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Determining the Predictive Numerical Value of Routine Cardiac Indices of Iron Overload in Transfusion Dependent Thalassemia Patients in Developing Countries

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Abstract

Introduction: Iron overload is the most common cause of mortality and morbidity in thalassemia patients. MRI-T2 is a sensitive and non-invasive method with high accuracy for detecting iron overload but, access to this method is limited in low-income countries. In this study, we try to compare the sensitivity and accuracy of * MRI-T2* with routine cardiac assessments including Electrocardiography (ECG), exercise testing, and echocardiography to find an alternative and inexpensive method for * MRI-T2.

Materials and Methods: Ferritin and T2* MRI were extracted as the main indicators of iron overload.

Therefore, we also evaluated the patients during one years (2018-2021). CRP test was measured to remove the false positive evaluation of ferritin. The ferritin kits were same in this study. ECG-Holter, and QTc, and QT dispersion, echocardiography (conventional & Doppler) and exercise test were compared with MRI-T2*.

Results: The sensitivity of the ECG-Holter and echocardiography test for detecting iron overload was 20%. The sensitivity of the exercise test was 100%, but the accuracy of this test is 50%. The sensitivity of the ferritin test for detecting iron overload is 95%, but the accuracy of this test is 75%. The sensitivity of the ECHO was 100%, but the accuracy of this test is 38%. The sensitivity of the Exercise test was 30%, but the accuracy of this test is 44%.

Conclusion: The combination of other tests can be an alternative to T2-MRI for detecting iron overload.

Keywords: Transfusion Dependent Thalassemia; MRIT2; Echocardiography; Holter monitoring; Ferritin; Electrocardiography; Iron overload

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Introduction

The most important cause of death in thalassemia major patients is iron overload. Iron deposition in the heart causes disability in these patients.

Heart failure is due to iron deposition on cardiac myofibrils, which is associated with myofibril fragmentation and a decrease in mitochondrial volume in myocardial cells [1]. In thalassemia patients, severe iron overload-induced heart disease is usually asymptomatic, but symptoms such as palpitations, shortness of breath, syncope, lower extremity edema, and decreased functional capacity on exercise testing are also seen in these patients [2].

Plasma ferritin levels have been recognized as the standard alternative to cardiac MRI dynamics and have long been accepted as the main indicator of total iron storage in the body. Although ferritin levels are proportional to cardiac iron overload, they are not linearly related. There is no direct relationship between plasma ferritin and iron deposited in the heart as assessed by dynamic cardiac MRI. In addition, ferritin levels can be affected by common clinical conditions such as inflammation, fever, and liver disease and, therefore, are not an ideal parameter for monitoring the effectiveness of iron depletion therapy [3].

Cardiac assessment assesses the early stages of heart disease in thalassemia patients, which can lead to early treatment.

Diagnostic measures for assessing heart disease in thalassemia patients include history, physical examination, cardiac evaluation including ECG, radiography, echocardiography, Exercise Test (ET), and Holter monitoring.

Changes in echocardiographic parameters in thalassemia patients include significantly higher E-wave diastolic function (2 m/s), higher E/A ratio, shorter E-wave deceleration time, and shorter IVRT (50 ms) all indicating diastolic dysfunction it is intense. The ratio of mitral E wave velocity to septal mitral ring Doppler tissue (E/e ratio) is significantly higher in this patient. Finally, the areas and volume of the left and right atria are significantly higher [4].

Cardiac arrhythmias are one of the leading causes of morbidity and mortality in patients with high iron-dependent beta-thalassemia and blood transfusions. These secondary dysrhythmias in addition to iron overload are usually resistant to antiarrhythmic drugs. Routine screening of thalassemia patients with Holter electrocardiogram is recommended. However, rare changes in electrocardiography of thalassemia patients limit its clinical utility.

Dynamic MRI (T2* MRI) can indirectly measure the iron content of the heart. Rest time T2* of the heart is inversely related to myocardial iron content. A low T2* value indicates a higher myocardial iron content. For easy classification of patients into different risk groups for cardiac iron overload, the following classification has been adopted: Patients with T2* >20 ms is considered to be without cardiac iron overload [5]. The connection between T2* and ventricular functions is digital. There is a strong correlation between myocardial T2* values (<20 ms) and LV dysfunction. Patients with LV dysfunction have the iron overload in the heart (abnormal T2 <20 ms) [6]. But achieving a dynamic heart MRI is not locally available in developing countries or outside of the big cities of the state. For this reason, thalassemia patients living in less developed areas have to move to large cities every year, which is difficult, costly, and risky.

