



The relation between serum ferritin level and echocardiographic findings in transfusion dependent thalassemic patients in Slemani City, Kurdistan Region of Iraq.

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Abstract

Background and objectives: Thalassemia patients are at risk of iron overload. Those with transfusion-dependent thalassemia are more likely to experience cardiac problems because repeated blood transfusions cause iron accumulation in the cardiac myocyte. Thus, this study aims to determine the relationship between serum ferritin levels and echocardiographic findings in transfusion-dependent thalassemia patients.

Methods: This retrospective analytical cross-sectional study was conducted on 131 patients with transfusion-dependent thalassemia between 1st December 2021 to 1st July 2022 at the Center for Thalassemia and Congenital Blood Disorder, Slemani, Iraq. The participant's information, including sociodemographic characteristics such as age, gender, body weight, height, hemoglobin level, serum ferritin, type and duration of chelation therapy, and echocardiographic findings, were collected from the hospital database using a questionnaire. Then, the correlation between serum ferritin levels and echocardiographic results was determined.

Results: The mean age of the patients was 21.24 ± 6.28 years, and most of them were males (55.7%), from the urban region (71%) and had an average body weight (68.7%). The mean serum ferritin level was 1876 ± 1743.63 $\mu\text{g/L}$. The interpretation of the echocardiography results showed 38 patients (29%) had valvular heart diseases. Body mass index has a reverse linear relationship with ejection fraction ($P=0.038$) and a direct relationship with age ($P<0.001$). However, no significant association was found between echocardiographic findings and serum ferritin ($P=0.83$).

Conclusions: We found valvular heart diseases among the most common heart disorders in the patients. Suitable interventions and measures can significantly help manage the condition and reduce illness complications.

Keywords: Echocardiography, Heart disease, Serum Ferritin level, Thalassemia

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Introduction

In the Middle East and other developing countries, β -thalassemia is a common genetic blood disorder.¹ It is characterized by a decrease or absence in the synthesis of the β -globin chain, which results in ineffective erythropoiesis and defective hemoglobin A (HbA).^{1, 2} β -thalassemia major is characterized by severe hemolysis and severe anemia, which requires repeated blood transfusions, resulting in the accumulation of iron in the blood and body organs, as well as an increase in serum ferritin.^{3, 4} The iron buildup could negatively impact the heart's structure and function, causing ventricular diastolic and systolic dysfunction. Cardiac rhythm disturbances, such as slowed electrical conduction, heart block, increased susceptibility to atrial fibrillation, frequent premature ventricular contractions, and sudden death, frequently accompany this.⁵ Cardiac hemosiderosis is relevant since it raises mortality and morbidity rates and is responsible for more than 60% of fatalities in thalassemic patients.⁶ Iron infiltrates transfusion-dependent thalassemia (TDT) patients' cardiac myocyte, leading to substantial diastolic dysfunction and increased wall thickness.⁷ In general, cardiomyopathy (CM) begins with iron-mediated cardiovascular damage, which results in altered excitation-contraction coupling and electrophysiology, followed by diastolic dysfunction, and finally, dilated biventricular CM.⁸

Serum ferritin measurement is one technique for assessing iron levels in thalassemic patients⁹. It is routinely used with Hb levels to determine the need for blood transfusions in these cases by suppressing ineffective erythropoiesis and its complications with keeping Hb levels around 10 g/dL. Simultaneously, serum ferritin should not exceed 300 ng/mL, and echocardiography should be performed periodically to maintain a balance between the effect of anemia on the

heart and the burden of cardiac iron overload.¹⁰ An ideal non-invasive diagnostic technique is echocardiography, which assesses the heart's systolic function, ejection fraction (EF), and left ventricle (LV) chamber dimensions and correlates the results with serum ferritin and Hb levels.¹¹ Thus, this study aimed to find the relationship between serum ferritin levels and echocardiographic outcomes in transfusion-dependent thalassemia patients.

