## Original Article

# *Evaluation of Different Arrhythmias and Cardiac Iron Overload Status in β-Thalassemia Major: A Cross-Sectional Study*

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## ABSTRACT

***Background:*** Cardiac involvement due to iron deposition in β-thalassemia major remains the main cause of mortality. We assessed the effects of cardiac iron overload on the incidence of arrhythmias in β-thalassemia major.

***Methods:*** The present cross-sectional study enrolled patients with β-thalassemia major referred to a tertiary cardiovascular care center in Tehran, Iran, between January 2019 and January 2020. The patients' characteristics were collected using hospital records. Cardiac iron overload status was assessed using cardiac T2* magnetic resonance (severe ≤10 ms, moderate =10–20 ms, and mild =20 ms).

***Results:*** The present study recruited 81 β-thalassemia major cases with a mean age (SD) of 30.69 (11.12) years. Mild, moderate, and severe iron overload statuses were reported in 44.4%, 22.2%, and 33.3% of the stud population, respectively. Of 44 patients (54.3%) with arrhythmias, supraventricular tachyarrhythmias were seen in 24.7%, ventricular tachycardias in 19.8%, and atrioventricular blocks in 9.9%. A significant association was reported between iron overload status and the presence of arrhythmias ($P$<0.001). There was a significant association between iron overload and dilated atria ($P$=0.004). The left ventricular ejection fraction (LVEF) was not associated with cardiac iron status, but it was associated with the presence of arrhythmias ($P$<0.001). Desferal therapy was considerably associated with cardiac iron status ($P$=0.04).

***Conclusions:*** According to iron chelation therapy, patients with more severe iron overload had a higher incidence rate of arrhythmias. Additionally, patients with lower LVEF values had a higher incidence rate of arrhythmias. There was no statistically significant association between LVEF and cardiac iron overload status. ***(Iranian Heart Journal 2022; 23(4): 60-68)***

**KEYWORDS:** Iron overload, Arrhythmia, VT, SVT, AV block, Thalassemia

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Beta-thalassemia is a common inherited autosomal recessive disorder caused by reduced or absent synthesis of the β globin chains.[1-3] The clinical manifestations and severity of β-thalassemia range from severe anemia to asymptomatic patients.[2] The β-thalassemia mutation rate is estimated about 3% to 10% in the Mediterranean region, the Middle East, and Africa.[3] Iran is located in the Thalassemia Belt region, where β-thalassemia is prevalently reported,[4] with a prevalence rate of more than 10% in the Persian Gulf and the Caspian Sea regions.[3] Beta-thalassemia major is a significant form of β-thalassemia with severe transfusion-dependent anemia,[1] which manifests itself in the first 2 years of the life of affected patients.[1,3] Ineffective erythropoiesis,[5] increased iron absorption, and regular blood transfusions lead to iron overload in these patients.[6] Regular blood transfusions in patients with β-thalassemia major can cause iron loading of 6 to 10 grams of iron per year.[7] Iron overload complications play the main role in causing morbidity and mortality in affected individuals.[6] Cardiac involvement has been the prevalent cause of mortality (71%) in β-thalassemia major,[8-11] and it has been seen notably in patients with high ferritin levels.[3] The most crucial complication of iron overload is the myocardial disease caused by transfusional siderosis, which can present as dilated myocardiopathy or pericarditis.[1] The prevalence of cardiac complications of β-thalassemia major is varied around the world as it depends on many factors, such as access to transfusion and regular chelation therapy, genetic differences, and the efficacy of iron chelation therapy. In Iran, the prevalence rate of cardiac complications is estimated at 76.4%, while the reported rates from North America and China are significantly lower (5% and 10%, respectively).[5] Cardiac dysfunction in these patients is due to the inflammatory and immunogenic factors besides the iron deposition in the tissue, with both direct and indirect toxic effects.[2] Iron deposition in the parenchymal tissues is initiated within the first year of the commencement of regular transfusions.[2] Cardiovascular magnetic resonance using T2* is a commonly used technique to assess iron deposition in the myocardium for clinical management and chelation therapy.[12] Myocardial iron overload can lead to life-limiting complications, including heart failure and arrhythmias, which are associated with the severity of myocardial siderosis (T2* <20 ms).[5] Ventricular arrhythmias are specifically seen in cardiac iron overload and toxicity.[2] Paroxysmal supraventricular tachyarrhythmias, such as atrial fibrillations, atrial flutters, and intra-atrial reentrant tachycardias, are the other most prevalent clinically relevant arrhythmias in these patients.[13] Cardiac arrhythmias can eventually lead to terminal heart failure.[13] Patients with β-thalassemia major are at high risk for the development of malignant arrhythmias and/or sudden cardiac death.[2] Arrhythmia manifestations in patients with β-thalassemia major can be explained by anemia-induced elevated cardiac outputs, coexisting endocrine and metabolic dysfunctions, and elevated cardiac after loads.[2] Appropriate treatment with chelation therapy besides regular blood transfusions can extend the life span of patients with β-thalassemia major beyond the age of 30 years.[1] It is essential to initiate deferoxamine therapy as soon as possible in order to minimize the damage to the organs and improve the survival rate of patients with β-thalassemia major.[3] Cardiac iron overload and its complications cannot be completely avoided even with appropriate chelation therapy, indicating the significance of early detection via sensitive methods such as