Therefore, finding alternative screening methods for thalassemia patients with diagnostic accuracy similar to T2* MRI, especially in small towns that do not have easy access to dynamic MRI, seems to be the case.

In this study, we compare the results of iron overload (T2* MRI) in thalassemia patients by combining simpler methods such as echocardiography and exercise testing and ECG-Holter monitor to see to what extent the results of these tests can play a predictive role T2* MRI).

We calculate the sensitivity and specificity of simpler diagnostic methods than dynamic MRI and can distinguish between high-risk and low-risk patients, and in fact, suggest an alternative diagnostic method for cardiac dynamic MRI.

Electrocardiogram – the ECG or EKG

- Electrocardiogram iron overload is often abnormal in patients with thalassemia, but the changes are usually nonspecific. These changes usually include depolarization changes in the T-waves and ST sections of the anterior thoracic leads, the T-wave axis, and the QT interval. Sometimes P-waves are also affected, indicating enlargement of both atria. First-degree heart block and conduction disturbance may be seen as a branch block, but higher degrees of conduction disturbance are rare. Given that ECG changes in these patients are nonspecific and the reversibility of these changes with iron chelation has not been established, it is important to begin regular childhood monitoring to detect new ECG changes.
- When new ECG abnormalities appear during follow-up, more research is needed to identify the cause. This is especially true of changes that indicate an increase in the right heart force. These may reflect pulmonary hypertension, which is a
- QT dispersion (QTd) is measured as the difference between the longest and the shortest QT distances on the 12-lead surface ECG. Corrected QT dispersion (QTcd) is calculated as the difference between the maximum and the minimum corrected QT distances.
- The common complication of intermediate thalassemia but less common in thalassemia major [7].

Ambulatory monitoring of ECG

- The standard method for diagnosing and evaluating cardiac arrhythmias is by recording an ECG Holter for 24 h. There are currently several types of recorders suitable for diagnosing intermittent cardiac arrhythmias.

Exercise ECG

- Exercise testing with a treadmill may be helpful in identifying patients at risk for cardiac arrhythmias or to assess functional capacity. Adequacy in the treatment of heart disease can also be measured by the performance of exercise testing [8].

Echocardiography

- Echocardiography is widely available, relatively inexpensive, and easy to perform. Many parameters can be obtained from cardiac ultrasound examination, but even the simplest measurement of chamber size can provide immediate and valuable data on heart status and clinical progression, provided that it is performed by a skilled physician and followed. Obtained from a standard protocol. The minimum data set must include the following:
- Dimensions
- LV in diastole and systole.
- Dimensions and areas of the atrium
- Pulmonary artery and aortic root.
- D abdominal thickness.
- Dimensions/volume of LV and RV.
- Performance
- LV EF with standardized methods that should include: Teicholz and Simpson methods.
- Diastolic function
- Mitral Doppler
- Tissue Doppler cyclic velocities
- Pulmonary vein Doppler profile
- Evaluate Doppler current
- Triple failure jet speed (TRj Vmax).
- Pulmonary artery flow, diastolic jet acceleration/velocity.

- Morphology
- Structure and function of valves.
- Removal of thrombosis in the right atrium in patients with implanted lines
- Room morphology.
- D Existence of shunt or foramen oval [9].

This is not a complete list, but it does include most of the parameters that determine heart function in thalassemia patients. Subtle longitudinal changes in parameters may be apparent if collected, which highlights the need for more serious follow-up with CMR imaging. Iron cardiomyopathy first presents with borderline systolic volume and borderline mutations. Progression to dilated cardiomyopathy is a belated and ominous finding. A combination of normal and tissue Doppler should be used to evaluate diastolic function. Isolated diastolic dysfunction may occur but is relatively rare.

Key commentary

The important point is that each center should develop a specific protocol for its patients that can be used to monitor the heart condition of thalassemia patients and early understanding of changes.

Evaluating the ventricular response to exercise with echocardiography may also be helpful, identifying individuals with subclinical disease in whom the ejection fraction in response to simulated exercise using intravenous dobutamine does not increase or even decrease.

Cardiac Magnetic Resonance Imaging (cMR or MRI)

- For a decade, tissue iron loads have been measured using non-invasive Magnetic Resonance Imaging (MRI) imaging. The T2* heart parameter has been confirmed as an accurate reflection of the iron content of the heart. It is now a matter of basic clinical standards that cardiac T2* in every transfusion-dependent thalassemia patient should be performed as early as possible. In most centers, it is done from the age of 10, but in some cases up to the age of 7, if there is an iron overload [10].