Patients and methods

This retrospective cross-sectional study was conducted on 131 patients with TDT who were admitted to the Center for Thalassemia and Congenital Blood Disorders, Slemani, Iraq, from 1st December 2021 to 1st July 2022. Regarding the inclusion criteria, patients aged > 10 years with transfusion-dependent β -thalassemia were enrolled. In contrast, patients with other iron overload causes, such as viral hepatitis, acute infection and hepatic failure, were excluded from the study.

The patients' data (sociodemographic and clinical) were obtained from the hospital database. In this regard, a validated questionnaire was used to collect the sociodemographic information of each patient, such as age, gender, height, weight at diagnosis, residency and body mass index (BMI). At the same time, the same questionnaire was used to collect each patient's first and last Hb count, serum ferritin level, initial ultrasound of the abdomen and echocardiographical findings, including hypokinesia, systolic and diastolic dysfunction, valvular heart disease, myocardial texture, dilated chambers, cardiac hypertrophy, and ejection Fraction.

The study protocol was approved by the ethical committee of the College of Medicine, University of Slemani, while verbal consent was taken from the patients or their parents for disclosing their information. Finally, the collected data were analyzed using Statistical Package for Social Science (SPSS, version 22,

Chicago, USA). Then, descriptive, chi-square, and Pearson correlation tests were used to determine the correlations. A p-value of less than 0.05 was considered significant.

Results

The socio-demographic data showed that the mean age of the patients was 21.24 ± 6.28 years, while their mean age at diagnosis was 11.11 ± 10.53 years. Most patients (55.7%) were males, and 44.3% were females. Most patients (71%) were from urban areas, and 29% were from rural areas. The patients' mean weight was 51.66 ± 11.24 kg, and the mean height was 156.05 ± 9.65 cm. Their mean BMI was 20.97 ± 3.22 kg/m². Regarding body weight, 26 patients (19.8%) were underweight, 90 (68.7%) had average weight, and 15 (11.5%) were overweight, Table (1).

Table (1): Sociodemographic characteristics of the studied participants

Variable		No (%)
Gender	Male	73 (55.7)
	Female	58 (44.3)
Residency	Urban	93 (71.0)
	Rural	38 (29.0)
Body weight	Underweight	26 (19.8)
	Normalweight	90 (68.7)
	Overweight	15 (11.5)
Total		131 (100)

Regarding the clinical characteristics of patients, the mean Hb level was 8.26 ± 0.88 g/Dl (93.1% had a Hb level of ≥ 7 and 6.9% had a Hb level of < 7), and the mean serum ferritin was 1876.4 ± 1743.6 μ g/L. Most patients (59.5%) had a ferritin level of ≥ 1000 μ g/L, and 53 patients (40.5%) had a ferritin level of

< 1000 μ g/L. The echocardiography results showed that the mean EF of the patients was 64.56 ± 5.47 .

The interpretation of echocardiography results of the patients showed that 61 patients (46.6%) had a normal heart condition, 2 patients (1.5%) had left ventricular diastolic dysfunction, 38 patients (29%) had valvular heart diseases (mainly tricuspid valve; 20 cases among 38 cases), 1 patient (0.8 %) has increased heart echo texture (mild increase in iron deposit), 4 patients (3.1%) had dilated chambers (3 cases of left atrium dilatation and one case of right-sided heart dilatation), 1 patient (0.8%) had left ventricular hypertrophy, and 24 patients (18.2%) had a combination of these diseases. Also, the percentage of patients' left ventricular ejection fraction (LVEF) was 64.56 ± 5.48 ; 14 patients (10.7%) had LVEF of less than 60%, while 117 had LVEF of more than 60%. The results of iron chelation therapy showed that 89 patients (67.9%) used deferasirox, 2 patients (1.5%) deferiprone, 1 patient (0.8%) deferoxamine, and 39 patients (28.8%) took a combination of these agents. Among the patients, 58 (44.3%) underwent splenectomy, as shown in Table (2).