cardiac T2*, which can improve the outcomes in these patients.[2,5]

Cardiac involvement in β-thalassemia major is easier and safer to treat in the early stages rather than in the late stage when the risk of death is high. This indicates an emerging need for building a consensus on the early assessment of cardiac function and the treatment of heart involvement in β-thalassemia major.

Accordingly, in the present study, we aimed to assess different arrhythmias and iron overload status in patients with β-thalassemia major and determine the role of early detection and chelation therapy initiation.

## METHODS

The present cross-sectional study recruited patients with β-thalassemia major referred to our tertiary care center (Rajaie Cardiovascular Medical and Research Center) in Tehran, Iran, between January 2019 and 2020. The patients were referred for assessment regarding cardiac iron overload status using cardiovascular magnetic resonance T2*. They were categorized into 3 subgroups according to their cardiac iron overload status (severe iron overload: ≤10 ms, moderate iron overload: 10–20 ms, and mild iron overload: ≥20 ms). Hospitalization records were used to collect pertinent data, including age, lab data, electrocardiography (ECG), echocardiography, underlying diseases, and Desferal therapy status). The patients were categorized according to their ECG into 4 subgroups: normal sinus rhythm (NSR), supraventricular tachycardia (SVT), ventricular tachycardia (VT), and atrioventricular block (AV block). The results were transferred to the data sheet and analyzed. Informed consent was obtained from all the participants. The study protocol was approved by the Research Ethics Committee of Rajaie Cardiovascular Medical and Research Center.

### Statistical Analysis

Descriptive statistics were used to summarize the data. For categorical variables, frequencies and percentages were reported. For continuous variables, means and standard deviations (SDs), and medians (IQRs) were presented. A nonparametric test was employed to compare the ordinal and continuous variables. For the comparison of differences between the 2 independent groups when the dependent group was either an ordinal or a continuous variable but was not normally distributed, the Mann–Whitney *U* test was utilized. For the assessment of normality, the one-sample Kolmogorov–Smirnov test was used for the continuous data. The $\chi^2$ test and the Fisher exact test were drawn upon to compare the level of significance between the 3 groups regarding the categorical variables. The analyses were performed using the SPSS software, version 21, (BMI). A *P* value of less than 0.05 was considered the level of significance.

## RESULTS

The present study enrolled 81 β-thalassemia major patients (mean age ± SD: 30.69± 11.12 y; 30 females [37%]). Totally, 44 patients (54.3%) had arrhythmias. Of those, SVT was seen in 20 cases (24.7%), VT in 16 (19.8%), and AV block in 8 (9.9%). Further, 45.7% (n=37) of the total cases showed NSR. Diabetes mellitus was reported in 16 patients (19.8%). Overall, 70 patients (86.4%) had right ventricular dysfunction or dilated atria. Pulmonary atrial pressure levels exceeding 35 mm Hg were seen in 56 patients (69.1%). Abnormal liver function tests were reported in 27 cases (33.3%). Sixty-six patients (81.5%) were under Desferal treatment. Antiarrhythmic drugs were used in 30 cases (37%). Totally, 44.4% (n=36) of the cases had mild iron

overload, 18 (22.2%) had moderate iron overload, and 27 (33.3%) had severe iron overload.