Key commentary

- The advantage of the T2* parameter is that it identifies people at risk for heart disease very early. That is, it detects before functional changes that are detected by simpler non-invasive methods such as echocardiography.

- Monitoring the patient's iron chelation has been shown to be very effective in adhering to treatment plans. Cardiac MRI is the gold standard for monitoring iron overload in patients with thalassemia major because it allows the heart's iron load to be estimated and is consistent in detecting clinical changes in the ejection fraction. Studies at 24, 12, and 6-month intervals are recommended for low-risk, standard, and high-risk patients. As a result of chronic anemia, heart volume norms and ejection fraction are different for thalassemia patients and should be considered when evaluating results.

Key commentary

The important point is that each center should develop a specific protocol for its patients that can be used to monitor the heart condition of thalassemia patients and early understanding of changes.

Evaluating the ventricular response to exercise with echocardiography may also be helpful, identifying individuals with subclinical disease in whom the ejection fraction in response to simulated exercise using intravenous dobutamine does not increase or even decrease.

Materials and Methods

- This cross-sectional study was performed on patients with thalassemia major referred to Shahid Madani Hospital in Khorramabad (Lorestan province) during 2019-2021. Indicators of iron overload including ferritin and T2 MRI, ECG findings, Holter monitor, echocardiographic features, and exercise testing of thalassemia patients were compared with variables such as splenectomy, type of iron chelator, diabetes mellitus, and type of anti-inflammatory drug. MRI-T2* was used as the main indicator of iron overload.

- MRI-T2* is usually performed once a year in the thalassemia major and ferritin management protocol, seasonal, echocardiography, Holter, and exercise testing once a year.

- In the study, we used the average amount of ferritin 4 times a year as an indicator. Because ferritin is an acute-phase protein, C-Reactive Protein (CRP) tests were performed at any point in time to evaluate the false-positive results of ferritin in patients. To prevent confounding factors and bias, ferritin was measured by the laboratory (Shahid Madani Hospital) with the same kit.

- We extracted left arterial index, isovolumic relaxation, deceleration time corrected, right ventricular index, post wall index, intraventricular septal index, relative wall thickening, LV mass index, stroke volume index, ejection fraction, mean arterial pressure/systolic volume ratio, isovolumic relaxation time, deceleration time corrected, isovolumic relaxation time corrected, tricuspid gradient, pulmonary acceleration time, body mass index, iron chelator drug type (DFO, DEF, DFX).

- The study protocol was approved by the Ethical Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1400.248). Written informed consent were obtained from the patients before starting the study.

- DFO: Defrasirox
- DEF: Deferiprone
- DFX: Defroxamine

- Iron overload in transfusion-dependent thalassemia patients affects heart contraction and heart rhythm. Holter echocardiography and 24-h heart rhythm monitoring were used as indicators of heart function. An exercise test was also used to assess the functional capacity of the heart muscle.

- Two-dimensional and M-shaped measurements of cardiac cavities were performed. Doppler failure jets were continuously recorded with tricuspid and pulmonary valves. Left ventricular diastolic function was assessed with mitral valve flow pulse Doppler. For clinical correlation with echocardiographic findings, patients were divided into three groups (<2.5 m/s, 2.5-2.9 m/s, and ≥ 3 m/s) based on the rate of tricuspid regurgitation.

- 24-h outpatient electrocardiogram monitoring and echocardiography were evaluated in patients with beta-thalassemia major who had no clinical signs of arrhythmia and abnormal heart function.

- Increased Heart Rate (HR) and QT-corrected long-term repolarization abnormalities (QTc) including QT/QTc prolongation, left T-axis displacement, and interpretation of ST/T wave morphology were examined by a cardiologist. If one of these changes was on the ECG-24 h, Holter monitoring was positive for iron overload. For each patient, QT-QTc intervals and QT-QTc dispersions were calculated. Increased QT dispersion is a predictor of sudden death and

- ventricular arrhythmias in the patients with Chronic Heart Failure (CHF), remote myocardial infarction, hypertrophic obstructive cardiomyopathy, non-insulin-dependent diabetes mellitus, peripheral vascular disease, arrhythmogenic right ventricular cardiomyopathy, and essential hypertension.

