Review Article

Cardiac Dysfunction in β-Thalassemia: A Narrative Review

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Highlights

- Iron overload is the primary driver of heart problems. Patients with β-thalassemia major require lifelong blood transfusions to survive.
- Early detection is critical because symptoms appear late. Cardiac dysfunction often remains hidden (subclinical) until the disease is advanced.
- Management focuses on iron chelation and monitoring. Since the body cannot naturally remove excess iron, the primary treatment to prevent or reverse cardiac damage is iron chelation therapy.

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ABSTRACT

Introduction: β-thalassemia, particularly the major form, is associated with significant morbidity, as it requires lifelong maintenance transfusion therapy to manage the condition. This transforms thalassemia from a fatal childhood disease into a chronic disorder. Nonetheless, this therapeutic approach presents challenges due to its pathological adverse effects on cardiac health, including heart failure and arrhythmias.

Discussion: Multiple lifelong transfusions, combined with the pathological effects of thalassemia—such as hemolysis and ineffective erythropoiesis—exacerbate excessive iron deposition, primarily in the liver but most critically in the heart. This creates a vicious cycle between iron overload and cardiac dysfunction. Due to their high dependence on blood transfusions, thalassemia major patients are predisposed to left-sided heart failure, resulting from both dilated and restrictive cardiomyopathy, as well as life-threatening arrhythmias and electrical disturbances. These complications arise from the heart's overwhelmed capacity to clear free radicals. Cardiac dysfunction represents a critical complication requiring early detection and prompt intervention, underscoring the limitations of conventional echocardiography in diagnosing subclinical and systolic dysfunction—the latter often appearing only in advanced disease. Earlier risk stratification is essential, with recent studies highlighting the role of genetic predisposition, biomarkers, and advanced noninvasive imaging (MRI) in facilitating timely treatment initiation, such as iron-chelating therapy, to improve survival outcomes.

Conclusions: Iron overload is an inevitable consequence for thalassemia major patients requiring transfusions, as the human body lacks mechanisms to eliminate excess iron. These patients require careful observation, monitoring, and timely diagnosis according to standard guidelines to facilitate chelation therapy and prevent its harmful effects. This review examines the complex interplay between symptomatic management of thalassemia, subsequent iron overload, and cardiac dysfunction in treated patients, with the goal of promoting early detection of therapeutic complications and timely intervention.

Keywords: β-thalassemia; Cardiac Dysfunction and Arrhythmias; Iron Chelation; Treatment and Guidelines; Management

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Introduction

One of the most common monogenic diseases in the world is thalassemia. Ninety million people worldwide, or 1.5% of the total population, are thought to be β-thalassemia gene carriers.[1] The vast majority of these individuals live in developing nations. β-thalassemia's are a group of inherited, autosomal recessive diseases characterized by reduced or absent synthesis of the β-globin chains of the hemoglobin tetramer, resulting in phenotypes ranging from severe anemia to clinically asymptomatic individuals.[2] Clinically, the thalassemia spectrum is divided into two principal categories based on the patient's need for blood transfusions. Patients with thalassemia major (TM) typically develop severe anemia in early childhood, necessitating regular transfusions as lifelong therapy for survival. In contrast, individuals with thalassemia intermedia (TI) generally develop mild-to-moderate anemia in later childhood or even adulthood, and in some clinical settings, they may require only occasional or short-term regular transfusions.[3]

Thalassemia, once thought to be a disease that would quickly kill a child, is now considered a chronic condition with a longer life expectancy, thanks to blood transfusions, which have significantly improved its prognosis.[4] While transfusions have increased patients' life expectancy, they have also led to iron overload caused by the accumulation of iron from hemolysis, transfused red blood cells, and ineffective erythropoiesis. For this reason, iron chelation therapy is essential to prevent iron buildup in the heart, endocrine system, and liver.[5] Chelation therapy has been shown to improve mortality rates; still, iron overload–related cardiomyopathy remains the primary cause of morbidity and mortality in this patient population. It is estimated that 71% of deaths worldwide in patients with β-TM are attributable to cardiac complications.[6]

The primary cardiac abnormalities associated with TM and iron overload include pericarditis, valvulopathies, arrhythmias, left ventricular systolic and diastolic dysfunction, and pulmonary hypertension.[7] The leading causes of death in these patients are pulmonary hypertension, arrhythmias, and left ventricular systolic and diastolic dysfunction.[8,9] Although iron accumulation occurs more frequently in the liver than in the heart, cardiac iron overload also contributes, albeit to a lesser extent, to the development of these complications. In TI, the underlying pathophysiology can increase cardiac output, cause volume overload, promote endothelial dysfunction, trigger inflammation, and induce hypercoagulability, all of which can lead to cardiac complications.[8,10] Cardiac iron has been detected in one-third of pediatric patients with β-thalassemia between the ages of 15 and 18, with most of them remaining asymptomatic, despite the higher prevalence of these complications in adults.[11] Early detection of cardiac abnormalities remains challenging.

Echocardiographic abnormalities and symptoms typically appear later in the disease course. Systolic dysfunction develops in the later stages, although patients generally retain normal exercise capacity.[12] Consequently, several studies have focused on identifying potential genetic predispositions and biomarkers that may aid in detecting the disease in its early stages, thereby improving opportunities for management and intervention.