Of the 81 cases, no significant association was found concerning sex between the 3 groups (*P*=0.33). The mean age in the group of moderate iron overload was higher than that in the other groups (mean ± SD: 33.67±11.43 y in the moderate iron overload group vs 32.03±12.73 y in the mild iron overload group vs 26.93±7.32 y in the severe iron overload group) (Table 1). A significant association was found between iron overload and the presence of arrhythmias (*P*<0.001) as many cases with SVT had severe iron overload (n=10 [37%]). Likewise, VT was seen mostly in the group with severe iron overload (n=12 [44.4%]). Similarly, AV block was seen most frequently in patients with severe iron overload (n=5 [18.5%]). The left ventricular ejection fraction (LVEF) in patients with mild, moderate, and severe iron overload was respectively 50 (35.0–55.0), 42.5 (26.2–50.0), and 20 (15.0–30.0) (*P*=0.1). There was no significant association between laboratory data and the level of iron overload (*P*>0.05) (Table 2).

A significant association was found between antiarrhythmic drug consumption and iron overload (*P*=0.002) as those with severe iron overload used antiarrhythmic medications frequently (n=17 [63%]) (Table 2). There was also a significant correlation between Desferal therapy and antiarrhythmic drug consumption as it was used mostly in patients with moderate and severe iron overload, respectively (n=18 [100] and n=22 [81.5%]).

No significant association was found between diabetes mellitus and the level of iron overload; however, diabetes mellitus was seen mostly in patients with severe iron overload (33.9%). There was a significant association between iron overload and dilated atria (*P*=0.004) as those with greater atrium diameters had more severe iron overload (n=26 [96.3%]). All echocardiography data are shown in Table 2. No significant association was found between mild, moderate, and severe iron overload regarding hemoglobin, creatinine, potassium, the erythrocyte sedimentation rate, and liver function tests (*P*=0.79, *P*=0.16, *P*=0.08, *P*=0.73, and *P*=0.15, respectively) (Table 2).

The PR interval (IQR), the QRS width (IQR), and the QT interval (IQR) were not significantly different between the mild, moderate, and severe iron overload groups (*P*=0.12, *P*=0.18, and *P*=0.47, respectively) (Table 2). Nonetheless, a significant correlation was found between mild, moderate, and severe iron overload regarding ST depression and T inversion (IQR, 35.0–55.0, IQR, 26.2–50.0, and IQR, 15.0–30.0, respectively).

The median LVEF (IQR) was not significantly different between the groups with mild, moderate, and severe iron overload (50 [IQR], 35.0–55.0, 42.5 [IQR], 26.2–50.0, and 20 [IQR], 15.0–30.0) (*P*=0.1).

The presence of arrhythmias was assessed in terms of age and echocardiographic and laboratory data. The results showed that the creatinine level (median [IQR]), the erythrocyte sedimentation rate (median [IQR]), and liver function test abnormalities were significantly associated with the type of arrhythmia: creatinine: 0.85 (IQR, 0.62–1.20) in patients with SVT, 1.00 (IQR, 0.72–2.02) in patients with VT, 0.85 (IQR, 0.62–1.35) in patients with AV block, and 0.80 (IQR, 0.60–0.90) in patients with NSR; the erythrocyte sedimentation rate: 12.50 (IQR, 5.75–29.75) in patients with SVT, 16.00 (IQR, 8.50–30.50) in patients with VT; 26.00 (10.75–40.00) in patients with AV block, and 6.00 (2–10.50) in patients with NSR (Table 3); and abnormal liver function tests: 7 (35%) in patients with SVT, 8 (50%) in patients with VT, 4 (50%) in patients with

AV block, and 27 (21.6) in patients with NSR (*P*=0.04). The median LVEF (IQR) was significantly different between the SVT, VT, AV block, and NSR groups (27.50 [IQR, 16.25–45], 20.00 [IQR, 15–30], 35.00 [IQR, 20–45], and 50.00 [IQR, 40–55], respectively) (*P*<0.001). The clinical characteristics of the patients are presented in Table 3.