- SPSS software version 21 was used for data analysis. The standard error is 5% and the confidence interval is 95%.

- The results were reported in terms of accuracy, sensitivity, specificity, positive and negative predictive value.

Limitations

1. Relative small number of sample size.
2. The study was conducted in a single center.
3. Most of the involved subjects were males.

Statics indexes

- **Sensitivity:** The ability of a test to correctly identify patients with a disease. Sensitivity is the ability of a test to correctly identify people who have a given disease or disorder. For example, a certain test may have proven to be 90% sensitive. That is, if 100 people known to have a certain disease are tested with that method, the test will correctly identify 90 of those 100 cases of disease. The other 10 people who were tested also have the disease but the test will fail to detect it. For that 10%, the finding of a "normal" result is a misleading false-negative result. A test's sensitivity becomes particularly important when you are seeking to exclude a dangerous disease.

- The more sensitive a test, the fewer "false-negative" results it produces. A false-negative result fails to identify disease states even though they are present.

- **Specificity:** the ability of a test to correctly identify people without the disease. True positive: The person has the disease and the test is positive. Specificity is the ability of a test to correctly exclude individuals who do not have a given disease or disorder. For example, a certain test may have proven to be 90% specific. If 100 healthy individuals are tested with that method, only 90 of those 100 healthy people will be found to be "normal" (disease-free). The other 10 people also do not have the disease, but their test results seem to indicate they do. For that 10%, their "abnormal" findings are a misleading false-positive result.

- The more specific a test is, the fewer "false-positive" results it produces. A false-positive result can lead to misdiagnosis and unnecessary, possibly challenging, or life-altering, diagnostic procedures, and therapies. It is important to confirm a diagnosis that requires dangerous therapy and a test's specificity is one of the crucial indicators.

- Although few if any tests succeed in diagnosing disease correctly 100% of the time, most tests produce only a small proportion of false-positive or false-negative results. Laboratories are required through laboratory accreditation to use the most sensitive and specific tests available.

- **Positive predictive value** is the probability that subjects with a positive screening test truly have the disease. It is the ratio of patients truly diagnosed as positive to all those who had positive test results (including healthy subjects who were incorrectly diagnosed as patient). This characteristic can predict how likely it is for someone to truly be patient, in case of a positive test result.

- **Negative predictive value** is the probability that subjects with a negative screening test truly don't have the disease. Negative predictive value is the proportion of the cases giving negative test results who are already healthy [3]. It is the ratio of subjects truly diagnosed as negative to all those who had negative test results (including patients who were incorrectly diagnosed as healthy).

Accuracy

- A test method is said to be accurate when it measures what it is supposed to measure. This means it is able to measure the true amount or concentration of a substance in a sample.

- Picture a bull's-eye target with a dart correctly hitting the center ring and you see what an accurate test produces: The method is capable of hitting the intended target [11].

What is Weighted Average and how is it calculated?

- Normally, to calculate the mean, we add all the numbers and divide the sum by the number. In this case, the importance of each data is the same as other data, and in fact the weight coefficient of each number is 1.

- In calculating the weighted average, a weight coefficient is used to make some data more important and others less important. In this way, first each data is multiplied by its weighting factor and then the sum result is calculated. Finally, the sum product is divided by the sum of the weight coefficients.

- In calculating the score, score, outcome, and other things, if the factors are of different importance, we should always use the weighted average instead of the normal average to create a balance between the factors [12].

Results

In this study, 74 patients were studied, of which 46 (62.2%) were male and 28 (37.8%) were female. The mean age of men was 22.1 ± 22.2 years and the mean age of women was 9, 20, 20.5 years. The mean age of patients was 21.5 7 ± 7.4.

The sensitivity of the Holter ECG test to diagnose iron overload is 20%, which means that it diagnoses 20% of cases correctly. The characteristic of the ECG Holter for the detection of iron overload is 100%, i.e., it separates 100% of healthy cases. But the accuracy of this test is 50%. The positive predictive value of an ECG Holter test is close to 100%. The implication is that if a test is reported in an abnormal person, there is a 100% chance that the person is ill.

The negative predictive value of the ECG Holter for detecting iron overload is 43%. On the other hand, this test can predict a non-sick person, with a 43% probability that the person is not sick (Table 1, 2).

The sensitivity of the ferritin test in the diagnosis of iron overload is 95%, i.e., it detects 95% of patients' cases correctly. The specificity

Table 1: Clinical findings and hematologic profile.