To prevent or treat cardiac complications, this narrative will first describe the most common cardiac complications experienced by patients with β-thalassemia. It will then explain the pathophysiological mechanisms underlying these complications and underscore the significance of early patient identification through appropriate diagnostic tools, biomarkers, and genetic predisposition.

Discussion

Iron overload as the primary etiology of cardiac dysfunction in thalassemia patients

Cardiac iron deposition, influenced by various pathophysiological and genetic factors, represents the principal mechanism of myocardial impairment.[13] The underlying pathophysiology of iron accumulation differs between TM and TI. In TI, ineffective erythropoiesis drives iron overload, while in TM, repeated blood transfusions constitute the major contributing factor.[14] The excess unpaired α-globin chains in bone marrow erythroid

precursors damage red blood cell membranes, leading to hemolysis and subsequent ineffective erythropoiesis.[15] Heme is released during erythrocyte breakdown. The liver-produced peptide hormone hepcidin regulates dietary iron absorption through its release into circulation. When hepcidin becomes suppressed, iron absorption increases, resulting in excessive iron storage in organs rather than utilization for erythropoiesis.[16,17] Further, erythroid progenitor lysis triggers compensatory bone marrow stimulation, which causes unbalanced progenitor proliferation and leads to immature cell production. This proliferation imbalance, combined with bone marrow hyperplasia, results in extramedullary erythropoiesis and subsequent bone deformities.[18] In transfusion-dependent TM patients, iron overload primarily results from repeated transfusions. Notably, TI patients develop iron overload through the same mechanism once they begin regular transfusion therapy.[19]

The human body lacks efficient iron excretion mechanisms, leading to substantial iron accumulation in transfusion-dependent thalassemia (TDT) patients.[20] In both transfusion-related and ineffective erythropoiesis-mediated iron overload, oxidative stress generates toxic reactive oxygen species and membrane lipid peroxidation. These processes induce endothelial dysfunction and ultimately cause cardiac damage.[16,18] Cardiac complications represent the most severe manifestations in thalassemia patients, responsible for 71% of mortality in β-TM cases.[6] Notably, cardiac siderosis-induced arrhythmias and heart failure constitute the primary life-threatening conditions in these patients.[1,21]

The pathological mechanism underlying these cardiac complications involves iron-mediated impairment of calcium ion (Ca^{2+}) current inactivation, leading to increased Ca^{2+} influx. During early disease stages, this process progressively impairs diastolic ventricular function.[22] The resulting restrictive cardiomyopathy, combined with pulmonary iron deposition, elevates pulmonary arteriolar resistance, causing right ventricular dilatation and subsequent heart failure.[21] This progression frequently results in pulmonary hypertension. With further iron accumulation, competitive Fe^{2+} inhibition of Ca^{2+} entry develops, ultimately causing systolic dysfunction. The end-stage manifestation is congestive heart failure, characterized by dilated cardiomyopathy and impaired contractility. [23]

Cardiac abnormalities in β-thalassemia patients

Cardiac dysfunction is a complex clinical syndrome characterized by a variety of signs and symptoms. It results from any anatomical or functional abnormality that impairs blood ejection or ventricular filling. Most patients with heart failure develop symptoms due to impaired left ventricular myocardial function, although these symptoms can also arise from metabolic abnormalities or disorders of the pericardium, myocardium, endocardium, heart valves, or great arteries.[24] Among patients with thalassemia, the prevalence of heart failure remains at 2.5%, despite a reduction of more than 50% over the past decade.[25] Iron overload is believed to play a major role in the development of cardiac siderosis, as it can lead to late impairment of left ventricular ejection fraction and an increase in end-systolic volume. In addition, alterations in right ventricular systolic function may also occur.[26,27]

In TM, heart failure primarily results from impaired left ventricular systolic function with concomitant ventricular dilatation. Clinical studies demonstrate that 83% of TM patients with heart failure present with left-sided failure, characterized by left ventricular dilatation and reduced contractility. The remaining 17% exhibit right heart failure, manifested by significant tricuspid regurgitation, right ventricular dilatation and dysfunction, elevated pulmonary artery pressure, and restrictive left ventricular filling patterns.[28,29] Notably, patients with left ventricular failure tend to be younger and present with acute symptom onset compared with those with right-sided failure, who typically show progressive clinical deterioration.[27] Early echocardiographic evaluations are essential to confirm ventricular dysfunction and exclude less common causes of cardiovascular compromise, such as cardiac tamponade or pulmonary embolism.[26]

Arrhythmia

An irregularity or disturbance in the regular activation or beating of the cardiac myocardium is known as a cardiac arrhythmia.[30] Hearts that are

iron-overloaded frequently experience arrhythmias.[31] Since the prevalence of cardiac arrhythmias has varied between studies, it is challenging to determine it accurately in the β-TM population. In one study, for instance, cardiac arrhythmias were found in 3.2% of 481 β-TM patients, whereas in another study, 64% of thalassemia patients had arrhythmias.[32,33]