Table (2): Clinical characteristics of studied participants

Variable		No (%)
Hb (g/dL)	< 7	9 (6.9)
	≥ 7	122 (93.1)
Ferritin (µg/mL)	< 1000	53 (40.5)
	≥ 1000	78 (59.5)
Echocardiography result	Normal heart condition	61 (46.6)
	Diastolic dysfunction	2 (1.5)
	Valvular heart disease	38 (29.0)
	Increased myocardial texture	1 (0.8)
	Dilated chamber	4 (3.1)
	Cardiac hypertrophy	1 (0.8)
	Combined abnormalities	24 (18.2)
Left ventricular ejection fraction%	< 60	14 (10.7)
	60≥	117 (89.3)
Iron chelating agents	Deferasirox	89 (67.9)
	Deferiprone	2 (1.5)
	Deferoxamine	1 (0.8)
	Combined agents	39 (28.8)
Splenectomy	Yes	58 (44.3)
	No	73 (55.7)
Total		131 (100)

The relationship between BMI, serum ferritin, EF%, and age was done with Pearson's statistical test. The results showed that BMI had a reverse linear relationship with EF% ($r=-0.182$ and $P=0.038$), and it was directly related to age ($r=0.538$ and $P<0.001$), while it had no

ties with serum ferritin. On the other hand, an inverse relationship of EF% with age ($r=-0.261$ and $P=0.003$) was found with no relation to serum ferritin. Also, there was no association between serum ferritin and any other variables, as shown in Table (3).

Table (3): Relationship between BMI, EF%, serum ferritin, and age of studied participants.

Parameter		BMI	EF%	Serum Ferritin	Age
BMI	Pearson correlation	1	-0.182*	-0.067	0.538**
	Sig. (2-tailed)		0.038	0.445	0.000
EF%	Pearson correlation	-0.182*	1	0.108	-0.261**
	Sig. (2-tailed)	0.038		0.221	0.003
Serum Ferritin	Pearson correlation	-0.067	0.108	1	-0.092
	Sig. (2-tailed)	0.445	0.221		0.294
Age	Pearson correlation	0.538**	-0.261**	-0.092	1
	Sig. (2-tailed)	0.000	0.003	0.294	
*: Correlation is significant at the 0.05 level (2-tailed)					
**: Correlation is significant at the 0.01 level (2-tailed)					
BMI: Body Mass Index, EF: Ejection Fraction					

In comparing echocardiographic findings between two groups of patients with serum ferritin levels (Group A: ≥ 1000 and group B: < 1000 $\mu\text{g/L}$), 39 patients in group A and 22 in group B had normal cardiac status. At the same time, 1 patient from each group had diastolic dysfunction. Moreover, 20 patients in group A

and 18 in group B had valvular heart diseases, 2 patients from each group had dilated chambers, and 1 patient in group A had cardiac hypertrophy. Furthermore, 14 patients in group A and 10 in group B had other heart problems, with no significant differences between the two groups ($P=0.83$), as shown in Table (4).

Table (4): Comparison of echocardiographic findings between two groups of patients with various serum ferritin levels.

Echo findings	Serum ferritin (µg/L)		Total	p value
	≥1000	<1000		
	Number, %			
Normal	39 (36.1)	22 (63.9)	61	0.83
Diastolic dysfunction	1 (50.0)	1 (50.0)	2.0	
Valvular heart disease	20 (52.6)	18 (47.4)	38	
Increased myocardial texture	1 (100.0)	0 (0.0)	1.0	
Dilated chamber	2 (50.0)	2 (50.0)	4.0	
Cardiac hypertrophy	1 (100.0)	0 (0.0)	1.0	
Others	14 (41.7)	10 (58.3)	24	

Discussion

One of the main survival factors of thalassemia patients is good heart function. Thalassemic patients can live a long life if they do not have heart problems,¹² and the increase in iron overload is the leading cause of death in these patients.¹³

The mean age of patients in this study was 21 years which is less than that found by Heris et al.¹⁴, but it is higher than that found by Ahmed et al.¹⁵. The results of various studies have shown that the gender of the studied patients was male, which is consistent with the results of the present study.^{16, 17} Regarding the patients' age at disease diagnosis, an earlier age was found in this study than in other studies.¹⁸,¹⁹ Most patients had average weight and BMI, and only 11% were overweight. In contrast,

Lidoriki et al. found most patients had average weight and BMI, and the frequency of overweight patients was higher than in this study.²⁰ Also, Ghandi et al.²¹ mentioned that most patients had higher BMI than the present study.

