Original Paper

Evaluation of the Relationship Among Pulmonary Artery Pressure with Serum Ferritin Level and CMR T2* in Thalassemia Major

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ABSTRACT: Background: Pulmonary hypertension is one of the most common cardiac complications among patients with β-thalassemia major (β-TM). The aim of this study is to investigate the correlation of pulmonary artery pressure (PAP), serum ferritin level, and cardiac T2* MRI in patients with β-TM. Method: This cross-sectional study was performed on 50 patients older than 7 years old. Echocardiography, electrocardiography, and cardiac T2* MRI were performed on all patients and their serum ferritin levels were measured. Based on the echocardiographic the patients were divided into two groups of PAP>30 and <30 mmHg. Results: 40% had PAP higher than 30 mmHg, 32% had abnormal T2* MRI, and 36% had serum ferritin levels higher than 1500ng/dl. there were significant negative correlations between CMRI *T2 and PAP (-0.36) and the P-pulmonary (-0.29). the serum ferritin level was positively correlated with PAP (0.44) and the P pulmonary in ECG (0.30). in the patients with PAP>30, the means of age, serum ferritin level, and P-pulmonary were significantly higher than patients with PAP<30 (P=0.001). In the patients with PAP>30mmHg, CMRI *T2 had higher accuracy (80%), sensitivity (65%), and specificity (90%) compared to the measurement of serum ferritin levels. Conclusion: The PAP was positively correlated with serum ferritin levels and negatively with T2MRI. The accuracy of 80% for T2MRI as a method to diagnose or even anticipate PH among patients with TM suggested that this method is a useful and accurate method of PH diagnosis and can be used as an alternative among clinicians.

KEYWORDS: *B-Thalassemia Major, Cardiac T2* MRI, Pulmonary Artery Pressure, Serum Ferritin Levels.*

Introduction

Cardiac siderosis in patients with β-thalassemia major (β-TM) is the consequence of frequent blood transmission. It commonly causes cardiac complications including conduction system impairment, dysfunction in cardiomyocyte contractility, delayed electrical conduction, increased electrophysiological heterogeneities, and pulmonary hypertension (PH) [1-3].

These complications are common causes of morbidity and mortality among patients with β-TM.

There are two methods of checking iron overload in the cardiac tissue. Measuring serum ferritin levels is one of the ways of estimating iron overload in the body but not the best way. It can be affected by different conditions such as inflammation, infection, liver injury, and the level of vitamin C [4]. Cardiac T2* MRI (CMRI *T2) is the best way to estimate the amount of iron in the myocardium and liver tissues. The normal range of cardiac CMRI *T2 is the speed of higher than 20ms and the measures less than 20ms are considered as iron overload, which means patients are at a higher risk of cardiac dysfunction [5,6].

Signs of iron overload sometimes can be detected in electrocardiogram (ECG) test, for example, fragmented-QRS waves and the existence of P pulmonale are two signs of iron overload in the myocardium [7].

Various factors are involved in the development of PH among patients with β-TM such as chronic hemolysis, iron overload due to transfusion therapy, hypercoagulation, and circulating cells' changes in case of splenectomy, but the exact pathophysiology of PH is still not clear.

Echocardiography and angiography are two methods of assessing pulmonary artery pressure (PAP). The tricuspid regurgitation velocity (TRV) parameter in echocardiography is commonly used to predict PH [8].

TRV is the retrograde blood flow across the tricuspid valve during systole and estimates right ventricular systolic pressure (RVSP). The TRV greater than 2.9m/sec in the general population and greater than 2.5m/sec in those with chronic hemolytic anemia, such as thalassemia and sickle cell disease, represent PH [9].

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Another echocardiographic parameter is pulmonary regurgitation velocity (PRV) which is the retrograde flow of blood across the pulmonary valve during diastole and estimates PAP.

Therefore, it appears that there are different methods for estimating PH among patients with β-TM. Considering all the mentioned methods, this study mainly aims to assess the correlation between PH, serum ferritin levels, and CMRI T2* among patients with β-TM. It is expected that the findings of this study will be useful for physicians to choose the most appropriate method for the diagnosis of PH among patients with β-TM.

Methods

A descriptive cross-sectional study was conducted on 50 patients, older than 5 years old, with β-TM from Nov 2019 to Oct 2020. All the patients or their legal guardians received the informed consent form and were informed about their rights during the study. Ethical principles were observed and followed based on the ethical code approved by the Ethics Committee of Arak University of Medical Sciences (IR.ARAKMU.REC.1397.153).