Arrhythmia has a complex pathophysiology that includes chronic anemia, elevated cardiac afterload, endocrine disruptions, and cardiac iron toxicity.[31,34] Electrical activity disturbances and lipid membrane damage are known effects of cardiac iron poisoning.[35] Cardiomyocytes loaded with iron appear to have a lower overshoot potential than cardiomyocytes devoid of iron.[36] A reduction in the overshoot potential could cause the action potential to shorten. This electrophysiological variability, particularly the patchy pattern of cardiac iron deposition, may contribute to the development of arrhythmias and cardiac issues in patients with TM, in addition to acting as a substrate for triggered and reentry activity.[37,38]

Most patients do not have any symptoms at first. The severity of symptoms is correlated with the degree of ventricular impairment as cardiac dysfunction advances. Left ventricular iron overload is more common, and changes in QTc and QT, which are thought to be arrhythmia precursors, have been linked to left ventricular septal and posterior wall thickness.[39] Complete heart block or syncope brought on by ventricular tachycardia are examples of unusual clinical manifestations.[40]

While ventricular arrhythmias are more specific to iron cardiotoxicity, paroxysmal supraventricular tachyarrhythmias, such as atrial fibrillation, atrial flutter, and intra-atrial reentrant tachycardia, are common rhythm dysfunctions among TM patients.[1] A retrospective cohort analysis of British β-thalassemic patients revealed that the most common cardiac dysfunction among TM patients was atrial fibrillation.[41] Since individuals with atrial fibrillation have a five-fold higher risk of stroke or embolism than those with sinus rhythm, it is of great significance to diagnose them promptly. [1] Two ECG parameters, maximum P-wave duration (>35.5 ms) and P-wave dispersion (>111 ms), are thought to be independent risk factors for the development of atrial fibrillation.[42]

Cardiomyopathy

Cardiomyopathies are a group of diseases characterized by structural and functional abnormalities of the heart. These diseases may have primary causes, including genetic and acquired conditions, or secondary causes, such as inflammatory, toxic, or infiltrative etiologies.[43] According to the American Heart Association, they are a class of heart conditions marked by inappropriate ventricular hypertrophy that may ultimately result in cardiovascular death or progressive heart failure.[44] In patients with thalassemia, cardiomyopathy is one of the leading causes of death. In fact, according to the Greek series by Ladis et al.,[14] cardiomyopathy accounted for 71% of all deaths.[45] Myocardial iron overload is the traditional explanation for thalassemia-related cardiomyopathy in the era of systematic transfusion therapy. Between 11.4% and 15.1% of TDT patients experience cardiomyopathy as a result of iron accumulation.[46]

Cardiomyopathy in thalassemic patients can present as one of two distinct phenotypes: (i) dilated cardiomyopathy, characterized by reduced contractility and left ventricular dilation, ultimately leading to congestive heart failure; and (ii) restrictive cardiomyopathy, characterized by restrictive left ventricular filling, pulmonary hypertension, right ventricular dilation, and heart failure.[14] The pathophysiology of dilated-type left ventricular failure in β-thalassemia is multifactorial, with a significant contribution from immunoinflammatory and inherited components that remain unclear, rendering the underlying mechanism complex.[14,47,48]

One major factor that appears to influence the pathophysiology of cardiomyopathy in β-thalassemia is myocarditis. Patients with β-thalassemia may be more vulnerable to infections due to potential immune system deficiencies. Furthermore, iron overload may increase their susceptibility to infections.[11] It is worthy of note that, although patients with TM who develop cardiomyopathic manifestations have a higher risk of heart failure and death, the pattern of iron deposition in the heart is primarily in the epicardial layer, and tissue studies have suggested that even severe cardiac iron overload may be reversible.[49] Using advanced diagnostic techniques, including echocardiography and cardiac magnetic resonance

T2* (CMR T2*), along with a thorough clinical evaluation, it is essential to accurately diagnose cardiomyopathic manifestations in patients with TM to assess their reversibility and prevent potential heart failure.[50]

Pulmonary hypertension

The hallmark of pulmonary hypertension is a mean pulmonary artery pressure exceeding 25 mm Hg at rest.[51] Hemoglobinopathies, particularly thalassemia's, are among the most common causes of pulmonary hypertension the world over.[52] In non-transfusion-dependent thalassemia (NTDT), specifically TI, heart failure—primarily driven by protein toxicity—is the most frequent cardiovascular complication.[53] An echocardiography-based study of 110 TI patients found pulmonary hypertension in 60% of cases.[54] Earlier studies reported higher rates (75%–79%) in small cohorts of untreated TM patients, who predominantly exhibited systolic left ventricular dysfunction.[40,55] Recent studies in well-managed TM populations, nevertheless, show a significantly lower incidence (~10%), with most cases presenting only borderline pressure elevations.[56]

The high prevalence of pulmonary hypertension in NTDT/TI patients compared with TM may stem from chronic anemia due to less frequent transfusions.[57] While regular transfusions in TM prevent severe anemia, they contribute to iron overload, left ventricular dysfunction, and eventual right heart impairment (Figure 1).[58] These mechanisms may ultimately lead to pulmonary hypertension in advanced disease stages.

