among children with beta-thalassemia major receiving chelation therapy. The protocol identified the setting as DHQ Hospital, Dera Ghazi Khan, and specified a cross-sectional design with non-probability consecutive sampling.

The sample size was calculated using the WHO sample size calculator by taking an anticipated proportion of 20%, a 95% confidence level, and an absolute precision of 8%. Based on these assumptions, the required sample size was 100 patients. All eligible patients presenting to the outpatient department or admitted through the inpatient/pediatric emergency services of the Department of Pediatric Medicine were enrolled consecutively until the required sample size was achieved.

Children of both genders aged 5–15 years with a confirmed diagnosis of beta-thalassemia major were included. Beta-thalassemia major was defined as a previously diagnosed case confirmed by hemoglobin electrophoresis. Only patients who had been receiving oral deferasirox chelation therapy for at least one year were enrolled. Patients were excluded if informed consent was not provided by parents or guardians, if they had any thalassemia type other than beta-thalassemia major, if they were not receiving chelation therapy, if they were receiving chelation therapy other than deferasirox, or if they had heart failure attributable to causes other than thalassemia, including congenital heart disease or other causes of anemic heart failure.

After approval from the institutional ethical review committee, eligible patients were

assessed according to the study protocol. Written informed consent was obtained from the parent or legal guardian before enrollment. Demographic and clinical information, including age, gender, parental consanguinity, duration of disease, annual hospital admissions, transfusion requirements, and chelation therapy history, was recorded on a predesigned proforma. Relevant clinical history and examination findings were documented, with particular attention to symptoms and signs suggestive of cardiac involvement.

A 5 ml venous blood sample was collected from each enrolled patient and sent to the institutional thalassemia center for hemoglobin electrophoresis where required. The protocol specified that electrophoresis assessment was to be performed by a consultant pathologist with at least three years of post-fellowship experience. Additional investigations included complete blood count, serum ferritin level, chest radiography, and echocardiography. These investigations were used to document hematological status, iron overload, radiological cardiomegaly, and cardiac functional status.

The primary outcome variable was the presence of heart failure. Heart failure was assessed using predefined clinical and echocardiographic criteria. Clinical evidence of heart failure included raised jugular venous pressure, pitting edema after pressure application for 10 seconds, hepatomegaly, basal crepitations, and respiratory distress. Echocardiography was used as the key cardiac investigation, and an ejection fraction of less than 60% was considered consistent with cardiac dysfunction in the study protocol. Chelation therapy was defined as treatment with oral deferasirox.

Data were entered and analyzed using SPSS version 20.0. Quantitative variables, including age and duration of thalassemia, were summarized as mean and standard deviation. Qualitative variables, including gender, transfusion requirements, chelation status, consanguinity, and presence or absence of complications, were summarized as frequencies and percentages. Stratification was performed for age, gender, consanguinity, transfusion requirements, and chelation therapy to assess their relationship with the frequency of heart failure and other complications. After stratification, the chi-square test was applied to evaluate statistical associations. A p-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 100 children with diagnosed beta-thalassemia major receiving chelation therapy were included in the study. The mean age of the participants was 9.8 ± 2.9 years, with an age range of 5–15 years. Most children were male, belonged to consanguineous families, and had a disease duration of more than five years. The mean duration of beta-thalassemia major was 6.7 ± 2.7 years. Heart failure was identified in 20 children, giving an overall frequency of 20.0% among beta-thalassemia major patients on chelation therapy. The baseline demographic and clinical profile of the study population is shown in Table 1.

Table 1. Demographic and Baseline Clinical Characteristics of Beta-Thalassemia Major Patients on Chelation Therapy

Variable	Frequency / Mean	Percentage / SD
Total patients	100	100.0
Age, years	9.8	±2.9
Age group		
5–7 years	30	30.0
8–10 years	34	34.0
11–15 years	36	36.0
Gender		
Male	56	56.0
Female	44	44.0
Residence		
Urban	38	38.0
Rural	62	62.0
Mode of presentation		
Outpatient department	71	71.0
Pediatric emergency/inpatient	29	29.0
Parental consanguinity		
Present	64	64.0

Absent	36	36.0
Duration of thalassemia, years	6.7	±2.7
Duration of disease		
<5 years	22	22.0
5–8 years	38	38.0
>8 years	40	40.0
Hospital admissions per year		
0–1 admission	40	40.0
2–3 admissions	40	40.0
≥4 admissions	20	20.0
Family history of thalassemia		
Present	46	46.0
Absent	54	54.0

The mean pre-transfusion hemoglobin level was 8.6 ± 1.1 g/dL, while the mean serum ferritin level was 3778 ± 1675 ng/mL. Most children required packed red cell transfusion every two to three weeks. All patients were receiving oral deferasirox, as required by the eligibility criteria. However, reported regularity of chelation intake varied, with only 43.0% showing good regularity. Laboratory, transfusion-related, and chelation-related characteristics are presented in Table 2.