Variable	Male (n= 46)	Female (n=28)	P-value
Body surface area (m^2)	1.65 ± 0.16	1.73 ± 0.16	0.01
Heart rate (beat/min)	81 ± 11	85 ± 14	0.05
Systolic BP (mmHg)	104 ± 5	123 ± 15	0.001
Diastolic BP (mmHg)	65 ± 5	68 ± 7	NS
Mean Hb(g/dL)	9.7 ± 0.4	9.2 ± 1.2	0.01
Mean serum ferritin (ng/mL)	1,815 ± 804	1,270 ± 918	0.001
Peak serum ferritin (ng/mL)	3,876 ± 2,770	2,276 ± 1,125	0.001
Splenectomy	21 (20.6)	13 (17.8)	0.001
Age (year)	27.9 ± 5.9	28.2 ± 7.4	NS

Table 2: Echocardiographic measurements in patients without evident heart disease, defined as congestive heart failure, reduced LV contractility, or considerable pulmonary hypertension.

Variable	Men (n=46)	Women (n=28)	P-value
Left arterial index (cm/m^2)	2.1 ± 0.3	2.4 ± 0.3	0.001
Right ventricular index (cm/m^2)	1.2 ± 0.2	1.3 ± 0.2	0.05
LVED index (cm/m^2)	3.1 ± 0.2	3.2 ± 0.3	0.001
LVES index (cm/m^2)	1.9 ± 0.2	1.9 ± 0.2	NS
Post wall index (cm/m^2)	0.5 ± 0.1	0.5 ± 0.1	NS
Intraventricular septal index (cm/m^2)	0.5 ± 0.1	0.5 ± 0.1	NS
LV mass index (g/m^2)	94 ± 19	123 ± 28	0.001
Relative wall thickening	0.34 ± 0.03	0.34 ± 0.02	0.001
Shortening fraction %	39 ± 5	42 ± 4	NS
LVEDV index (mL/m^2)	74 ± 11	90 ± 17	0.001
LVESV index (mL/m^2)	23 ± 6	25 ± 6	0.001
Stroke volume index (mL/m^2)	50 ± 8	65 ± 13	0.001
Ejection fraction %	68 ± 6	72 ± 5	0.001
Cardiac index (L/min/m^2)	4.0 ± 0.6	5.4 ± 1.3	0.001
Total peripheral resistance (dyne.s.cm^{-2})	933 ± 165	754 ± 215	NS
Mean arterial pressure/systolic volume ratio	0.96 ± 0.16	0.80 ± 0.19	NS
End systolic stress	107 ± 19	113 ± 17	0.001
E (m/s)	0.95 ± 0.13	0.99 ± 0.16	0.05
A (m/s)	0.57 ± 0.09	0.66 ± 0.16	NS
E/A	1.72 ± 0.34	1.58 ± 0.46	0.001
Deceleration time (ms)	151 ± 29	146 ± 24	NS
Isovolumic relaxation time (ms)	70 ± 12	45 ± 14	0.001
Deceleration time corrected	5.52 ± 1.05	5.44 ± 0.95	NS
Isovolumic relaxation time corrected	2.56 ± 0.45	1.70 ± 0.46	0.001
Tricuspid gradient (mmHg)	23.2 ± 5.6	27.4 ± 6.0	0.001
Pulmonary acceleration time (ms)	125 ± 20	117 ± 22	0.05
Mean pulmonary artery pressure (mm Hg)	18 ± 7	22 ± 8	0.001
Total pulmonary vascular resistance (dyne.s.cm^{-2})	256 ± 152	359 ± 224	0.05

of the ferritin test in the diagnosis of iron overload is 95%, i.e., 95% of non-patient cases are correctly diagnosed.

The accuracy of this test is 75%. The positive predictive value of a ferritin test is 73%, meaning that if a test is reported in an abnormal person, it is 73% more likely to be ill. The negative predictive value of the ferritin test for the detection of iron overload is 83%. In other words, this test can predict that if a test is reported in a normal person, there is an 83% chance of being ill (Table 3).

Table 3: ECG-Holter factors in thalassemia patients.