The condition's pathophysiology is complicated, including splenectomy, hypercoagulability, iron buildup, left ventricular dysfunction, elevated cardiac output, and decreased availability of nitric oxide (NO).[53,59] Insufficient levels of NO and its precursor, arginine, have been linked to increased resistance and vasodilation that is dependent on NO, both of which promote vascular resistance and raise the risk of pulmonary hypertension.[60]

Myocardial siderosis

Heart damage caused by excess iron accumulation is known as myocardial siderosis. Myocardial siderosis remains the leading cause of death in patients with β-TM.[61] Increased gastrointestinal iron absorption and recurrent blood transfusions can result in iron overload. Because the body has no natural mechanism to remove excess iron, and each transfusion contains approximately 200 mg of iron, a significant increase in total body iron concentration is inevitable.[27] Ferritin, hemosiderin, and labile cellular iron are the three forms of iron present in the heart.[62] Oxidative stress from hydroxyl radicals produced by labile cellular iron damages cardiac cells.[35] This damage impairs mitochondrial respiratory chain function, which results in clinical manifestations such as heart failure.[63]

Elevated levels of iron accumulation are observed in the epicardium and ventricles.[27] Myocardial iron accumulation can cause cardiomyopathy, and heart failure resulting from iron overload remains the principal cause of death in TM patients.[35] Patients with TDT are more likely to develop cardiomyopathy, whereas those with NTDT, particularly after splenectomy, are more prone to pulmonary hypertension.[63] Myocardial siderosis can also disrupt the heart's electrical activity, potentially causing arrhythmias and heart block.[35]

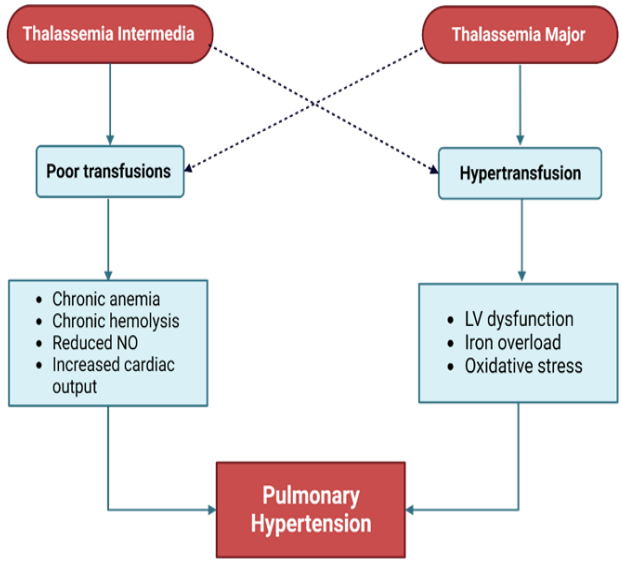

Figure 1. The image depicts the pathophysiology of pulmonary hypertension among thalassemia major and thalassemia intermedia patients. LV: left ventricle, NO: nitric oxide

Early detection of cardiac dysfunction

a. *Clinical features*

Early identification of cardiac complications in thalassemia patients is crucial, as prompt

diagnosis enables intensive chelation therapy initiation and may improve survival outcomes. Clinicians must recognize characteristic clinical manifestations in these patients. Those developing cardiovascular involvement typically exhibit exertional dyspnea, fatigue, reduced exercise tolerance, palpitations, and chest pain. Advanced heart failure may present with anorexia, paroxysmal nocturnal dyspnea, and orthopnea.[7]

The compensatory high-output state in thalassemia-related heart failure manifests through distinctive hemodynamic features: sinus tachycardia, wide pulse pressure, elevated jugular venous pressure, and cardiomegaly with S3 gallop.[7,64] On auscultation, a loud pulmonary component of the second heart sound may be audible, reflecting either pulmonary hypertension or the presence of S3 gallop.[65]

b. *CMR*

Since many cardiac abnormalities remain asymptomatic until the disease is advanced, patients with β-thalassemia should undergo regular clinical examinations and assessments to evaluate their overall cardiac function through a variety of diagnostic and imaging techniques. Cardiac T2* MRI is one such method. Cardiac T2* MRI, a noninvasive technique for assessing cardiac iron, is considered the gold standard for the early detection of cardiac iron deposition.[66] The development of T2* MRI has significantly improved survival rates for patients with TDT.[67]

A myocardial T2* value of less than 20 ms typically indicates an abnormally high level of cardiac iron, which may increase the risk of ventricular dysfunction.[68] Notably, a corresponding decrease in cardiac ejection fraction has been observed when T2* falls below 20 ms, suggesting a direct link between elevated cardiac iron and cardiac dysfunction.[69] One study reported that most patients with an initial cardiac T2* <10 ms eventually developed heart failure during follow-up, even when using the lower cutoff value of 10 ms.[66] Similarly, Kirk et al.[70] demonstrated that the prospective risk of symptomatic heart failure over one year was 50% for a T2* <6 ms, 30% for T2* between 6 and 8 ms, and 14% for T2* between 8 and 10 ms. These findings indicate that T2* is a strong predictor of clinical cardiac risk, with longitudinal risk closely mirroring cross-sectional study projections.