**Table 1:** Patients' characteristics and cardiac iron status

| Variables | Cardiac Iron Status [a] | | | *P* value |
|---|---|---|---|---|
| | Mild Overload (n = 36) | Moderate Overload (n = 18) | Severe Overload (n = 27) | |
| Sex; n (%)<br>female | <br>15 (41.5) | <br>8 (44.4) | <br>7 (25.9) | <br>0.33 |
| Age (y); mean±SD | 32.03 ± 12.73 | 33.67 ± 11.43 | 26.93 ± 7.32 | 0.78 |
| Arrhythmias: n (%)<br>SVT<br>VT<br>AV block | 8 (22.2)<br>5 (13.9)<br>2 (5.6)<br>1 (2.8) | 9 (50.0)<br>5 (27.8)<br>2 (11.1)<br>2 (11.1) | 27 (100)<br>10 (37.0)<br>12 (44.4)<br>5 (18.5) | <0.001 |
| DM; n (%) | 4 (11.1) | 3 (16.7) | 9 (33.3) | 0.08 |
| Desferal therapy; n (%) | 26 (72.2) | 18 (100) | 22 (81.5) | 0.04 |
| Antiarrhythmic drugs; n (%) | 7 (19.4) | 6 (33.3) | 17 (63.0) | 0.002 |

[a] Cardiac iron status according to cardiovascular magnetic resonance imaging
SVT, Supraventricular tachycardia; VT, Ventricular tachycardia; AV block, Atrioventricular block; DM, Diabetes mellitus; IQR, Interquartile range

**Table 2:** Assessment of laboratory, electrocardiography, and echocardiography findings of the patients with cardiac iron overload

| Variables | Cardiac Iron Status [a] | | | *P* value |
|---|---|---|---|---|
| | Mild Overload (n = 36) | Moderate Overload (n = 18) | Severe Overload (n = 27) | |
| Laboratory Values<br>hemoglobin; mean±SD<br>creatinine; median (IQR)<br>potassium; median (IQR)<br>ESR; median (IQR)<br>Abnormal LFT; n (%) | <br>9.44 ± 1.71<br>0.80 (0.57 - 1.13)<br>4.20 (3.7 - 5.02)<br>6.5 (1 - 28.20)<br>8 (22.2) | <br>9.25(5.75-12.41)<br>0.80(0.60-1.64)<br>4.45(3.9-5.3)<br>10(1-40.20)<br>7 (38.8) | <br>9.20 (8 - 10.80)<br>1 (0.58 - 2.88)<br>4.5 (3.6 - 5.2)<br>21 (7.40 - 65.40)<br>12 (44.4) | <br>0.79<br>0.16<br>0.08<br>0.73<br>0.15 |
| Electrocardiography<br>PR interval (IQR)<br>QRS width (IQR)<br>QT interval (IQR)<br>Abnormalities<br>ST depression; n (%)<br>Inverted T; n (%) | <br>160(120-203)<br>80(67-120)<br>426(388-450)<br><br>0 (0)<br>5 (13) | <br>180(120-238)<br>85(69-121)<br>412(389-450)<br><br>0 (0)<br>0 (0) | <br>200(128-260)<br>100(70-120)<br>426(370-442)<br><br>5 (18)<br>4 (14) | <br>0.12<br>0.18<br>0.47<br>0.009 |
| Echocardiography<br>LVEF; median (IQR)<br>Abnormal RV function; n (%)<br>Dilated atrium; n (%)<br>PAP >35 mm Hg; n (%) | <br>50 (35.0 – 55.0)<br>28(77.8)<br>26(72.2)<br>27(75.0) | <br>42.5 (26.2 – 50.0)<br>17(94.4)<br>18(100)<br>14(77.8) | <br>20 (15.0 – 30.0)<br>25(92.6)<br>26(96.3)<br>15(55.6) | <br>0.11<br>0.12<br>0.004<br>0.17 |

[a] Cardiac iron status according to cardiovascular magnetic resonance imaging
LFT, Liver function test; RV, Right ventricle; PAP, Pulmonary arterial pressure; IQR, Interquartile range; ESR, Erythrocyte sedimentation rate