The participants had been receiving blood transfusions every 3-4 weeks to maintain hemoglobin levels equal to or higher than 10g/dl. All patients were also under iron chelation therapy by deferiprone (DFP) and deferoxamine (DFO). The exclusion criteria were the presence of any simultaneous infection, renal failure, congenital heart disease, blood pressure>140/90, arrhythmia, left ventricular ejection fraction (LVEF) less than 55%, and receiving any therapy due to cardiac disease.

Each patient went under investigation for two days. On the first day, which was a blood transfusion session, the demographic data were obtained. The serum ferritin level was measured using the Enzyme-linked immunosorbent (ELISA) method. The ECG test was performed to find the P wave height and determine if a patient had a P pulmonale (P wave greater than 2.5mm in the inferior leads). Echocardiographic assessment on the parasternal short-axis and the apical four chambers were also done, using a 3-8MHz probe by ViVid 6 (GE Medical Systems, general electric, USA). To confirm the echocardiographic findings, cardiac function was assessed during five consecutive cardiac cycles (according to American society echocardiography). Based on the echocardiographic findings, the patients were divided into two groups of PAP>30mmHg and PAP<30mmHg, with the aim of diagnosing patients with definite PH, not those with the borderline PAP (25 to 30mmHg).

On the second day of assessment for each patient, an approximately 30 minute-CMRI *T2 was performed, using a Magneto Symphony Graniand 32, 1.5 Tesla (Siemens, Germany, 2003). The MRI machine's cut-off points were as follows: normal >20ms, mild: 14-20ms, moderate: 10-14ms, and severe <10ms.

Statistical Analysis

All the variables were expressed as mean ±standard deviation. Data analysis was performed by SPSS version 20, using independent samples student t-test and chi-square test with a significant level of P-value<0.05. Pearson's and Spearman's linear correlation coefficient analyses were used to assess the relationship between echocardiography parameters and cardiac T2 MRI findings.

Results

Out of 50 participants, 30 were females and 20 were males with the mean age of 24.58 (95% CI: 16.7-29.9). A total of 15 patients had a splenectomy including nine females and six males. Among all 50 patients, 32% had CMRI *T2 of lower than 20ms. PAP was higher than 30mmHg in 40% of the participants. All the demographic, clinical, laboratory, and echocardiography data were shown in Table 1.

Table 1. Mean and standard deviation of demographic, clinical, laboratory and echocardiography information.

Variables	Mean	SD
Age	24.58	7.7
Weight	54.72	12.32
Height	160.02	13.95
BMI	21	2.44
BSA	1.55	0.24
Hb	9.06	1.13
Ferritin	1458.18	995.83
HR	84.84	4.46
RR	19.28	1.12
SBP	103.1	8.38
DBP	63.2	4.6
ECG	3.08	0.39
T2*MRI	22.63	7.17
TRV	2.27	0.14
PRV	2.78	0.18
PAP	30.88	3.7

BMI: body mass index, BSA: body surface area, Hb: hemoglobin, HR: heart rate, RR: respiratory rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, ECG: electrocardiogram, TRV: TR velocity, PRV: PR velocity, PAP: pulmonary artery pressure.

In Table 2, the correlation of CMRI *T2 and cardiography findings were indicated as well as the correlation of serum ferritin levels and the cardiography findings. Cardiography findings included echocardiography and electrocardiography parameters. Based on the results, there were significant negative correlations between CMRI *T2 and PAP, TRV, PRV, and the P wave height in ECG. In Contrast, the serum ferritin level was positively correlated with PAP, TRV, PRV, and the P wave height in ECG. The strongest Pearson Correlation Coefficient was found between PAP and serum ferritin levels.

Table 2. Univariate correlation between T2*MRI and Ferritin with PAP, TRV, PRV, and ECG.