Due to the deficiency of equipment and medicine during several periods of war and unrest, thalassemia was neglected in Iraq,²² considering that the organs of the human body damage them. Also, based on the different results of the mentioned studies, we need to conduct more studies on the effect of these factors to prevent various complications, including functional and structural heart disorders.

The role of serum ferritin as a risk factor for cardiovascular diseases is getting more attention every day.²³ The mean serum ferritin



in the present study was $1876 \pm 1743.63 \mu\text{g/L}$. In the survey conducted by Yuksel et al.²⁴, the mean serum ferritin was higher than in the present study, but in terms of the frequency of patients with ferritin <1000 and ≥ 1000 , their findings were consistent with this study. Our mean of serum ferritin was higher than that found by Klip et al.²⁵

The mean Hb of patients in the current study was higher than that found by Wongtong et al.²⁶. At the same time; it was lower than that observed by Derchi et al.²⁷. The mean EF% in the present study was 64.56 ± 5.47 , which was lower than that shown by Digra et al.²⁸ and Abtahi et al.²⁹. Valvular heart disease was the most common heart disorder in this study based on echocardiography findings. However, 60 patients did not have heart problems. Furthermore, the frequency of cardiac conditions in other studies was different. In this regard, Khalilian et al.³⁰ found LVSD as the most common disorder. In contrast, Chen et al.³¹ found subclinical systolic dysfunction, and Deraz et al.³² seen end-systolic diameter and LV end-diastolic diameter as the most common disorders.

Regarding heart function, most patients had normal heart function (LVEF of $\geq 60\%$), which is consistent with the findings of other studies.^{33, 34} The result of iron chelation showed that most patients used deferasirox, and 28% of patients used combined agents. At the same time, Olivieri et al.³⁵ also reported higher usage of deferasirox. In the study of Sanpakit et al.³⁶ 60% of patients underwent splenectomy, which is consistent with the findings of this study.

Our study showed a negative correlation between BMI and EF% and a direct correlation between BMI and age. These results align with previous studies^{37, 38} that reported a direct relationship between EF% and age, while Mohammed et al.³⁹ found an inverse correlation. In this study, EF%, serum ferritin, Hb and echocardiographic findings did not show a significant relationship to gender. Also, no meaningful relationship was observed

between echocardiography findings and serum ferritin, while Helmi et al.⁴⁰ reported a controversial result.

Conclusions

Valvular heart diseases were among our studied patients' most common heart disorders. Consequently, timely interventions and measures can help a lot in the disease management process and reduce the complications of the disease.

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References

1. Kremastinos DT, Farmakis D, Aessopos A, et al. β -thalassemia cardiomyopathy: history, present considerations, and future perspectives. *Circ Heart Fail.* 2010;3(3):451-58.
2. Pennell DJ, Udelson JE, Arai AE, et al. Cardiovascular function and treatment in β -thalassemia major: a consensus statement from the American Heart Association. *Circ.* 2013;128(3):281-308.
3. ALSaadi E. Disturbances of Lipid Profile, hemoglobin and Serum Ferritin Levels in Thalassemia Patients in Misan City, Amara, Iraq. *J Med Chem Sci.* 2022;5(5):779-86.
4. Sumneang N, Siri-Angkul N, Kumfu S, et al. The effects of iron overload on mitochondrial function, mitochondrial dynamics, and ferroptosis in cardiomyocytes. *Arch Biochem Biophys.* 2020; 680:108241.
5. Kremastinos D, Farmakis D. Iron overload cardiomyopathy in clinical practice. *Circ.* 2011;124(20):2253-63.