	Male (*n*=46)	Female (*n*=28)	*P* value
Age (year)	23.7±11.9	23.3±11.8	0.87
transfusion duration (min)	110.7±28.9	110.9±36.1	0.69
DM (n, %)	2 (0.7)	1 (0.3)	0.01
BMI (kg/m^2)	21.3±3.5	21.8±3.0	0.49
PVC (n, %)	26 (78.8)	7 (21.2)	0.01
Hb (g/dl)	10.4±1.0	10.5±1.2	0.78
ferritin (g/dl)	2213.8±340.4	2313.9±0.235	0.5
Heart rate (b/min)	122.3±10.3	132.2±11.2	0.51
ARB (n, %)	4 1.5)	2 (1.4)	0.45
β blocker (n, %)	4 (1.6)	3 (1.4)	0.72
Ca channel blockers (n, %)	7 (1.5)	3 (1.3)	0.63
QT-interval(s)	18.9±3.4	17.8±3.5	0.3
U wave (+/-)	4.4±0.8	4.2±0.7	0.47
ST-change (+/-)	9.1±1.3	9.3±1.3	0.49
T-change (+/-)	8.3±1.2	9.1±1.7	<0.001
PAC (+/-)	7.7±3.7	8.2±2.5	<0.001
⊿Sys blood pressure (mmHg)	35.3±19.9	33.0±18.6	0.05
⊿Dia blood pressure (mmHg)	14.5±7.8	13.2±8.1	0.47
QT-dispression (mean+-SD)	51.7644 ± 23.5766	37.0588 ± 16.2161	0.004
QTCD (mean ± SD)	55.7021 ± 21.9988	40.0256 ± 16.0532	0.001
TeD (mean ± SD)	45.9021 ± 22.0518	38.2062 ± 32.1659	0.086

DM: Diabetes Mellitus; BMI: Body Mass Index; PVC: Premature Ventricular Contraction; Hb: Hemoglobin; Alb: Albumin; ARB: Angiotensin Receptor Blocker; Ca: Channel blockers Calcium channel blockers; SDNN: Standard Deviation of the NN Interval; SDANN: Standard Deviation of sequential five-minute N-N interval means

The sensitivity of the exercise test to diagnose iron overload is 30%, which means that it diagnoses 30% of the disease correctly. The specificity of exercise testing for the detection of iron overload is 15%, i.e., 15% of non-patient cases are correctly identified. The accuracy of this test is 40%. The positive predictive value of an exercise test is 25%, meaning that if a test is reported in an abnormal person, there is a 25% chance that the person is ill. The negative predictive value of the exercise test for diagnosing iron overhead is 20%. In other words, this test can predict that if a test is reported in a normal person, there is a 20% chance that they will be healthy.

The sensitivity of the echocardiographic test to diagnose iron overload is 100%, which means that it is 100% accurate in diagnosing the patient. The echocardiographic test feature for diagnosing iron overload is 10%, meaning that 10% correctly detects non-patient cases. The accuracy of this test is 38%. The positive predictive value of the EF echocardiographic test is 0%. The negative predictive value of the EF echocardiographic test for the diagnosis of iron overload is 38%. In other words, this test can predict that if a test is reported in a normal person, there is a 38% chance that the person is healthy.

The weighted average sensitivity for diagnosing iron overload is 61.25%, which means that it diagnoses 61.25% of the disease correctly. The Weighted Average for the specificity of exercise testing for the detection of iron overload is 77.5%, i.e., 77.5% of non-patient cases are correctly identified. The weighted average for accuracy of these tests

Table 4: Average of the previous year.

Variable	Male	Female	P value
Age (years)	(31.3 ± 6)	(36.1 ± 6.6)	
Sex (M/F)	46	28	
Weight (kg)	58.7 ± 10.6	59.7 ± 10.2	NS
Height (m)	1.62 ± 0.07	1.62 ± 0.07	NS
BSA (m^2)	1.62 ± 0.16	1.62 ± 0.16	NS
HR (bpm)	84.6 ± 13	79.8 ± 18	NS
SBP (mmHg)	114 ± 17	112 ± 15	NS
Ferritin (ng/ml)†	3187 ± 2177	2276 ± 1125	NS
Hemoglobin (g/dl)†	11 ± 0.5	10.3 ± 0.5	<0.0001
Estimated value of hemoglobin in the echo's day (g/dl)	11.5 ± 1.1	11.3 ± 1.1	NS
Splenectomy (YES/NO)	21	13	
Iron input (mg/kg/die)†	0.32 ± 0.07	0.38 ± 0.08	0.0002
Chelators:			
DFO	7	4	
DFO + DFP	6	7	
DFP	2	1	
DFX	29	18	
Compliance (%)	97.2 ± 5.3	88.5 ± 13.3	0.0002
MRI-T2* of the heart†	37.7 ± 11	41 ± 15.7	NS

BSA: Body Surface Area; HR: Heart Rate; SBP: Systolic Blood Pressure; DFO: Deferoxamine; DFP: Deferiprone; DFX: Deferasirox

is 50.75%. The Weighted Average for the positive predictive value of an exercise test is 74.5%. percent, meaning that if a test is reported in an abnormal person, there is a 74.5% chance that the person is ill. The Weighted Average for the negative predictive value of the exercise test for diagnosing iron overhead is 46%. In other words, this test can predict that if a test is reported in a normal person, there is a 46% chance that they will be healthy (Tables 4-6).