Variables	T2*MRI		Ferritin	
	r	P-value*	r	P-value*
PAP	-0.36	0.010	0.44	0.001
TRV	-0.32	0.021	0.39	0.005
PRV	-0.36	0.006	0.41	0.003
ECG	-0.29	0.040	0.30	0.037

*Pearson correlation coefficient was calculated in 95% levels of CI; ECG: electrocardiogram, TRV: TR velocity, PRV: PR velocity, PAP: pulmonary artery pressure

Table 3 shows the multivariate analysis of the correlation between cardiographic findings, including PAP, TRV, PRV, and ECG and CMRI *T2 as well as serum ferritin levels; considering the potential effects of age, gender, and Hb levels. Based on the results, gender and Hb levels were not meaningfully correlated with other variables. However, age was positively correlated with the cardiographic parameters and serum ferritin levels. In other words, an increase in both variables of age and serum ferritin level was related to an enhancement in the cardiographic parameters including PAP, and the P wave height in ECG.

Table 3. Multivariate analysis of correlation between PAP, TRV, PRV, and ECG with T2*MRI and ferritin.

Variables	PAP		TRV		PRV		ECG	
	r	P-value	r	P-value	r	P-value	r	P-value
T2*MRI	-0.16	0.213	-0.15	0.247	-0.21	0.124	-0.13	0.333
Ferritin	0.46	0.001	0.42	0.002	0.40	0.004	0.34	0.016
Age	0.40	0.002	0.43	0.001	0.36	0.006	0.47	0.001
Hb	0.05	0.655	0.12	0.314	0.05	0.676	0.04	0.731

*Pearson correlation coefficient was calculated with regression analysis in 95% levels of CI
ECG: electrocardiogram, TRV: TR velocity, PRV: PR velocity, PAP: pulmonary artery pressure

Table 4 indicates the comparison of variables between CMRI *T2 of more than 20ms and less than 20ms. According to the results, the mean of serum ferritin levels, P wave height in ECG, TRV, PRV, and PAP were significantly higher in participants with CMRI *T2 <20 compared to the participants with CMRI *T2 >20.

Table 4. Comparison of variables mean between T2*MRI levels.

Variables	T2*MRI		P-value
	<20	>20	
Age	26.56±6.32	23.64±8.19	0.107
Weight	53.56±12.46	55.26±12.4	0.326
Height	160.06±13.40	160.0±14.39	0.492
BMI	20.65±2.47	21.17±2.45	0.246
BSA	1.53±0.23	1.56±0.25	0.376
Hb	8.85±1.22	9.17±1.09	0.178
Ferritin	2052.3±1002.9	1178.6±873.8	**0.001**
HR	85.18±4.95	84.67±4.29	0.355
RR	19.0±0.96	19.41±1.18	0.115
SBP	101.25±8.85	103.97±8.14	0.144
DBP	62.18±4.06	63.67±4.81	0.145
ECG	3.36±0.37	2.94±0.32	**0.000**
TRV	2.4±0.13	2.22±0.10	**0.000**
PRV	2.93±0.17	2.70±0.13	**0.000**
PAP	34.12±3.61	29.35±2.63	**0.000**

*Independent t-test was calculated in 95% levels of CI
BMI: body mass index, BSA: body surface area, Hb: hemoglobin, HR: heart rate, RR: respiratory rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, ECG: electrocardiogram, TRV: TR velocity, PRV: PR velocity, PAP: pulmonary artery pressure

Table 5 represents a comparison of variables based on different levels of serum ferritin. The means of weight, BMI, BSA, CMRI *T2, and SBP in patients with ferritin<1500ng/dL were significantly higher than patients with ferritin>1500ng/dL. Contrarily, the means of P wave height in ECG, TRV, PRV, and PAP were significantly lower in patients with ferritin <1500ng/dL compared to the patients with ferritin>1500ng/dL.

Table 5. Comparison of variables mean between ferritin levels.

Variables	Ferritin		P-value
	<1500ng/dL	>1500ng/dL	
Age	25.5±7.54	22.94±7.91	0.132
Weight	57.62±10.87	49.55±13.33	**0.012**
Height	162.03±11.10	156.44±17.74	**0.083**
BMI	21.73±1.87	19.71±2.85	**0.002**
BSA	1.60±0.20	1.46±0.28	**0.020**
Hb	9.21±1.11	8.81±1.14	0.116
T2*MRI	24.0±7.16	20.19±6.71	**0.035**
HR	84.09±4.28	86.16±4.60	**0.058**
RR	19.31±0.99	19.22±1.35	0.394
SBP	104.84±8.84	100.0±6.64	**0.024**
DBP	63.9±4.87	61.94±3.88	**0.074**
ECG	3.0±0.29	3.22±0.50	**0.026**