Table 2. Laboratory Profile, Transfusion Pattern, and Chelation-Related Characteristics

Variable	**Frequency / Mean**	**Percentage / SD**
Pre-transfusion hemoglobin, g/dL	8.6	±1.1
Hemoglobin category		
<8 g/dL	35	35.0
8–10 g/dL	55	55.0
>10 g/dL	10	10.0
Serum ferritin, ng/mL	3778	±1675
Serum ferritin category		
≤2500 ng/mL	31	31.0
2501–5000 ng/mL	42	42.0
>5000 ng/mL	27	27.0
Transfusion interval		
Every 2 weeks	45	45.0
Every 3 weeks	37	37.0
Every 4 weeks	18	18.0
Mean transfusions per month	1.7	±0.6
Duration of deferasirox therapy		
1–2 years	32	32.0
3–4 years	40	40.0
>4 years	28	28.0
Reported chelation regularity		
Good	43	43.0
Partial	35	35.0
Poor	22	22.0
Mean duration of chelation therapy, years	3.2	±1.4
History of missed chelation doses in previous month	49	49.0
Prior admission for severe anemia	37	37.0

Heart failure was documented in 20 patients. Among clinical findings, hepatomegaly was the most frequent sign, followed by respiratory distress, basal crepitations, pitting edema, and raised jugular venous pressure. On echocardiography, reduced ejection fraction was present in all children classified as having heart failure. The mean ejection fraction among children with heart failure was 52.4 ± 4.7%, compared with 64.8 ± 3.8% among children

without heart failure. The frequency and clinical pattern of heart failure are shown in Table 3.

Table 3. Frequency and Clinical Characteristics of Heart Failure among Beta-Thalassemia Major Patients

Variable	Frequency / Mean	Percentage / SD
Overall heart failure	20	20.0
No heart failure	80	80.0
Clinical findings among heart failure patients		
Hepatomegaly	18	90.0
Respiratory distress	15	75.0
Basal crepitations	13	65.0
Pitting edema	11	55.0
Raised JVP	8	40.0
Chest X-ray findings		
Cardiomegaly present	35	35.0
Cardiomegaly absent	65	65.0
Cardiomegaly among heart failure patients	15	75.0
Cardiomegaly without clinical heart failure	20	25.0
Echocardiographic EF in heart failure group, %	52.4	±4.7
Echocardiographic EF in non-heart failure group, %	64.8	±3.8
EF 50–54% among heart failure patients	12	60.0
EF 55–59% among heart failure patients	8	40.0

Among cardiac complications, anemic heart failure was the most common presentation, followed by dilated cardiomyopathy, pulmonary hypertension, restrictive cardiomyopathy, and myocarditis. Some children had overlapping echocardiographic abnormalities. The pattern of cardiac complications is summarized in Table 4.

Table 4. Pattern of Cardiac Complications Detected on Clinical Assessment, Chest X-Ray, and Echocardiography

Cardiac complication	Overall frequency, n	Overall percentage	Among heart failure patients, n	Percentage within heart failure group
Anemic heart failure	12	12.0	12	60.0
Dilated cardiomyopathy	9	9.0	9	45.0
Pulmonary hypertension	5	5.0	5	25.0
Restrictive cardiomyopathy	4	4.0	4	20.0
Myocarditis	2	2.0	2	10.0
Cardiomegaly on chest X-ray without clinical heart failure	20	20.0	—	—
Any cardiac abnormality on CXR/ECHO	40	40.0	20	100.0

Stratification showed that heart failure was more frequent among older children, males, children with parental consanguinity, longer disease duration, frequent transfusion requirements, low pre-transfusion hemoglobin, high serum ferritin levels, poor chelation regularity, and cardiomegaly on chest X-ray. Statistically significant associations were observed for transfusion interval, serum ferritin category, hemoglobin category, poor chelation regularity, and cardiomegaly on chest X-ray. Age group, gender, consanguinity, and disease duration showed higher observed frequencies but did not reach statistical significance. The stratified analysis is shown in Table 5.

Table 5. Stratification of Heart Failure According to Demographic, Clinical, Transfusion, and Laboratory Variables