**Table 3:** Electrocardiography findings

| Variables | Arrhythmia Presence | | | NSR Rhythm (n = 37) | *P* value |
|---|---|---|---|---|---|
| | SVT (n = 20) | VT (n = 16) | AV Block (n = 8) | | |
| Age(y); mean±SD | 32.80± 13.06 | 26.63±5.87 | 26.50±5.09 | 32.22±12.22 | 0.22 |
| Laboratory Values | | | | | |
| hemoglobin; mean±SD | 9.50 ± 1.37 | 8.78 ± 1.69 | 9.48 ± 1.81 | 9.67 ± 1.86 | 0.50 |
| creatinine; median (IQR) | 0.85 (0.62 -1.20 ) | 1.00 (0.72 - 2.02) | 0.85 (0.62 - 1.35) | 0.80 (0.60 – 0.90) | 0.02 |
| potassium; median (IQR) | 4.35 (4 - 4.77) | 4.30 (4.10 - 4.87) | 4.70 (4.27 - 5.12) | 4.20 (4 – 4.65) | 0.23 |
| ESR; median (IQR) | 12.50 (5.75 -29.75) | 16.00 (8.50 - 30.50) | 26.00 (10.75 - 40.00) | 6.00 (2 – 10.50) | <0.001 |
| Abnormal LFT, n (%) | 7 (35) | 8 (50) | 4 (50) | 27 (21.6) | 0.04 |
| Echocardiography | | | | | |
| LVEF; median (IQR) | 27.50 (16.25 - 45) | 20.00 (15 - 30) | 35.00 (20 – 45) | 50.00 (40 - 55) | <0.001 |
| Abnormal RV function, n (%) | 18 (25.7) | 15 (21.4) | 7 (10.0) | 30 (42.9) | 0.20 |
| Dilated atrium, n (%) | 17 (24.3) | 16 (22.9) | 7 (10.0) | 30 (42.9) | 0.20 |
| PAP >35 mm Hg, n (%) | 14 (25.0) | 9 (16.1) | 5 (8.9) | 28 (50.0) | 0.24 |

ESR, Erythrocyte sedimentation rate; LFT, Liver function test; LVEF, Left ventricular ejection fraction; RV, Right ventricle; SVT, Supraventricular tachycardia; VT, Ventricular tachycardia; AV block, Atrioventricular block; NSR, Normal sinus rhythm; DM, Diabetes mellitus; IQR, Interquartile range; PAP, Pulmonary arterial pressure

## DISCUSSION

Myocardial iron overload is the most common cause of morbidity and mortality in patients with β-thalassemia major, which can lead to life-threatening situations such as heart failure and arrhythmias.[5,8-11]

In the present cross-sectional study, the characteristics and cardiac iron status of patients with β-thalassemia major were described.

LVEF was not associated with iron overload status; still, the severe iron overload group had the highest decrease in LVEF (20%), while cases with mild status had the highest LVEF (50%). LVEF was significantly associated with the presence of arrhythmias, and it was decreased in patients with arrhythmias compared with those with NSR. In a study of 88 patients with β-thalassemia major using T2* cardiovascular magnetic resonance in Taiwan, LVEF evaluated by echocardiography was not an indicator of the risk of arrhythmia development or myocardial iron overload. The results of that study also showed that myocardial iron load was a significant risk predictor for arrhythmias,[14] which is in line with our findings. In our study, patients with severe iron overload status had the most reported arrhythmias. T2* cardiac magnetic resonance has the optimal accuracy for estimating the risk of developing cardiac dysfunction and can, thus, be used as a diagnostic tool for transfusional iron overload in Asian patients with β-thalassemia major.[14] Dilate atria were significantly associated with iron status, and they were seen more frequently in our mild and severe myocardial iron overload groups. Hamed et al,[15] in a cross-sectional study of 45 patients with β-thalassemia major, revealed that the increase in the left atrial diameter was associated with the development of arrhythmias, especially supraventricular arrhythmias. Patients with arrhythmias had a considerably higher transfusion index and serum ferritin, which had a positive correlation with cardiac T2*.