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TRV	2.24±0.10	2.34±0.17	**0.006**
PRV	2.72±0.11	2.87±0.24	**0.003**
PAP	29.75±2.43	32.88±4.70	**0.001**

*Independent t-test was calculated in 95% levels of CI
BMI: body mass index, BSA: body surface area, Hb: hemoglobin, HR: heart rate, RR: respiratory rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, ECG: electrocardiogram, TRV: TR velocity, PRV: PR velocity, PAP: pulmonary artery pressure

Comparison of the variables based on PAP levels was demonstrated in Table 6. For the patients with PAP>30, the means of age, serum ferritin level, and P wave height in ECG were significantly higher than patients with PAP<30; while the means of RR and CMRI *T2 were lower in patients with PAP>30 compared to patients with PAP<30.

Table 6. Comparison of variables mean between PAP levels.

Variables	PAP		P-value
	<30	>30	
Age	21.9±8.2	28.6±4.68	**0.001**
Weight	54.0±14.43	55.8±8.45	0.309
Height	158.06±15.65	162.95±10.62	0.114
BMI	21.04±2.85	20.94±1.74	0.447
BSA	1.53±0.28	1.58±0.16	0.222
Hb	9.14±1.0	8.96±1.32	0.293
Ferritin	1089.763.1	2011.9±1063.37	**0.000**
HR	84.33±4.85	85.6±3.8	0.165
RR	19.53±1.16	18.9±0.96	**0.025**
SBP	104.0±7.92	101.75±9.07	0.178
DBP	63.0±4.66	63.5±4.61	0.355
ECG	2.85±0.24	3.42±0.30	**0.000**
T2*MRI	24.47±4.83	19.86±9.15	**0.012**

*Independent t-test was calculated in 95% levels of CI
BMI: body mass index, BSA: body surface area, Hb: hemoglobin, HR: heart rate, RR: respiratory rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, ECG: electrocardiogram, TRV: TR velocity, PRV: PR velocity, PAP: pulmonary artery pressure

Finally, tables 7 and 8 represent the accuracy, sensitivity, and specificity of CMRI *T2 and serum ferritin levels as two tests to diagnose the PH among the patients. CMRI *T2 had higher accuracy (80%), sensitivity (65%), and specificity (90%) compared to the measurement of serum ferritin levels.

Table 7. The association between ferritin and PAP results.

Ferritin result	PAP result		
	Positive (%)	Negative (%)	Total
Positive	12 (66.67)	6 (33.33)	18
Negative	8 (25.0)	24 (75.0)	32
Total	20	30	50
Diagnostic test evaluation indicators of ferritin with considered PAP as a gold standard			
Indicators		%	95% CI
Accuracy		72	(57.5-83.8)
Sensitivity		60	(36.0-80.8)
Specificity		80	(61.4-92.3)
Positive predictive value		66.7	(41.0-86.6)
Negative predictive value		75	(56.6-88.5)

Table 8. The association between T2*MRI and PAP results.

T2*MRI result	PAP result		
	Positive (%)	Negative (%)	Total
Positive	13 (81.25)	3 (18.75)	16
Negative	7 (20.59)	27 (79.41)	34
Total	20	30	50
Diagnostic test evaluation indicators of T2*MRI with considered PAP as a gold standard			
Indicators		%	95% CI
Accuracy		80	(66.3-90.0)
Sensitivity		65	(40.8-84.6)
Specificity		90	(73.5-97.9)
Positive predictive value		81.2	(54.3-95.9)
Negative predictive value		79.4	(62.1-91.3)

Discussion

PH is defined as a mean pulmonary artery pressure of higher than 25 mmHg at rest or ≥ 30mmHg during exercise [10]. Chronic hemolytic anemia is one of the important risk factors for PH. In patients with β-TM, the development of PH is related to the severity of hemolysis. Yet, in those patients who are receiving chronic transfusion therapy, PH can be also related to iron overload and consequently, cardiac dysfunction, rather than hemolysis. Besides echocardiography, CMRI *T2 is another tool to determine the risk of PH in patients and also useful to measure the iron overload's degree in patients receiving frequent blood transmission [11,12]. It is crucial to consider all the causes of PH in a patient diagnosed with PH for the first time.