Beyond estimating cardiac iron burden, this diagnostic tool provides consistent identification of preclinical changes in ejection fraction. It has also been crucial for monitoring the effectiveness of chelation therapy in individual patients, which has improved adherence to treatment programs and, consequently, patient outcomes.[71] Several studies have suggested lowering the age at which patients with TM should undergo their first T2* screening from 10 years to as young as 5 years, promoting earlier detection of iron loading in pediatric patients.[72] For all its advantages, cardiac T2* MRI remains costly and is not widely available, particularly in developing countries where β-thalassemia is more prevalent. Moreover, interpretation of results requires consultation with an expert.[73]

c. *Echocardiography*

Recent advances in cardiac assessment have demonstrated the utility of tissue Doppler echocardiography for evaluating early myocardial dysfunction in both pediatric and adult thalassemia patients. While CMR remains the gold standard for detecting cardiac iron deposition, its high cost and limited availability in developing countries often preclude routine use for early screening in TM patients.[66] For arrhythmia evaluation in β-thalassemia, transthoracic echocardiography and ECG serve as essential noninvasive diagnostic tools.[11] Echocardiography provides comprehensive data on cardiac morphology, hemodynamics, ventricular dimensions, and systolic function. While basic chamber measurements offer clinically relevant information, complementary CMR studies may be necessary for a complete assessment.[13]

Conventional echocardiographic parameters such as ejection fraction and fractional shortening lack sufficient sensitivity for the early detection of cardiac iron overload.[74] Emerging evidence highlights the superior diagnostic value of advanced echocardiographic techniques, including strain imaging[76] and tissue Doppler imaging,[75] for identifying subclinical myocardial dysfunction. Tissue Doppler imaging, which detects low-velocity intramyocardial motion, has proven particularly valuable for early disease detection. This modality shows a strong correlation with serum ferritin levels and serves as a reliable indicator of significant iron overload. Characteristic tissue Doppler findings include reduced systolic myocardial velocity (Sm)

and diminished early diastolic velocity (Em), reflecting myocardial stiffening and diastolic impairment.[7]

Multiple studies have evaluated the correlation between echocardiographic parameters and CMR findings in thalassemia patients. Aypar et al. [77] demonstrated significant associations between CMR T2* values and both septal systolic myocardial velocity (SM) and septal early diastolic myocardial velocity (EM) in their study of 33 thalassemia patients. Magri et al.[78] similarly reported strong correlations between CMR T2* values and systolic strain measurements of the right ventricular free wall, septal wall, and lateral wall in their investigation of 30 patients. Recent research suggests that global longitudinal strain (GLS) may serve as a valuable alternative for detecting myocardial iron deposition, particularly in resource-limited settings where CMR availability is restricted.[74] For functional assessment, stress echocardiography with either dobutamine infusions or treadmill exercise has shown prognostic value, where a failure to increase left ventricular ejection fraction by ≥5% demonstrates high specificity for predicting future overt heart failure development.[7]

d. *ECG*

Although ECG abnormalities are common, they are usually non-specific.[13] These alterations likely reflect the preclinical effects of cardiac iron overload. Repolarization abnormalities, including bradycardia, prolonged QT and corrected QT (QTc) intervals, and ST- and T-wave abnormalities, are thought to occur in iron-loaded hearts. Arrhythmias and conduction disturbances appear to be more closely associated with myocardial iron levels than with the conduction system itself.[27]

In a study of 47 TM patients without systolic heart failure, TM patients exhibited longer P waves and QRS durations than healthy controls. In fact, TM patients were found to have longer and more dispersed P waves, linked to an increased risk of paroxysmal atrial fibrillation.[79] Additionally, P-wave dispersion has been shown to correlate with cardiac iron overload as determined by CMR. Similarly, a recent study found a significant association between increased odds of iron overload in TM patients and prolonged QTc dispersion, as well as decreased heart rate deceleration capacity.[80]

Biomarkers for iron overload and cardiac dysfunction

Patients with thalassemia should be particularly concerned about cardiac dysfunction caused by iron overload, as excessive iron accumulation in the heart can lead to a variety of cardiovascular complications. Prevention of such complications requires close monitoring and management of iron overload. Serum ferritin is one of the primary biomarkers used to evaluate iron overload in cardiac thalassemia dysfunction. Ferritin, the principal protein responsible for storing iron in the body, is secreted into the plasma in trace amounts. Plasma ferritin concentration is frequently used as an indirect measure of the body's iron stores.[81]

Serum ferritin has been used to predict cardiac complications in thalassemia patients. Lower ferritin levels (<2,500 ng/mL or 2,500 µg/L) are associated with better survival outcomes.[86] Be that as it may, ferritin levels may be unreliable in the presence of liver disease. This is primarily because other conditions, such as fever, acute infections, and chronic inflammatory disorders, can also elevate serum ferritin levels.[81,82]

The proBNP amino-terminal fragment, or NT-proBNP, is another commonly used biomarker. This marker appears to be a reliable indicator for detecting isolated diastolic dysfunction and is primarily released in response to elevated cardiac volume and pressure overload.[83,84] Moreover, patients with cardiac siderosis exhibited significantly higher levels of NT-proBNP than those without cardiac siderosis. Specifically, NT-proBNP levels exceeded the upper limit of normal in 49% of patients without cardiac siderosis and in 70% of patients with cardiac siderosis. These findings indicate a significant correlation between cardiac iron concentration and plasma NT-proBNP levels in patients with β-TM.[85]

In addition, serum cystatin C has recently emerged as a potentially useful biomarker. It may serve as an indicator for subclinical cardiovascular dysfunction in patients with thalassemia. According to a study by M. Beshir et al.,[86] patients with sickle cell disease and β-thalassemia exhibited higher serum cystatin C levels than controls. Further, patients with sickle cell disease and β-thalassemia who had left ventricular systolic dysfunction (shortening fraction <30% or reduced ejection

fraction) showed significantly elevated cystatin C levels.