Discussion

The most important cause of death in patients with thalassemia major is cardiac complications. Iron overload in transfusion-dependent thalassemia patients is caused by regular blood transfusions or increased intestinal iron absorption in intermediate thalassemia patients. Iron overload in the heart leads to systolic and diastolic dysfunction.

The cause of death in most patients is congestive heart failure, but in some patients, arrhythmia leads to sudden death. Arrhythmias such as tachycardia and supraventricular fibrillation lead to death [13].

Karimi et al. Using generalized estimator equations in their study showed that the exponential model is a better model for expressing the relationship between MRIT2-* heart and ferritin level and the quadratic model is a better model for expressing the relationship between MRI-T2* liver and ferritin. Also, this study showed that ferritin level, splenectomy status, Deferoxamine, and Osveral dose (Iranian deferasirox) were significantly associated with iron overload. In our study, about 60% of patients with abnormal ferritin had abnormal MRIT2 [14].

Also, in the exercise test was shown that there is a weak correlation between cardiac overload and echocardiographic but Doppler findings and color Doppler echocardiography is preferable to conventional echocardiography. In our study, the results are similar [15]. But in this study diagnostic accuracy didn't measure.

In Zhenxing study the diagnostic accuracy rate for and misdiagnosis rate echocardiography were 90.6% and 9.4% respectively in Coarctation of the Aorta. Preoperative echocardiographic evaluation offers a very satisfactory anatomic assessment in most of these patients. It makes preoperative angiography unnecessary. Thus, transthoracic echocardiography should be the first-line method for the diagnosis of coarctation of the aorta [16].

In our study diagnostic accuracy of echocardiography for iron overload screen which is not an anatomic parameter was 38%. Echocardiography may be an alternative method, especially Doppler echocardiography in high-risk thalassemia patients [17]. Our study also showed that Doppler echocardiography is sensitive to detecting iron overload, but this is not true about conventional echocardiography. The first evaluation in this group is MRIT2*.

The color Doppler imaging is useful in predicting myocardial iron overload in thalassemia patients. Therefore, it can be used to screen patients with thalassemia major [18].

The oxy-echocardiography with the Doppler tissue technique can greatly predict iron overload in the myocardium of the heart. Administration of heart rate recorder, which is a measure of cardiac exercise testing, could predict dysrhythmia in thalassemia patients [19].

Their results in echocardiography are similar to our study, but in exercise testing the methods were different. The difference between echocardiographic measurements in men and women and the improvement of the majority of these cases in women may be due to better control of iron overload and more adherence of thalassemia hematologists by women compared to male patients.

There is a direct and significant relationship between T2 MRI in the heart and Ejection Fraction (EF) in the right ventricle and EF in the left ventricle, but this correlation is inverse between T2 and left ventricular volume and RVEDV and RVESV and stroke volume. In echocardiography, pulmonary hypertension was not predictive of iron stores [20].

In our study, echocardiographic parameters such as EF and left ventricular echocardiographic index were valuable and sensitive to the symptoms of iron overload (Table 2).

Assessment of cardiac iron overload by T2* MRI was directly related to worsening left and right ventricular dysfunction, which was more pronounced for T2 values less than 14 milliseconds [21]. T2* MRI is the most important tool in predicting the need for treatment of ventricular failure [22]. When heart T2* falls below 20 milliseconds, there is a gradual decrease in heart contraction and heart function in patients with T2* MRI worsens by less than 10 milliseconds [23]. Cardiac dysfunction in patients with thalassemia major with clinical signs of heart failure are 76%, 41%, and 68% specificity, sensitivity, and efficiency, respectively [24].

All of the alternative methods due to MRIT2* have failed. For example, serum ferritin levels may vary in different diseases and inflammatory conditions, making iron overload difficult to diagnose because this marker increases in many other disorders. Cardiac abnormalities can be diagnosed using echocardiography, but usually,

Table 5: Comparison of accessory tests and MRIT2 for iron overload detection.