6. Ghanavat M, Haybar H, Pezeshki SMS, et al. Cardiomyopathy in thalassemia: quick review from cellular aspects to diagnosis and current treatments. *Lab Med*. 2020;51(2):143-50.
7. Rubis P. The diagnostic work up of genetic and inflammatory dilated cardiomyopathy. *EJ Cardiol Pract*. 2015;13(19):1-11.
8. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. *J Card Fail*. 2010;16(11):888-900.
9. Crawford B, Kasmidi M, Korompis F, et al. Factors influencing progress in establishing community-based marine protected areas in Indonesia. *Coas Manage*. 2006;34(1):39-64.
10. Ghandi Y, Eghbali A, Rafie F. Correlation between mean serum ferritin levels and atrial electrocardiographic markers in beta-thalassemia major. *IJBC*. 2018;10(3):76-81.
11. Wood JC. Cardiac complications in thalassemia major. *Hemoglobin*. 2009;33(sup1):S81-S86.
12. Khaled A, Ezzat DA, Salem HA, et al. Effective method of evaluating myocardial iron concentration in pediatric patients with thalassemia major. *J Blood Med*. 2019:227-33.
13. Shah F, Huey K, Deshpande S, et al. Relationship between Serum Ferritin and Outcomes in β -Thalassemia: A Systematic Literature Review. *J Clin Med*. 2022;11(15):4448.
14. Heris HK, Nejati B, Rezazadeh K, et al. Evaluation of iron overload by cardiac and liver T2* in β -thalassemia: Correlation with serum ferritin, heart function and liver enzymes. *J Cardiovasc Thorac Res*. 2021;13(1):54-60.
15. Ahmed RA, Salih AF, Omer SH, et al. Early Detection of Iron Overload Cardiomyopathy in Transfusion Dependent Thalassemia Patients in Sulaimaniyah City, Iraq. *Ther Clin Risk Manag*. 2022:259-71.
16. Esfahani H, Tanasan A, Rezanejad M, et al. Heart involvement in transfusion-dependent beta-thalassemia with conventional echocardiography. *Caspian J Intern Med*. 2021;12(3):243-48.
17. Fayed H, Mawgood E, Qubaisy H. Echocardiography in Transfusion Dependent Beta Thalassemia Major Egyptian Children: Correlation with Thyroid Function Status and Ferritin Level. *JCDR*. 2018;12(4):1-7.
18. Hassan ZF, Shukur Alghanimi MK, Abbood A. Role of Tissue Doppler in Early Detection of Left Ventricular Dysfunction in β Thalassemic Patients of Pediatric Age Group. *Indian J Public Health Res Dev*. 2020;11(4):1334-39.
19. Koohi F, Kazemi T, Miri-Moghaddam E. Cardiac complications and iron overload in beta thalassemia major patients—a systematic review and meta-analysis. *Ann Hematol*. 2019;98:1323-31.
20. Lidoriki I, Stavrou G, Schizas D, et al. Nutritional Status in a Sample of Patients With β -Thalassemia Major. *Cureus*. 2022;14(8):e27985.
21. Ghandi Y, Habibi D, Eghbali A, et al. Influence of Average Annual Mean Serum Ferritin Levels on Left Ventricular Function in Patients With β Thalassemia. *Acta Med Iran*. 2020;58(6):279-84.
22. Al-Numan A, Mohammed S, Al-Shamaa G. Screening of beta-thalassemia major patients below 18 years for acute cytomegalovirus infection by IGM serology in Mosul. *Acta Med Mediterr*. 2021;37:1009.
23. Suárez-Ortegón M-F, McLachlan S, Fernandez-Real J-M, et al. Serum ferritin and incident cardiometabolic diseases in Scottish adults. *Cardiovas Diabetol*. 2022;21(1):26.
24. Yuksel IO, Koklu E, Kurtoglu E, et al. The association between serum ferritin level, tissue Doppler echocardiography, cardiac T2* MRI, and heart rate recovery in patients with beta thalassemia major. *Acta Cardiol Sin*. 2016;32(2):231-38.
25. Klip IT, Voors AA, Swinkels DW, et al. Serum ferritin and risk for new-onset heart failure and cardiovascular events in the community. *Eur J Heart Fail*. 2017;19(3):348-56.