As noted earlier, TM patients exhibit elevated peroxidative damage markers and reduced antioxidant capacity secondary to iron-mediated oxidative stress.[87] Ischemia-modified albumin, an oxidative stress-induced variant of serum albumin, has emerged as a sensitive marker for the early detection of myocardial ischemia and acute coronary syndromes.[88] Recent investigations demonstrate significantly higher serum ischemia-modified albumin levels in β-TM patients than in healthy controls, with strong correlations to serum ferritin levels. These findings suggest the potential utility of ischemia-modified albumin for identifying β-TM patients at risk of developing subclinical cardiopulmonary complications.[89]

Another promising biomarker, fatty acid-binding protein 4 (FABP4), warrants consideration. This adipokine, primarily expressed in adipocytes and macrophages, participates in inflammatory and metabolic pathways associated with cardiovascular disease and metabolic syndrome.[90] Elevated FABP4 levels have been linked to left ventricular dysfunction.[91] A recent study in TM patients revealed significant correlations between serum FABP4 levels, serum ferritin concentrations, and cardiac function parameters. These observations indicate that FABP4 may serve as a clinically relevant biomarker for iron toxicity-induced cardiac dysfunction in TM, potentially mediated through metabolic and inflammatory pathways.[92]

Prognostic stratification and risk scores in cardiac dysfunction of β-TM

Accurate prognostic classification is critical for identifying high-risk patients and guiding treatment decisions. As previously noted, the gold standard for assessing cardiac risk in TM is T2* CMR.[64] A T2* value of 20 ms serves as the lower threshold, indicating that normal patients do not have significant myocardial iron deposition. Patients with cardiac T2* <10 ms are at increased risk of developing heart failure. These thresholds inform the initiation and intensity of chelation therapy. Importantly, T2* values <6 ms are associated with a 50% risk of developing heart failure within 12 months if no adjustments in iron chelation therapy are made.[70]

GLS provides another assessment method. Measured by speckle-tracking echocardiography, GLS can serve as a diagnostic marker for early myocardial dysfunction. A GLS score <–19.5% predicts elevated cardiac iron levels with 92.8% sensitivity and 34.63% specificity, correlating with T2* abnormalities and early myocardial damage. GLS is particularly useful for longitudinal follow-ups in settings where CMR is unavailable.[75]

NT-proBNP is also a valuable circulating biomarker for detecting preclinical heart failure in TM, as previously described. An NT-proBNP threshold of 81 pg/mL has been used to identify diastolic dysfunction, with a sensitivity of 87.5% and a specificity of 85.7%.[93] Despite the increasing use of these markers, no unified risk scoring system currently exists to stratify patients across the spectrum of cardiac involvement. Nevertheless, combining these approaches with the patient's clinical presentation can guide decision-making regarding the initiation of chelation therapy.

Concerning chelation therapy, stratification is typically based on cardiac and hepatic iron burden. Guidelines recommend the measurement of serum ferritin at least each three months monitoring for a value of serum ferritin of between 500 and 1000 µg/L. If serum ferritin exceeds the 1000 µg/L or the liver iron concentration exceeds 5 mg/g dry weight, iron chelation treatment should be initiated.[94] Patients having cardiac T2* <10 ms* can benefit from enhanced treatment.[95] Although there is no formal scoring system, these thresholds are used as risk-guided criteria in medical practice.

Risk scores in cardiac dysfunction in β-thalassemia patients

Cardiac T2* value [72]	Cardiac T2* <10 ms carries a higher risk of heart failure development. Cardiac T2* < 6 ms is associated with a 50% risk of heart failure development within 1 year if left untreated.
GLS score [77]	GLS <19.5 indicates a myocardial iron overload risk.
NT-proBNP value [A]	NT-proBNP > 81 pg/mL shows a risk of diastolic dysfunction.