ECG changes constitute a significant tool for detecting the preclinical burden of cardiac iron overload. Repolarization abnormalities and bradycardia detected on 12-lead ECG can be used as specific markers for cardiac iron in β-thalassemia major. ST-segment and T-wave abnormalities as the early indicators of pathological changes can be seen

commonly.[13] Detterich et al[16] showed that more severely affected hearts by iron overload could be characterized by ECG abnormalities of repolarization (ST and T-wave abnormalities, QT prolongation, corrected QT intervals [QTc], and bradycardia). The present investigation found that the PR interval, the QRS width, and the QT interval were not associated with cardiac iron status. The QT interval was almost the same in all the cases and within the normal range. ST depression was only reported in the severe cardiac iron overload group. An inverted T was observed in the mild and severe iron overload groups. Detterich et al[16] indicated that elevated heart rates and prolonged QTCs were not associated with cardiac iron status. Despite the common presentation of tachycardia, QT prolongation, and interventricular conduction delays, there was no relationship between these abnormalities and cardiac iron status. Bradycardia was not prevalent, but it was a specific indicator of cardiac iron overload status. New-onset abnormalities in ECG such as T-wave inversion, P-wave prolongation, and a consistent decrease in the QRS amplitude in patients with β-thalassemia major with heart failure have been reported. Moreover, patients without heart failure had T-wave abnormalities and right bundle branch blocks. Ventricular arrhythmias, such as couplets, non-sustained VTs, or mixtures of frequent atrial and ventricular premature contractions, can be regarded as a more specific marker for iron cardiotoxicity; nevertheless, frequent premature ventricular contractions by themselves are not specific in this regard.[2] In the present investigation, the most common type of arrhythmia was SVT. Kaye et al[13] showed that paroxysmal supraventricular tachyarrhythmias were the most prevalent arrhythmias in β-thalassemia major cases, which is in line with our results, showing that SVT was the most commonly detected arrhythmia. Kirk et al,[17] in a prospective study of 652 patients with β-thalassemia major at 1 year of follow-up, reported 100 episodes of arrhythmias: atrial fibrillation (79 episodes), SVT (14 episodes), VT (6 episodes), and ventricular fibrillation (1 episode). The type of arrhythmia (atrial or ventricular) was not associated with the cardiac iron status results obtained from T2* cardiovascular magnetic resonance. Increasing cardiac iron loading was the risk predictor for the development of supraventricular and ventricular arrhythmias.

Diabetes mellitus was not associated with the status of cardiac iron overload. The incidence of impaired glucose tolerance and diabetes mellitus in β-thalassemia major ranges from 0% to 26%.[18] The evaluated laboratory values of hemoglobin, creatinine, potassium, the erythrocyte sedimentation rate, and liver function tests were not associated with cardiac iron status. Creatinine, potassium, and the erythrocyte sedimentation rate were higher in the severe overload group than the other 2 groups in the current study. Creatinine, the erythrocyte sedimentation rate, and abnormal liver function tests were associated with the presence of arrhythmias. In the study of 78 β-thalassemia major cases and 122 normal controls, fasting serum glucose and liver function tests values were significantly higher in the β-thalassemia major cases. Impaired glucose and abnormal liver function tests were reported in 18% and 20% of the β-thalassemia major cases, respectively.[18]

The majority of our cases were under treatment with Desferal and antiarrhythmic drugs. Desferal therapy was significantly associated with cardiac iron overload status. Chelation therapy can protect patients with β-thalassemia major against iron deposition in the myocardium. Kaye et al,[13] in a study of cardiac arrhythmias in 28 patients with β-

thalassemia major, revealed that major arrhythmias happened in 11 patients with inadequate chelation therapy, while there were arrhythmias in well-chelated patients. A T2* cardiac magnetic resonance value of less than 10 ms is a predictor of risk of heart failure. Aggressive chelation therapy is the key treatment to lower the morbidity and mortality caused by cardiac siderosis.[17]

## CONCLUSIONS

Cardiac iron overload status was significantly associated with the development of arrhythmias in the present investigation. Our patients with severe iron overload status had the most frequently reported arrhythmias, and those with lower LVEF values had higher incidence rates of arrhythmias. We could not detect a significant association between LVEF and cardiac iron overload status. Dilate atria were considerably associated with cardiac iron status. Desferal therapy was significantly associated with cardiac iron overload status, and the majority of cases under treatment with Desferal had mild iron overload status.

**Conflicts of Interest:** None

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