Variable	Total, n	Heart failure present, n (%)	Heart failure absent, n (%)	p-value
Age group				0.105
5–7 years	30	3 (10.0)	27 (90.0)	
8–10 years	34	6 (17.6)	28 (82.4)	
11–15 years	36	11 (30.6)	25 (69.4)	
Gender				0.365
Male	56	13 (23.2)	43 (76.8)	
Female	44	7 (15.9)	37 (84.1)	
Parental consanguinity				0.096
Present	64	16 (25.0)	48 (75.0)	
Absent	36	4 (11.1)	32 (88.9)	
Duration of disease				0.184
<5 years	22	2 (9.1)	20 (90.9)	
5–8 years	38	7 (18.4)	31 (81.6)	
>8 years	40	11 (27.5)	29 (72.5)	
Hospital admissions/year				0.065
0–1 admission	40	4 (10.0)	36 (90.0)	
2–3 admissions	40	9 (22.5)	31 (77.5)	
≥4 admissions	20	7 (35.0)	13 (65.0)	
Transfusion interval				0.010
Every 2 weeks	45	15 (33.3)	30 (66.7)	
Every 3 weeks	37	4 (10.8)	33 (89.2)	
Every 4 weeks	18	1 (5.6)	17 (94.4)	
Hemoglobin category				0.032
<8 g/dL	35	12 (34.3)	23 (65.7)	
8–10 g/dL	55	7 (12.7)	48 (87.3)	
>10 g/dL	10	1 (10.0)	9 (90.0)	
Serum ferritin category				0.004
≤2500 ng/mL	31	2 (6.5)	29 (93.5)	
2501–5000 ng/mL	42	7 (16.7)	35 (83.3)	
>5000 ng/mL	27	11 (40.7)	16 (59.3)	
Chelation regularity				0.041
Good	43	5 (11.6)	38 (88.4)	
Partial	35	7 (20.0)	28 (80.0)	
Poor	22	8 (36.4)	14 (63.6)	
Chest X-ray cardiomegaly				<0.001
Present	35	15 (42.9)	20 (57.1)	
Absent	65	5 (7.7)	60 (92.3)	

DISCUSSION

The present study found heart failure in 20.0% of children with beta-thalassemia major receiving chelation therapy, indicating that clinically relevant cardiac morbidity persists despite chelation exposure. This frequency is close to the Pakistani study by Hussain et al., who reported congestive heart failure in 17.6% of beta-thalassemia children at the National Institute of Child Health, Karachi, while overall cardiac complications were found in 54.8% [11]. Similarly, Sarwar et al. reported cardiac complications in 60.45% of thalassemia major children in Faisalabad, with congestive heart failure in 24.69%, cardiomyopathy in 14.81%, and pulmonary hypertension in 8.64% [12]. The slightly lower overall frequency in our cohort may be due to the present study focusing specifically on heart failure rather than all cardiac abnormalities.

Serum ferritin was significantly associated with heart failure, with the highest frequency among children with ferritin levels above 5000 ng/mL. This finding supports Ahmed et al., who observed that transfusion-dependent thalassemia patients with higher iron burden showed evidence of early iron-overload cardiomyopathy [13]. However, ferritin is an

imperfect surrogate for myocardial iron. Meloni et al. demonstrated that left ventricular global function index was associated with myocardial iron overload and heart failure in thalassemia major [14], while another Meloni et al. study showed that increased myocardial extracellular volume was associated with myocardial iron overload and previous heart failure [15]. Nadar et al. also reported abnormal diastolic function and impaired global longitudinal strain in thalassemia patients on long-term chelation, suggesting that conventional ejection fraction may miss early myocardial dysfunction [16].

The clinical pattern in our study showed hepatomegaly, respiratory distress, basal crepitations, edema, and raised jugular venous pressure among heart failure cases. Anemic heart failure was the most frequent complication, followed by dilated cardiomyopathy and pulmonary hypertension. The significant association between low pre-transfusion hemoglobin and heart failure supports the contribution of chronic anemia and high-output cardiac stress. Mohammad et al. reported Doppler-defined pulmonary hypertension in beta-thalassemia major patients and highlighted its association with chronic hemolysis, iron overload, and disease severity [17]. Saadatifar et al. further showed that cardiac biomarkers may correlate with myocardial iron overload on T2* MRI [18]. Newer imaging work by Taleie et al. and Meloni et al. supports the role of advanced echocardiographic, radiomic, and CMR-based strain techniques for identifying early myocardial injury before overt systolic failure develops [19,20].

Chelation regularity was significantly associated with heart failure in the present study, with the highest frequency among children reporting poor regularity. Pala et al. showed that increasing ferritin was associated with impaired left ventricular functional measures in beta-thalassemia major with iron overload [21]. Mohamed et al. reported unsatisfactory adherence to iron chelation among adolescents with transfusion-dependent thalassemia [22], while Keowmani et al. identified non-adherence as a persistent problem among children with beta-thalassemia major [23]. A systematic review by Reddy et al. also confirmed that adherence to chelation therapy in children and adolescents is variable and influenced by treatment burden, family support, psychosocial factors, and health-system barriers [24]. These findings suggest that chelation programs should move beyond prescribing medication and include adherence monitoring, caregiver counseling, toxicity surveillance, and affordability support. Overall, the present findings are consistent with contemporary evidence that iron overload causes myocardial injury through oxidative stress, inflammation, mitochondrial dysfunction, and progressive cardiomyopathy [25]. In Pakistani thalassemia centers, routine ferritin monitoring, transfusion optimization, regular echocardiography, improved chelation adherence, and referral for cardiac MRI where feasible may reduce preventable heart failure.

CONCLUSION

Heart failure remains a considerable complication among children with beta-thalassemia major despite chelation therapy. The findings suggest that inadequate iron control, low hemoglobin levels, frequent transfusion needs, poor chelation regularity, and cardiomegaly are important warning indicators. Regular cardiac screening, improved chelation adherence, and better transfusion optimization may help reduce preventable cardiac morbidity in these patients.

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