GLS: global longitudinal strain

Genetic predisposition to cardiac diseases

β-thalassemia is an autosomal recessive disorder caused by point mutations or small deletions in the *HBB* gene encoding the β subunit of hemoglobin.[96,97] While molecularly heterogeneous with over 350 identified alleles, approximately 40% of these mutations account for more than 90% of global β-thalassemia cases.[98] Emerging evidence suggests genetic factors significantly influence cardiovascular risk in these patients. The severity of cardiac manifestations in β-thalassemia depends on multiple genetic variables, including the specific β-globin allele variant, relative expression levels of α-like and β-like globin genes, and co-inheritance of α-thalassemia.[99]

Modifier genes play a pivotal role in determining disease variability and complications, including cardiac involvement. These genes can ameliorate disease severity by rebalancing α-to-β globin chain ratios, potentially converting TDT into milder NTDT forms.[100] The molecular background appears to modulate myocardial susceptibility to iron toxicity, influencing iron-mediated pathogenesis. Significantly, the apolipoprotein E ε4 allele has been specifically associated with increased risk of left ventricular failure, likely through its association with impaired antioxidant defenses.[14]

According to a different study by Mokhtar et al.,[101] individuals with the GSTM1 null genotype—which is also linked to lower antioxidant activity—are more likely to develop iron overload-related problems in β-TM. Increased tissue damage, lipid peroxidation, chronic vascular instability, elevated cardiac iron burden, increased left ventricular end-diastolic diameter, and a shortened ejection time are some of these consequences.[102] Due to their correlation with T2* values, certain genetic variants (CYP1A11189 CC, ABCG2 421 GA, CYP24A1 8620 GG, and VDR TaqI CC) have been linked to cardiac iron overload. Drug metabolism, transport, and vitamin D breakdown are all impacted by these genetic variations in the CYP1A1, ABCG2, CYP24A1, and VDR genes. More precisely, these genetic variations may impact cardiac T2* values and the pharmacokinetics of DFX.[103] More specifically, CYP1A1 encodes enzymes involved in drug metabolism and lipid synthesis.[104] Further, ABCG2 regulates drug distribution and excretion.[105]

The CYP24A1 gene mediates vitamin D catabolism, while VDR (vitamin D receptor) is essential for calcitriol signaling.[106,107] A significant association exists between heart failure in TM and the human leukocyte antigen allele *HLA-DQA1*0501.[14] Clinically, elevated troponin I levels have been observed in TM patients without acute coronary syndromes, particularly in those with permanent atrial fibrillation and elevated ferritin concentrations.[108]

Cardiac iron deposition shows no gender disparity until age 20; still, male patients beyond this age demonstrate higher susceptibility to arrhythmias, ventricular dysfunction, and heart failure.[109] This sexual dimorphism may reflect greater oxidative DNA damage in males, whereas females appear more resilient to chronic iron toxicity—a phenomenon potentially linked to differential oxidative stress responses.[109]

These findings underscore the need for personalized therapeutic strategies (e.g., gene therapy and optimized transfusion/chelation regimens) and mechanistic studies elucidating genetic contributions to cardiac pathology.[110]

Management of cardiac complications through iron chelation therapy

Since the human body lacks a mechanism to excrete excess iron, iron overload is an inevitable complication for thalassemia patients undergoing regular blood transfusions. Ineffective erythropoiesis and suppressed hepcidin further increase the body's iron level.[111,112] In addition, phlebotomy is not feasible in patients with β-TM due to anemia. [113] Iron chelation therapy is, therefore, the most effective strategy for managing iron overload by enhancing iron excretion during transfusions.[112] Indeed, iron chelation therapy has been shown to significantly improve left ventricular function and myocardial T2* values, thereby preventing or reducing cardiac and hepatic dysfunction.[114]

Recent guidelines from the Thalassemia International Federation (TIF, 2025, 2021) and the American Society of Hematology (ASH, 2023) provide criteria for initiating chelation therapy in

symptomatic patients with TDT. Therapy with an iron chelator is generally initiated in children between the ages of 2 and 4 years, typically after 10–20 red blood cell transfusions, when serum ferritin exceeds 1,000 ng/mL and liver iron concentration is >3 mg/g dry weight, as determined by MRI or liver biopsy. In cases of cardiac complications, such as arrhythmias or myocardial siderosis (e.g., cardiac T2* <20 ms), intensified chelation therapy is recommended to prevent worsening cardiac dysfunction and iron-induced toxicity.[115,95]

Accordingly, a combination of iron chelators is recommended, with further details provided later. Desferrioxamine (DFO), deferiprone (DFP), and deferasirox (DFX) are the three primary iron chelators currently available for clinical use. [116] DFO has been used as the standard treatment for iron overload for the past 40 years, requiring multiple subcutaneous or intravenous injections 5 to 7 days per week. [117] In patients with TM, subcutaneous therapy has long been recognized as effective in preventing or treating asymptomatic cardiac disease. Indeed, the age at which treatment was initiated was a critical factor in the progressive decline in the incidence of iron-induced heart disease observed in various patient cohorts following the introduction of DFO.[112]

High-dose intravenous DFO therapy can reverse cardiac disease.[118] Lower doses (50–60 mg/kg/day) have been shown to achieve similar results with excellent long-term prognosis, and continuous dosing reduces drug-related toxicity.[112] Continuous intravenous administrations at 50–60 mg/kg/day typically normalizes left ventricular ejection fraction within 3 months, long before iron stores in the heart or liver return to baseline.[119]

Nonetheless, DFO therapy administered over 8 to 12 hours per day has limited efficacy and is associated with poor compliance due to side effects such as skin rash, hematological toxicity, and heart failure.[120] In many cases, these issues have also resulted in inadequate treatment.