		MRIT2		Total
		Abnormal	Normal	
ECG-holter test	Abnormal	14 (18.9%)	16 (21.6%)	26 (35.2%)
	Normal	26 (35.1%)	18 (24.3%)	48 (64.8%)
Total		40	34	74
		MRIT2		Total
		Abnormal	Normal	
QT-dispersion	Abnormal	28 (37%)	12 (16.2%)	40 (54 %)
	Normal	22 (29.7%)	12 (16.2%)	34 (46%)
Total		50	24	74
		MRIT2		Total
		Aabnormal	Normal	
Ferritin	Abnormal	44 (59.4%)	16 (21.6%)	60 (81.0%)
	Normal	2 (0.2%)	12 (16.2%)	14 (18.9%)
Total		46	28	74
		MRIT2		Total
		Abnormal	Normal	
Conventional Echocardiography	Abnormal	0	0	0
	Normal	46 (100%)	28 (100%)	74 (100%)
Total		46	28	74
		MRIT2		Total
		Abnormal	Normal	
Doppler Echocardiography	Abnormal in minimum One item	31 (41.8%)	0	31
	Normal	14 (18.9%)	18 (24.3%)	32 (43.2%)
Total		46	28	74
		MRIT2		Total
		Abnormal	Normal	
Exercise test	Abnormal	11 (14.8%)	8 (10.8%)	19 (25.6%)
	Normal	46 (62.1%)	9 (12.1%)	55 (74.4%)
Total		57	17	74

Table 6: Comparison of diagnostic value of alternative method for iron overload diagnosis.

Marker/static index	Sensitivity	Specificity	PPV	NPV	Accuracy
ferritin	95	95	73	83	75
echocardiography	100	10	10	38	38
ECG-Holter	20	100	100	43	50
QT-dispersion	83	71	75	85	65
Exercise test	30	15	25	20	40

the clinical signs are not detectable until the advanced stages of the disease. Asymptomatic diastolic dysfunction is an earlier event in thalassemia patients, but left ventricular dysfunction in systole, decreases life expectancy because an iron deposition is involved in the ventricular myocardium first and eventually in other heart tissues. Restrictive pericarditis, heart failure, and arrhythmia are the next events [25,26].

The ECG changes in patients with thalassemia major are directly related to serum ferritin levels ECG changes due to iron overload occur earlier than echocardiographic changes. They also coordinate more closely with serum ferritin levels [27].

Significant prolongation of QT corrected QT interval and increased QT dispersion was observed in patients with serum ferritin levels of more than 2,500 nanogram/milliliter. QT and QT dispersion had a positive linear correlation with serum ferritin levels. Electrocardiography could be a useful tool for the pre-clinical detection of cardiac involvement due to iron overload in Thalassemia Major Patients [28].

Approximately 14% of thalassemia-dependent blood transfusion and sickle cell patients had an abnormal EKG at screening or follow-up. Early detection of cardiac arrhythmias is critical for thalassemia patients. However, the Holter EKG method is a non-sensitive standard in thalassemia patients [29].

The presence of fQRS in the ECG could be a good predictor of cardiac iron overload in beta-thalassemia (β-TM) patients. The fQRS could indicate this change in electrocardiography and indicate the need for more careful monitoring for cardiac overload and treatment of invasive iron excretion [30].

In our study, the number of patients with Premature Ventricular Complex (PVC) is higher in men than women, but about Premature Atrial Complex (PAC), the opposite is true. This may be due to the higher volume of ventricular muscle to accept iron deposition and the fact that men had less control over iron overload than women.

Conclusion

Cardiac MRI-T2* and tissue Doppler echocardiography are reliable imaging studies for early detection of iron overload in thalassemia patients, but stress exercise testing and Holter ECG testing alone are not sufficiently valid. Therefore, MRI-T2* should be used in the first step for early diagnosis and monitoring of hemosiderosis in thalassemia patients because it is sensitive and non-invasive. Doppler echocardiography can be used as an alternative to MRI-T2*. Conventional ultrasound echocardiography alone is not accurate and sensitive. By combining this method with other methods with moderate accuracy, sensitivity and accuracy can be increased. The method of combining modalities with moderate sensitivity and accuracy may be useful as an alternative method for detecting iron overload in low-income countries with limited access to MRI-T2.

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