PH is associated with higher mortality and morbidity rates among patients with β-TM. According to the National Institutes of Health (NIH), the median survival rate of patients with primary PH was 2.8 years after diagnosis. While the different prevalence of PH in patients with β-TM has been reported, studies reported the prevalence of approximately 70% to 80% [13,14]. For example, in a study on 33 patients with β-TM, 28 participants had elevated pulmonary systolic pressure based on the echocardiographic findings [13]. Yet, some other studies indicated a significantly lower prevalence of PH, about 10%, among patients with β-TM [15-18]. These differences can be the result of different assessment methods to diagnose PH, such as right heart catheterization and echocardiography. Another reason might be the differences between populations under investigation. For example, patients with more severe anemia or those who received treatment with a delay will be more likely to suffer from

PH [19]. It is also suggested that the improvement in care for patients with β-TM can be another reason for the lower rate of PH among this population during recent years [20].

Researchers in the field tried to study different factors that might be related to cardiac complications of β-TM. In a study by Chueamuangphan et al., it was shown that PAP was associated with splenectomy and E/β-Thalassemia [21].

Another study by Dr. Eghbali et al. indicated a relationship between serum ferritin level with ejection fraction (EF) and fractional shortening [18]. Ultimately, the evidence showed that different factors and parameters such as echocardiography findings, EF, serum ferritin levels, CMRI *T2, splenectomy, age, and the onset of treatment could be related to and a predictor for cardiac complications in patients with β-TM.

In this study, out of 50 participants, 20 of them had PAP of higher than 30 mmHg which means nearly half of the patients suffered from PH. The two echocardiography parameters of TRV and PRV were the main indicative of PAP.

The existence of PH with higher levels of serum ferritin and lower speeds inCMRI *T2 demonstrated that iron overload is the cause of PH among this population. Therefore, we should immediately think about cardiac complications when we find high levels of serum ferritin in patients with TM.

The correlation of age and cardiographic parameters showed that the probability of higher PAP and the existence of P pulmonale in ECG is higher in older patients. It propounds the necessity of screening patients with higher ages for PH among this population.

Lastly, based on the sensitivity, specificity, and the accuracy of using CMRI *T2 and measuring serum ferritin levels for diagnosis of patients with PAP, CMRI *T2 was a more accurate method of diagnosing PH among these groups of patients with an accuracy of 80% compared to the serum ferritin level measurement with the accuracy of 72%. In other words, 65% of the patients with PAP>30mmHg had a CMRI *T2<20ms while 60% of them had serum ferritin levels higher than 1500ng/dL. Moreover, while just 80% of the patients with PAP<30 had serum ferritin levels lower than 1500ng/dL, 90% of them had CMRI *T2>20ms.

These results show us that both the methods, measuring serum ferritin levels and performing CMRI *T2, are indicative of PH in patients with TM besides showing iron overload. Therefore, it can be suggested that there is no need to perform nor the serum ferritin test neither CMRI *T2 if PAP is in the normal range and patients are not suspected of any cardiac complications based on their physical examinations. In contrast, if a patient does not have a high PAP, but her/his physician suspects the cardiac complication of iron overload in the myocardium tissue, CMRI *T2 is a more specific test to rule out cardiac complications.

In case of high rates of PAP in the patients, both of these methods are useful to confirm the diagnosis of PH, but CMRI *T2 is a more sensitive test and also can accurately predict the severity of iron overload and also other cardiac complications among the patients. It is ultimately the practitioner's decision to apply which test for which patient, considering all the circumstances including the physical examination, signs, symptoms, and also the cost of the test.

Limitations

This study had particular limitations, and the first one was the small sample size; however, it was not unavoidable as we could access just the patients from one center. Secondly, we could more accurately discuss PAP among the patients if a six-minute walk test and right hemodynamic angiography were performed for the participants as another method of evaluating PAP. Moreover, while splenectomy is a risk factor for PH, we did not exclude the patients with splenectomy as the sample size was limited. We suggest that splenectomy and platelet count should be considered as factors related to PH in future studies.

Conclusion

In conclusion, cardiac siderosis was one of the reasons for PH among patients with β-TM, and PH was correlated with serum ferritin levels and CMRI *T2 as patients with higher PAP had higher levels of serum ferritin and a lower CMRI *T2 index. The accuracy of 80% for CMRI *T2 as a method to diagnose or even anticipate PH among patients with β-TM suggested that this method is a useful and accurate method of PH diagnosis and can be used as an alternative among clinicians.

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Conflict of Interest

None declared.

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