DFP, an oral chelator administered three times daily, has been shown to be superior to DFO in removing cardiac iron, with additional therapeutic benefits.[114] In a study by Anderson et al.,[121] patients with β-thalassemia treated with DFP had significantly higher myocardial T2* values—a CMR parameter inversely correlated with tissue iron levels—than matched controls receiving DFO. Further, more than half (67%) of patients treated with DFO were not protected against cardiac siderosis, whereas heart siderosis was prevented in nearly 73% of patients receiving DFP. This improved efficacy can be attributed to DFP's higher affinity for myocardial cells, lower molecular weight, neutral charge, and increased hydrophilicity, making it more effective at removing iron deposits from the heart. Moreover, regardless of the level of iron overload, DFP has the additional ability to redistribute iron both within and between cells, increase ejection fraction, and reduce free radicals, thereby protecting the heart from iron-induced damage.[112,122] Nevertheless, its use remains limited due to potential adverse effects such as neutropenia or agranulocytosis.[116]

DFX, a once-daily oral iron chelator, has demonstrated safety and tolerability in both pediatric and adult populations during short- and long-term use. Five-year follow-up studies revealed no increased incidence of known adverse effects and no emergence of new safety concerns, with the frequency of common side effects decreasing over time.[123] DFX shows particular efficacy in preventing and reducing cardiac iron overload in TDT patients. Clinical studies have documented a 40.8% improvement in cardiac T2* values among 100 β-thalassemia patients over 2 years of treatment. Patients with normal baseline T2* (n=78) maintained stable values after 1 year, while those with baseline T2* between 10 and 20 ms achieved normalization after 2 years at a mean dose of 34.5±4.8 mg/kg/day.[124]

For cases with inadequate chelation response, significant cardiac siderosis (with or without heart failure), or high morbidity/mortality risk, combination chelation therapy is preferred over monotherapy.[123] This approach demonstrates additive effects on iron excretion and reduces plasma ferritin levels, particularly in patients unresponsive to DFP monotherapy.[125]

Tanner et al.[126] demonstrated that combination therapy significantly improved endothelial function, plasma ferritin levels, left ventricular ejection fraction, and myocardial T2* values—the primary endpoint—compared with DFO monotherapy. This approach has also shown promise in the acute management of iron overload-related heart failure. One study reported that T2* cardiovascular

magnetic resonance assessment and combined therapy with DFO and DFP significantly reduced mortality associated with cardiac damage.[67]

Studies have also investigated combinations of DFX with other chelating agents. Notably, compared with the combination of DFO and DFP, the combination of DFX and DFP resulted in greater improvement in cardiac T2*, better quality-of-life indices, a larger reduction in serum ferritin, and more favorable patient compliance.[127] Monitoring iron overload is the key to the proper regulation of chelation therapy and the prevention of organ damage in patients with transfusional-dependent β-thalassemia. According to the 2025 TIF guidelines, serum ferritin should be monitored every 1 to 3 months as a convenient but not specific marker of iron deposition. Concentration of liver iron should be assessed annually with the use of MRI (via R2 or R2* methods), and values >7 mg/g of dry weight show pronounced liver iron overload and >15 mg/g a high risk of complications. Cardiac iron should be monitored annually with cardiac T2* MRI, particularly among patients aged older than 10 years or with a history of recurrent blood transfusions. A cardiac T2*<20 ms is indicative of myocardial iron deposition and <10 ms a severe risk requiring immediate escalation of chelation therapy. These assessments allow dose individualization and timely intervention and decrease the morbidity and mortality associated with iron overload.[115]

While iron chelation remains the cornerstone of transfusion-dependent β-thalassemia management, emerging therapies show promise in addressing both anemia and cardiac complications. Luspatercept, an erythroid maturation agent, has demonstrated efficacy in reducing transfusion requirements among adults with β-thalassemia, potentially mitigating iron accumulation and its cardiac sequelae.[128] Gene therapy approaches like betibeglogene autotemcel (beti-cel) offer transformative potential, with reported cases of transfusion independence.[129] This dual benefit, resolving chronic anemia while preventing secondary iron overload, may provide long-term protection against myocardial siderosis and associated cardiac dysfunction. The integration of these novel therapies into clinical practice could substantially modify disease progression and improve cardiovascular outcomes, although further long-term real-world studies remain essential.

Conclusion

Significant advancements in the understanding, diagnosis, and treatment of thalassemia have emerged in recent decades, leading to improved life expectancy for patients. Be that as it may, cardiac complications remain a predominant cause of morbidity and mortality in β-thalassemia patients. These cardiovascular manifestations primarily result from iron accumulation, driven by three key mechanisms: chronic blood transfusions, ineffective erythropoiesis, and hepcidin suppression.

Early identification of high-risk patients through advanced diagnostic modalities, biomarker assessment, and genetic profiling enables timely initiation of intensive chelation therapy, which may significantly improve survival outcomes. When properly administered, iron chelation not only prevents but can also reverse cardiac complications, preserving myocardial function. Future efforts should focus on optimizing these therapeutic strategies while integrating emerging treatments to further enhance cardiovascular outcomes in this population.

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Ethical Approval

Ethical approval was not required for conducting this research.

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Conflict of Interest

Authors declare that they do not have any conflict of interest.

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