26. Wongtong N, Pornvipavee R, Ananwattanasuk T, et al. Relationship between Serum Ferritin Level and Left Ventricular Function in Thalassemia Patients. *HTIJ*. 2016;26(3):207-13.
27. Derchi G, Dessì C, Bina P, et al. Risk factors for heart disease in transfusion-dependent thalassemia: serum ferritin revisited. *Intern Emerg Med*. 2019;14:365-70.
28. Digra SK, Kumar D, Bhat S, et al. Echocardiographic Findings In Thalassemia Major Patients: An Experience From Jammu. *JK Sci*. 2019;21(1):8-10.
29. Abtahi F, Abdi A, Jamshidi S, et al. Global longitudinal strain as an Indicator of cardiac Iron overload in thalassemia patients. *Cardiovasc Ultrasound*. 2019;17:1-6.
30. Khalilian MR, Moghaddar R, Emami-Moghadam A, et al. Evaluation of the correlation between echocardiographic findings and serum ferritin in thalassemia major patients. *Glob J Health Sci*. 2016;8(12):190-96.
31. Chen MR, Ko HS, Chao TF, et al. Relation of myocardial systolic mechanics to serum ferritin level as a prognosticator in thalassemia patients undergoing repeated transfusion. *Echocardiography*. 2015;32(1):79-88.
32. Deraz SE, Abd El Naby SA, Mahmoud AA. Assessment of ventricular dysfunction in Egyptian children with Beta-thalassemia major. *Hematol/Oncol Stem Cell Ther*. 2021;14(3):206-13.
33. Casale M, Filosa A, Ragozzino A, et al. Long-term improvement in cardiac magnetic resonance in β -thalassemia major patients treated with deferasirox extends to patients with abnormal baseline cardiac function. *Am J Hematol*. 2019;94(3):312-18.
34. Darvishi-Khezri H, Karami H, Naderisorki M, et al. Moderate to severe liver siderosis and raised AST are independent risk factors for vitamin D insufficiency in β -thalassemia patients. *Sci Rep*. 2020;10(1):1-8.
35. Olivieri NF, Sabouhian A, Gallie BL. Single-center retrospective study of the effectiveness and toxicity of the oral iron chelating drugs deferiprone and deferasirox. *PLoS One*. 2019;14(2):e0211942.
36. Sanpakit K, Narkbunnam N, Buaboonnam J, et al. Impact of splenectomy on outcomes of hematopoietic stem cell transplantation in pediatric patients with transfusion-dependent thalassemia. *Pediatr Blood Cancer*. 2020;67(9):e28483.
37. Elalfy MS, Youssef OI, Deghedy MM, et al. Left Ventricular Structural and Functional Changes in Children With β -Thalassemia and Sickle Cell Disease: Relationship to Sleep-disordered Breathing. *J Pediatr Hematol/Oncol*. 2018;40(3):171-77.
38. Noori NM, Yazdanparast A, Teimouri A. The Correlation of Ferritin and Leptin Serum Levels with Cardiac Involvement in Thalassemia Patients Compared to Controls. *Int J Pediatr*. 2018;6(5):7623-38.
39. Mohammed R, Manaa DSM, Rasha A, et al. Cardiac Iron Overload: Correlation between MRI T2* & Two Dimensional Strain Echocardiography in Children with β -Thalassemia Major. *Med J Cairo Univ*. 2018;86(June):1707-12.
40. Helmi N, Choudhry H, Qari M, et al. Association of serum asymmetric dimethyl-arginine and troponin I levels as a risk of myocardial infarction in thalassemia. *Afr Health Sci*. 2018;18(3):720-26.